VALUE OF IN-VITRO DIAGNOSTICS IN APAC:

Value Assessment Framework

With Applications For

CORONARY ARTERY DISEASE AND HEART FAILURE

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Abbreviations	Definitions
ACS	Acute Coronary Syndrome
ADHERE-AP	Acute Decompensated Heart Failure Registry, Asia Pacific
APAC	Asia Pacific
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
ECG	Electrocardiogram
ED	Emergency Department
HF	Heart Failure
HRQOL	Health Related Quality Of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratios
IVD	In-Vitro Diagnostics
MSAC	Medical Services Advisory Committee
NICE	National Institute for Health and Care Excellence
NP	Natriuretic Peptide
NT-proBNP	N-terminal pro-brain Natriuretic Peptide
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trials
RWE	Real World Evidence
VAF	Value Assessment Frameworks
VODI	Value Of Diagnostic Information

Foreword

Diagnostics are the gateway to care, however less than half of the world population have access to these technologies. A major milestone in recognising their critical value was achieved in May 2023 with the World Health Assembly's Resolution on Strengthening Diagnostics Capacity. This monumental leap emphasizes diagnostics' pivotal role across all tiers of healthcare and urges governments to bridge existing gaps.

This announcement encourages the Asia-Pacific Medical Technology Association (APACMed) to continue its critical work, championing the cause of improved patient access to diagnostic innovations alongside multiple stakeholders of the ecosystem.

The recent COVID-19 pandemic highlighted these technologies as an essential public health tool, since diagnostics provide crucial data that guides treatment decisions: from diagnosing patients, to determining the scope, spread, and scale of infectious disease outbreaks. Their essential role has been highlighted in APACMed's first publication, "The Critical Role of Diagnostics in COVID-19 Management" (Feb 2021). The value diagnostics bring is further developed and expanded to all areas in the report entitled "Strengthening Healthcare Systems Through the Critical Role of Diagnostics: Co-Creating Opportunities for Asia-Pacific Governments & Payer Leaders" (April 2022).

Building on these publications, this paper aims to continue the conversation, advocating for enhanced recognition of the substantial value in-vitro diagnostics provide to patients, healthcare professionals, providers/laboratory professionals, policy-makers and payers in the Asia Pacific region. It outlines five policy recommendations for a fit-for-purpose value assessment framework, more tailored to in-vitro diagnostics (IVDs) within the Asia Pacific (APAC) region, distinct from drug and medical device assessment models. The recommendations come as the result of a comprehensive research and consultations with key healthcare stakeholders. Coronary artery disease (CAD) and heart failure (HF) were chosen as concrete cases to underscore the numerous benefits in-vitro diagnostics bring throughout the patient care pathway and to all stakeholders. These cardiovascular diseases were selected due to the significant strain they place on healthcare systems and society.

The paper's recommendations are applicable to policymakers in various healthcare systems. By showcasing the considerable value in-vitro diagnostics offer to patients, the paper advocates for sustainable funding and widespread availability of in-vitro diagnostics at all levels of care. This approach ensures that patients have access to high-quality diagnostics, leading to improved quality of care. We are thankful to the team from ANSEA Consulting for the close collaboration in putting together this White Paper.

This paper marks an important step, towards strengthening the dialogue around the value of in-vitro diagnostics in the local context. By enabling a better value recognition path for these technologies, their role in universal healthcare delivery can thrive, as envisioned in the 76th World Health Assembly's resolution.

Harjit Gill
CEO, APACMed

We are eager to continue this meaningful work with our members, driving forward better value recognition of diagnostics. Let us rise to this challenge, catalyzing change and driving better patient access to care together!

Executive Summary

During the recently held 76th World Health Assembly in May 2023 in Geneva, member countries endorsed a resolution on strengthening diagnostic capacity. The broad ranging resolution recognizes that diagnostic services are vital for the prevention, surveillance, diagnosis, case management, monitoring and treatment of many diseases. Diagnostics allow for the precise identification of diseases, and therefore the timely initiation of the correct treatments for better health outcomes.[1]

Diagnostics are central and fundamental to quality health care.[2] However, even though diagnostics influence approximately 66% of treatment decisions, they only account for 1-2% of healthcare expenditure,[3] suggesting a potential imbalance between the value these diagnostics generate and the amount they are funded.[2] Scholars attribute this imbalance to the lack of an appropriate assessment that can fully capture the value of these technologies, which results in diagnostics being assessed in a rather partial or suboptimal way. This leads to the under-appreciation of their value[2] when making funding and reimbursement decisions.[4] The contributions of diagnostics to the healthcare system are, therefore, under-recognized and undervalued.[5]

In this white paper, coronary artery disease (CAD) and heart failure (HF) were used as concrete cases due to the huge burden these diseases pose to the healthcare system and society. Of all cardiovascular diseases, the number of patients with heart failure (HF) has been rapidly increasing to an estimated 64 million patients worldwide, which is the so-called 'HF pandemic' and 1 in 5 people are expected to develop this disease in their lifetime.[6,7,8] Within APAC, patients present with HF at a much younger age than in Europe and North America and CAD has been identified as one of the top 3 co-morbidities in HF patients.[9,10] In view of the considerably younger age of patients within the APAC region, the socio-economic and clinical burden these diseases pose to the healthcare system is estimated enormous. Hence, it is crucial to recognise the full value cardiac biomarkers bring throughout the CAD/HF patient care pathway.

Through extensive research and interviews with various stakeholders in the healthcare system, this white paper proposes 5 policy recommendations to address the need for a fit-for-purpose value assessment framework for in-vitro diagnostics, separate from drugs and medical devices. Our proposal calls for a broad set of value criteria, allowing for an IVD's full value potential to be captured and appropriately assessed. The paper demonstrates the benefits cardiac biomarkers (IVDs) provide throughout a CAD/HF patient journey and to all stakeholders in the healthcare system and it recommends for other types of evidence such as real-world evidence to be used for value assessing IVDs.

These recommendations can be considered by governments and policy makers across different healthcare archetypes, independent of whether the funding decisions are made through a designated HTA agency or not. As the paper highlights and demonstrates the abundant value IVDs bring to a patient, it advocates for IVDs to be backed by sustainable funding and availability at all care levels to ensure patient access to high quality diagnostics which results in better quality care.

Recommendations

1. Recognise the crucial value in-vitro diagnostics such as cardiac biomarkers provide throughout the CAD/HF patient care pathway and ensure there is sustainable funding availability for patient access to high quality diagnostics.

2. Ensure appropriate value recognition of all intermediate value outcomes in-vitro diagnostics such as cardiac biomarkers provide to the different groups of stakeholders in the healthcare system.

3. Include the perspectives of multiple stakeholders such as healthcare professionals, laboratory professionals, providers, industry experts, academics, policy advisors, and patients for value assessment processes.

4. Include broader value outcomes outside the traditional clinical performance and safety metrics, such as indirect costs, spillover costs and non-health outcomes when assessing the value of a diagnostic test.

5. Support the use of various types of evidence such as real-world evidence when assessing the full value of diagnostics.

Background

Scope: Fit-for-purpose value assessment framework for in-vitro diagnostics, with applications in Coronary Artery Disease and Heart Failure

In-vitro diagnostics (IVDs) can provide essential information at every step of the coronary artery disease (CAD) and heart failure (HF) patient care pathway, from diagnosis to treatment to monitoring the progression of a condition post-discharge. One early lesson learnt from the COVID-19 pandemic was the critical importance of timely accurate diagnosis.[2] However, 47% of the global population has little to no access to diagnostics.[2] With the ultimate goal of improving health of well-defined patient groups, in-vitro diagnostics affect all stakeholders in the healthcare system at multiple levels spanning the individual to the societal perspective.[11]

This white paper outlines the benefits of in-vitro diagnostics across the entire CAD/HF healthcare continuum and to the various stakeholders involved in the healthcare system. Based on this value, the paper advocates for a comprehensive fit-for-purpose value assessment framework for IVDs, separate from drugs and devices, that is defined more broadly than by clinical and safety metrics alone. It recommends the inclusion of broader value criteria such as indirect costs, spill-over costs, and non-health outcomes such as the value of knowing. The proposed value assessment framework incorporates the perspectives of multiple stakeholders such as healthcare professionals, industry experts, academics, payers, laboratory professionals, providers and patients.

As the focus of this paper is in-vitro diagnostics, other diagnostic technologies such as imaging (X-ray, CT scans, MRIs, ultrasounds etc.), will not be discussed. This is to enable a consistent and focused view of the in-vitro diagnostic landscape in the CAD/HF patient care pathway.

Burden of CAD and HF

There are 423 million adults that live with cardiovascular diseases (CVDs) worldwide and every year, 18 million of them die.[12] As a proportion of total deaths from all-causes, CVD in the Asia–Pacific region ranges from less than 20% in countries such as Thailand, Philippines, and Indonesia to 20–30% in urban China, Hong Kong, Japan, Korea and Malaysia. Countries such as New Zealand, Australia and Singapore have relatively high rates that exceed 30–35%.[13]

Of all CVDs, the number of patients with heart failure (HF) has been rapidly increasing to an estimated 64 million patients worldwide[6], which is the so-called 'HF pandemic'[7] and 1 in 5 people are expected to develop this disease in their lifetime.[8] HF can cause irreversible damage to the heart, if not treated adequately, and it cannot be cured.[8] While HF can affect people of any age, its prevalence increases with age and most patients are over 60 years old.[8]

Within APAC, patients with acute HF are of a younger age (54 years) compared to western patients (75 years); have more severe clinical features, higher rates of mechanical ventilation, longer lengths of stay and higher in-hospital mortality.[9] Even at a younger age, HF patients within APAC have a higher burden of comorbidities than patients in Europe and North America.[6] For example, in patients with HF, coronary artery disease has been identified as one of the top 3 co-morbidities that increases the risk of developing HF and contribute to poorer clinical outcomes.[10]

Considering the relatively younger age of patients with HF within the APAC region as compared with Europe and North America, the socioeconomic and clinical effects of HF are estimated to be particularly large in APAC.[14] In APAC, the overall economic cost of HF was estimated at $25 billion per annum. Of this, direct costs accounted for 48% ($12 billion) and indirect costs accounted for 52%, ($13 billion) of the overall HF spend.[15] To address this burden, the following sections will present evidence to show that IVDs play a critical role in reducing this problem.

The critical role of in-vitro diagnostics in CAD and HF

In-vitro diagnostics are an essential part of disease management and therapy, helping physicians to stratify patient cohorts, choose more appropriate drug regimens, avoid adverse events, reduce the amount of uncertainty, facilitate therapeutic monitoring, and define the predisposition to disease.[16]

Diagnostic tests enable improved clinical decision-making and therapy selection, distinct from the value of the underlying therapy intervention itself.[17] Early deployment of an accurate diagnostic test leads to improved patient outcomes and quality of life (QOL) and cost reduction from unnecessary treatment.[5]

Cardiac diagnostic tests have applications throughout the pathway of care. (Figure 1 and Figure 2).[5] These tests are used to confirm, or rule out a specific diagnosis, monitor the course of a disease, or assess a patient's eligibility for or response to specific treatments.[17] Equipped with this knowledge, providers and health care systems benefit by avoiding ineffective or wasteful health care provision that accompanies less targeted, traditional treatment approaches.[18]

The need for a fit-for-purpose value assessment framework for IVD in APAC

Unlike drugs, which acts as a direct therapeutic intervention on patients, diagnostics indirectly affect patients by guiding doctors' diagnoses and subsequent treatment decisions.[16] As a result, a diagnostic test is too often looked upon as a low value adding service when assessed using a value assessment framework for drugs and devices. Failure to incorporate all dimensions of the value of in-vitro diagnostics runs the risk of under- or over- stating the worth of diagnostics, both from the patient and societal perspectives and runs the risk of biasing economic evaluations, leading to the misallocation of health-care resources.[19]

Therefore, to capture the full value potential of an IVD, there is a need for a fit-for-purpose value assessment framework for in-vitro diagnostics that includes a broad set of criteria other than the traditional clinical and safety metrics alone. Value assessments for IVDs should allow for the inclusion of criteria such as indirect costs, spillover costs and non-health outcomes such as the value of knowing and should also consider the numerous potential benefits in-vitro diagnostics offer throughout a patient's journey and to the different stakeholders within the healthcare system.

Given the range of diagnostic technologies and the diverse set of value each technology offers, the application of HTA to diagnostics cannot take a "one-size-fits-all" approach. HTA should be applied wisely and highly selectively, considering the investment of time, resources, and evidence-generation that a robust HTA process entails. Only high medical value technologies should undergo such a HTA assessment. This includes those which address a significant unmet need; represent a transformative potential; or demonstrate potential for major impact on patients, public health, and the health system.

With new IVDs coming to market at an ever-increasing rate, it is important that HTA for diagnostics must not place excessive pressure on HTA agencies or needlessly delay patient access to essential diagnostic technologies which could affect a patient's quality of care. In scenarios where it is determined that a detailed HTA assessment is needed, this paper proposes a linked-evidence approach that can be considered for HTA decision-making.

Policy Recommendation 1

Recognise the crucial value in-vitro diagnostics such as cardiac biomarkers provide throughout the CAD/HF patient care pathway and ensure there is sustainable funding availability for patient access to high quality diagnostics.

Value of cardiac biomarkers along the CAD and HF patient care pathway

Even following careful clinical assessment by an experienced clinician using chest X-ray and electrocardiogram (ECG), heart failure (HF) diagnosis may be uncertain in 30–50% of cases.[20] Thus the measurement of cardiac biomarkers is recommended as an essential test in the assessment of patients with suspected acute HF or coronary artery disease in a range of international clinical practice guidelines.[20]

However, in the ADHERE-AP (Acute Decompensated Heart Failure Registry, Asia Pacific), it was found that plasma natriuretic peptide (cardiac biomarker) assays were performed as an initial diagnostic strategy in only 16% of southeast Asia HF patients upon admission compared to North America (82%).[10]

This failure to incorporate cardiac biomarker measurement into clinical practice means that the proven benefits of cardiac biomarkers are not being realised.[20] Defining and quantifying the value of a test to support investment decisions requires a broad approach across the continuum of healthcare services and budgets.[20]

In the following CAD (Figure 1) and HF (Figure 2) patient journeys, we illustrate the various opportunities cardiac biomarkers offer in addressing the challenges along the patient care pathway (i.e., across the healthcare continuum). It shows the potential of cardiac biomarkers in diagnosing a patient and informing treatment decisions through appropriate triaging and care plans in both the acute and chronic phases. It also shows how biomarkers have a role in discharge planning and early detection through regular monitoring of these diagnosed patients.

For the purposes of this position paper, we have narrowed down the discussion of cardiac biomarkers to high sensitive troponin and natriuretic peptides, which includes B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP).

Coronary Artery Disease

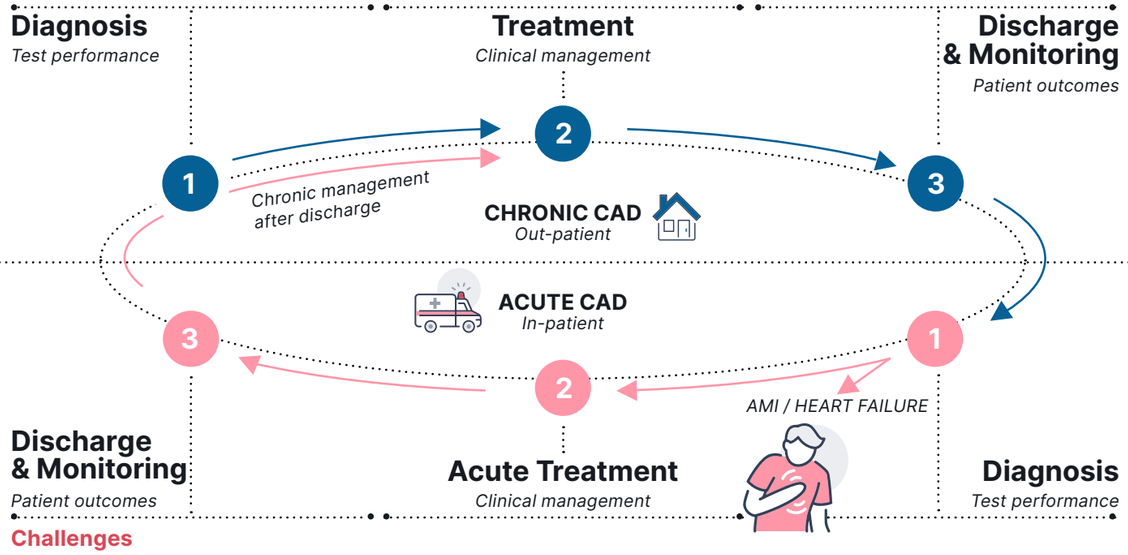
Coronary artery disease is characterized by inflammation and buildup of fatty deposits along the innermost layer of the coronary arteries. The thickening of fatty deposits narrows the arteries and decreases blood flow to the heart, which may result in heart attack.

Opportunities

The information provided by a cardiac biomarker: **Can be used to diagnose even mild CAD[52]**	*The information provided by a cardiac biomarker:* **Aids in the prediction of the risk of MACE and mortality[57]**	*The information provided by a cardiac biomarker:* **Can predict the incidence of heart failure and CV death even in patients with chronic CAD[59]**

Challenges

Physical examinations are often unrevealing in patients with Chronic CAD.[51]	During this waiting interval before intervention (CABG or angioplasty, eg.), the patient is at risk of death[55,56]	There is a significant lack of adherence (up to 70%) to cardiovascular medication usage within the Asian population.[60]



Challenges

In Singapore, the 30-day A&E and 30-day all-cause readmissions for AMI were 14.3% and 17.1% respectively[57]	Risk stratification is underutilized upon admission, leading to under treatment of higher-risk patients.[53] The in-hospital mortality rate of ACS in the region is often above 5%, which is high compared to the West.[72]	Nearly 1/3 of AMI patients are misdiagnosed upon admission due to incorrect ECG reading and failure to order appropriate diagnostic tests[48,49]

Opportunities

The information provided by a cardiac biomarker: **indicates prognosis for 30-day mortality rates in individuals diagnosed with acute myocardial infarction (AMI)[59]**	*The information provided by a cardiac biomarker:* **Allows for the correct triaging of patients with suspected AMI into low and high-risk groups[54,72]**	*The information provided by a cardiac biomarker:* **Can be used as a rule-out test in the emergency department[50,72]**

Figure 1: Coronary Artery Disease (CAD) Patient Journey

AMI: Acute Myocardinal Infarction
CABG: Coronary Artery Bypass Grafting
CAD: Coronary Artery Disease
CV: Cardiovascular
MACE: Major Adverse Cardiac Events

Heart Failure

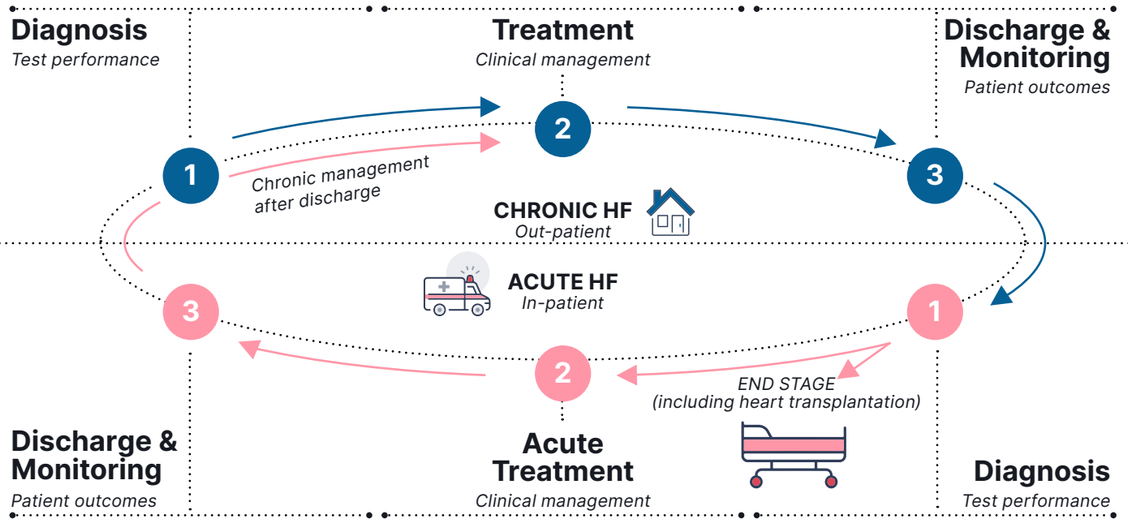
Heart failure is a progressive heart disease where the heart is unable to pump enough blood around the body.

Opportunities

The information provided by a cardiac biomarker: **Reduces the risk of missed diagnosis as further confidence is provided that HF will not be missed**[61]	*The information provided by a cardiac biomarker:* **Enables the identification of patients at risk of adverse events, allowing for intensified care of the patient (treatment optimization)**[61]	*The information provided by a cardiac biomarker:* **Can support continuous monitoring, which allows prediction of acute events such as cardiac decompensation as well as the risk of unpredictable events such as pump failure**[61]

Challenges

There are high rates of misdiagnosis as well as missed diagnosis as symptoms are not HF specific[61]	Patients with chronic HF are typically under-dosed, with multiple therapies applied incrementally and suboptimally.[61]	The lack of close monitoring often leads to patient non-adherence to lifestyle advice or to their medication impacting real world outcomes[61]



Challenges

Patients leaving the hospital after acute HF episodes remain at high risk of death and hospital re-admission for up to 3 months[61]	Hospitalisation costs, room and boarding fees are the greatest cost drivers in HF, contributing to 43% of the in-patient costs[61]	In acute cases of HF, clinicians require a rapid response following a test[61]

Opportunities

The information provided by a cardiac biomarker: Reduce the risk of re-hospitalisation and its associated cost;[61] allows for discharge planning and NP led guideline based therapeutic strategy[68,69]	*The information provided by a cardiac biomarker:* **Allows to predict the LOS of a patient in the hospital, aiding the planning of an efficient care strategy & discharge**[61]	*The information provided by a cardiac biomarker:* **Information on the likelihood of a HF diagnosis are also available as POCT. POCT is a tool for HCPs to make a timely decision that can be critical to the patient**[61]

Figure 2: Heart Failure (HF) Patient Journey

Source: MedTech Europe, The value of diagnostic information in HF[61]

HF: Heart Failure
HCP: Healthcare Provider
POCT: Point of care testing

Policy Recommendation 2

Ensure appropriate value recognition of all intermediate value outcomes in-vitro diagnostics such as cardiac biomarkers provide to the different groups of stakeholders in the healthcare system.

Value of cardiac biomarkers to different stakeholder groups

The use of cardiac biomarkers along the patient care pathway offers many intermediate value outcomes to the various stakeholders as shown in Table 1. These intermediate value outcomes should thus be thoroughly considered when assessing the full value cardiac biomarkers provide to the healthcare system and to the patients.

Table 1: Value of using cardiac biomarkers to different stakeholder groups

Healthcare professionals

VALUE OUTCOMES

- More accurate, rapid patient diagnosis
- Faster treatment initiation
- Better disease management for improved patient outcomes

EXAMPLES

- A meta-analysis suggest a 20-30% mortality reduction with biomarker-guided HF care over standard HF care[23]
- Receiving evidence-based therapies that can both reduce hospitalisation and enhance prognosis need a prompt diagnosis.[62,63] NP as part of a testing algorithm can diagnose the right patient for further care.[64]

Insurers / Payers

VALUE OUTCOMES

- Faster, accurate diagnosis and treatment, early discharge, and reduction in readmissions result in cost savings for the payer by avoiding high-cost interventions in later stages of disease progression.

EXAMPLES

NP testing strategy:

- In acute dyspnea management (one of HF symptom) led to a 25% cost reduction at 180 days through decreased hospitalization, intensive care, length of stay, and readmission rates.[66,70]
- Reduces costs for ED visits, hospitalisations, and outpatient services by 15% in 60 days vs. usual care.[71]

Patients

VALUE OUTCOMES

- Shorter length of hospital stays, requirement for intensive care, earlier discharge and reduced risk of readmission
- Greater patient satisfaction, less anxiety, improved quality of life
- Improve the value of knowing, deciding, and enhancing patient empowerment

EXAMPLES

Studies have shown that NP guided guideline based therapeutic strategy in the first 6 weeks following a HF hospitalisation led to reduced symptoms, better quality of life and reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care.[68,69]

A rapid NP diagnostic strategy resulted in:[66,67]

- lower hospitalization rates (75% vs 85%)
- decreased need for intensive care (15% vs 24%)
- and shorter hospital stays (8 vs 11 days)

Healthcare system / providers

VALUE OUTCOMES

- Improvement in turnaround time, patient triage efficiency and ED throughput
- Reduction in hospitalization, intensive care requirements, re-admission rates
- Reduction in operational costs and disease progression cost

EXAMPLES

- In the emergency department, NP measurements helped accurately triage close to 60% of patients with a final diagnosis of acute heart failure.[22]
- High-sensitivity troponin assays can potentially reduce admissions for around 40% of patients with suspected acute coronary syndrome.[21]
- Elevated NP concentrations in type 2 diabetes patients suspected of HF support further triaging for cardiac investigation.[65]

Policy Recommendation 3

Include the perspectives of multiple stakeholders such as healthcare professionals, laboratory professionals, providers, industry experts, academics, policy advisors, and patients for value assessment processes.

Importance of multi-stakeholder engagement

Value assessment processes should involve the perspectives of multiple stakeholders.[17] Although there are many commonalities among stakeholder goals such as safer, more effective, and affordable care, our research in the following section (Section 4.1) will show that there are also significant differences both across and within stakeholder groups[11]. The stakeholders interviewed had different views for which value criteria should be included in the value assessment framework for IVDs and which criteria they consider to be of higher value than another.

Thus, it is essential for the different groups of stakeholders such as payers, policy makers, industry experts, healthcare professionals, academics (researchers), laboratory professionals, providers and patients themselves to form partnerships to better understand the role and value of in-vitro diagnostics in healthcare.

Policy Recommendation 4

Include broader value outcomes outside the traditional clinical performance and safety metrics, such as indirect costs, spillover costs and non-health outcomes when assessing the value of a diagnostic test.

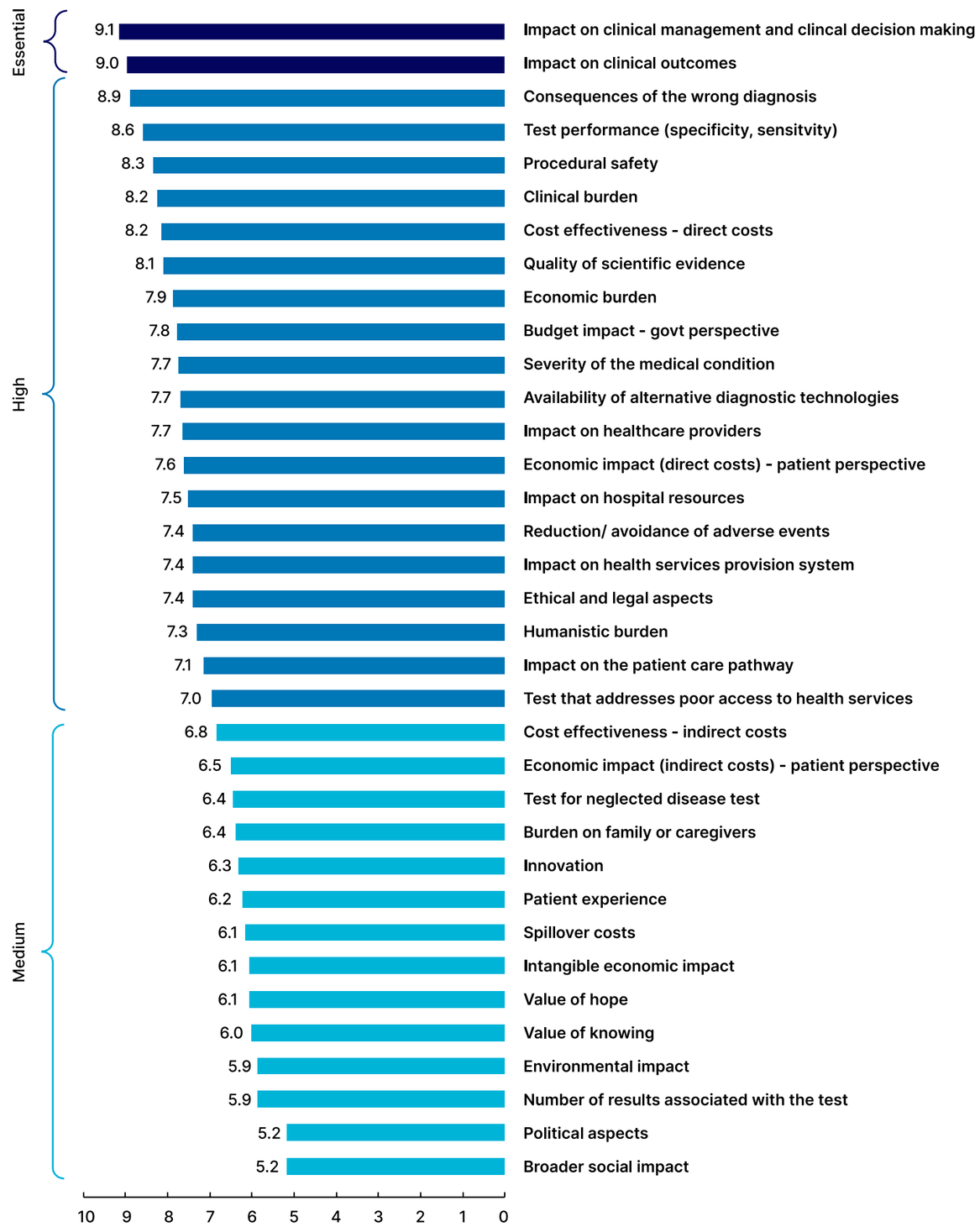
Proposed criteria for an IVD value assessment framework

We conducted an analysis of 35 different criteria, which were tested on various stakeholders including physicians, industry experts, policy advisors, academics, and patients. The results, shown in Figure 3, provide the average rating from the 19 respondents who participated in the primary interview (refer to Appendix A).

The impact of the diagnostic on clinical management and clinical decision making, as well as its impact on clinical outcomes, received high ratings with scores of 9.1 and 9.0, respectively. Approximately 54% of the criteria were considered highly important, while 40% were rated as moderately important.

Importantly, none of the criteria received low ratings or were deemed irrelevant. This implies that all groups of stakeholders support the inclusion of a comprehensive set of value criteria in an assessment framework for in-vitro diagnostics.

Figure 3: Value criteria ranking



Economic Evaluations

When deciding resource allocation, policymakers, payers and other decision-makers need to rationally evaluate the return on investment for any new health technology that will be adopted. They can use different approaches, such as value-based healthcare or cost-effectiveness analysis. Value-based health care focuses on the patient value, maximizing outcomes achieved per dollar spent. Its definition of value is multidimensional and more holistic, taking the patient's perspective. Although overlapping in many aspects to the increasingly prominent value-based healthcare concept, the traditional and established cost-effectiveness analysis takes the societal perspective instead and are often used by Health Technology Assessment (HTA) agencies in their evaluation processes. The economic models include comparative analysis of two or more diagnostic interventions in terms of their cost and consequences.

When resource allocation decision is needed, a cost-effectiveness or cost utility analysis is sometimes used by some HTA agencies but may not always be the best type of economic evaluation used based on their strengths and drawbacks. For example, cost-effectiveness analysis cannot compare interventions across disease areas when using disease specific endpoint.

When measuring costs in an economic evaluation, there are established guidances that can be utilised by health economists. However, when estimating effectiveness, it involves the clinical understanding of the intervention and its impact on patients. Failure of engagement on this issue between clinicians and economists can lead to a fundamentally flawed analysis on the value of a cardiac biomarker.[24]

Earlier in Table 1, we highlighted a wide range of potential intermediate value outcomes (i.e., effectiveness/ benefits) that cardiac biomarkers provide to the healthcare system. These value outcomes can and should be incorporated into economic analyses to assess and capture the full value of in-vitro diagnostics where appropriate. Methodologies traditionally employed for the assessment of drugs and devices (e.g. economic evaluation that employ QALYs) are not necessarily suitable for diagnostics.[25]

Direct and Indirect Costs

Direct costs usually represent the costs associated with medical resource utilization, which include the consumption of in-patient, out-patient, and pharmaceutical services within the health care delivery system.[26] Direct costs also encompass the actual costs of services rendered, including hospitalisation costs, diagnostic tests and procedures, medications, office visits and rehabilitation costs.[27]

There is convincing evidence that diagnostic tests have contributed to 30–50 % reductions in direct hospital and outpatient charges by identifying key alterations in health status and facilitating modifications in therapeutic interventions to improve patient outcomes.[5]

Indirect costs refer to those costs incurred not as a result of medical management of the disease but rather of other incurred losses such as lost wages, lost productivity, and costs resulting from the need for home care and childcare, transportation expenses associated with patient family that would otherwise not be incurred.[28]

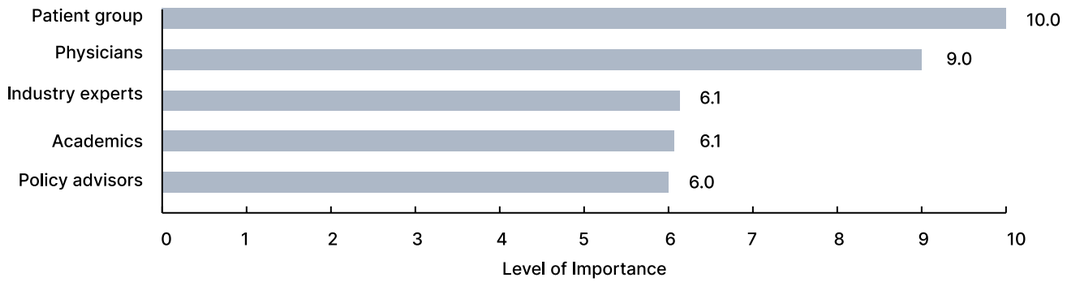
Studies have shown that direct costs account for ~60% and indirect costs account for ~40% of the overall costs of HF globally. However, in APAC, indirect costs (52%, $13 billion) account for an even higher portion of the overall HF spend compared to direct costs (48%, $12 billion).[15] Since indirect costs account for a significant percentage, Value Assessment Frameworks should allow for the presentation of indirect costs as part of the economic evaluations to correctly assess the value of in-vitro diagnostics to the healthcare system.

While indirect costs have historically been excluded in some frameworks because they are sometimes difficult to measure and quantify, our research across multiple stakeholder groups (Figure 4) shows that there is considerable support for the inclusion of indirect costs as part of the economic analysis.

The difficulty or uncertainty around measuring indirect costs should not result in its exclusion from economic evaluations as this would imply denying a significant part of economic reality, since indirect costs of disease do contribute to the scarcity of resources and hence decrease society's wealth.[29]

**Loss of productivity morbidity, premature mortality and welfare impact on others outside of allocated healthcare funds.*

Figure 4: Inclusion of indirect costs, by stakeholder groups



Indirect costs are also monetary costs; however, they are not directly related to treating the disease. They're about money loss due to being ill, especially as they may be too sick to work, and include for the individual - loss of income, employing someone to complete household tasks, travel costs related to treatment, such as taxi visits to the doctor. For the community - loss of productivity in the workplace, social security payments, less taxation revenue, people caring for the ill without being paid.

Spillover Costs

Health care interventions often affect the health and wellbeing of carers or family networks, in addition to the patient. This impact, sometimes described as 'spill over effects' can arise when the intervention substitutes or complements the patients' informal care, reducing the burden on the carer and in turn improving their health-related quality of life (HRQOL).[30]

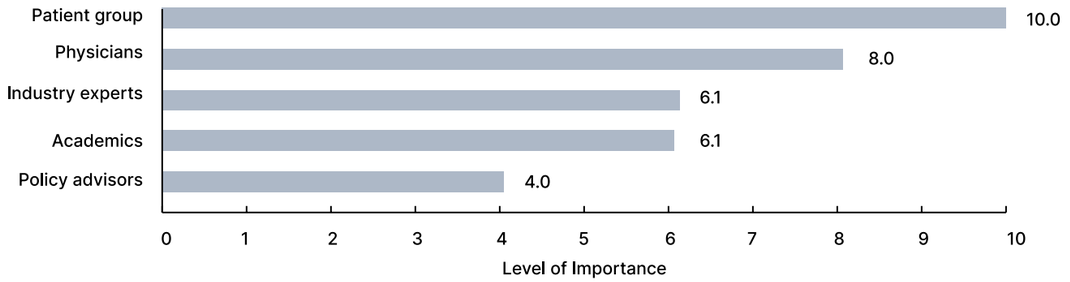
Conversely, the intervention may increase the patients' need for informal care and therefore negatively impact the carer's HRQOL.[30] Failing to account for these spillover effects in VAFs risks over- or under-valuing new technologies, and has consequences for equity and efficiency in the allocation of resources.[30]

Hence, it is unsurprising that NICE 2013 guidance requests, "... all direct health effects, whether for patients or, when relevant, carers" should be included.[31]

Figure 5 shows that all stakeholders still advocate for spill-over costs to be included in the framework even though they acknowledge that there is some level of difficulty in measuring them.

> ***The spillover costs are high and real due to an aging population. A lot of caregivers are very stressed and [there are] not enough resources out there like nursing homes and community care. A lot of Singaporeans are depending on domestic workers. But over time a lot of families are burnt-out. Sometimes just a domestic helper is not enough, [and] you need 2-3 people to take care of one patient.***
>
> *HF Specialist*

Figure 5 Spill over value, by stakeholder groups



Healthcare interventions that affect the well-being of the family and carers. The impact the test has on reducing the burden on the family and carer and in turn improving their health-related quality of life (HRQOL).

Non-Health Value and Value of Knowing

The value of diagnostic information (VODI) extends beyond conventional metrics of cost-effectiveness. It encompasses the "value of knowing" and the enhancements it brings to quality of life.[32] Patients value information from a test regardless of the impact on their treatment strategy. Reasons include a decreased level of ambiguity, reassurance (value of 'rule-out'), particularly to those already identified as 'at risk'.[33]

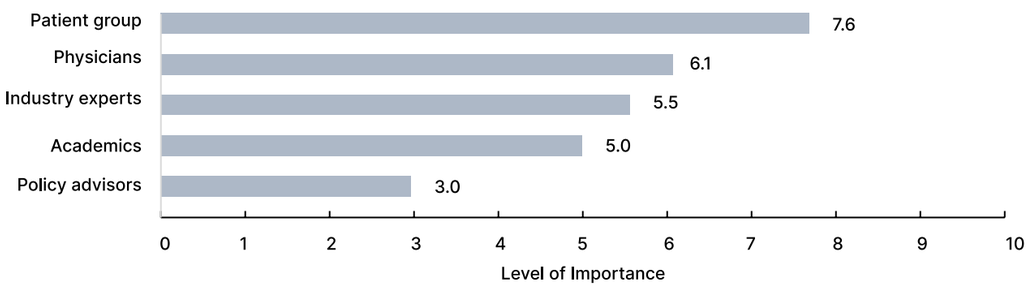
A cardiac biomarker can aid in the correct identification of HF, which can help patients adapt their lifestyle and have a sense of control over their own body or medical condition.[23] In some situations, diagnosing a condition may not change treatment choices or drive improved clinical outcomes but still provide personal or clinical utility gained from the "value of knowing".[17] For these reasons, diagnostics have an impact on patients' utility beyond quality adjusted life years (QALY)-oriented health outcomes, and these effects should be reflected in payers' decisions.[33]

A 2011 willingness to pay study showed that on average, patients would be willing to pay several hundred dollars for a test even in the absence of preventative measures or treatment for the disease.[19,34] When asked what they would do with the test information, respondents pointed to planning; for example, they would "sign advance directives, spend more time with family, get their finances in order, and/or buy long-term care insurance."[19]

Australia's MSAC is the only HTA agency that considers the value of knowing in their assessment framework.[35,36] For example, MSAC recommended funding genetic testing for cardiomyopathies. The main benefit of genetic testing in this case is for the family members of the person with cardiomyopathy. If a family member also has a genetic variant, then they can be monitored, make lifestyle and behavioural changes and, sometimes, start early treatment and management before they show any symptoms. If a family member does not have a genetic variant, they do not need to be monitored or treated. This is also cost-effective for the health system.

While value of knowing is a new concept to most of the stakeholder groups interviewed, there was still a significant portion of interviewees who said that the value of knowing criteria should be included in a value assessment framework (Figure 6).

Figure 6: Value of Knowing, by stakeholder groups



Value of the information provided by the test in special situations which may not lead to any change in management of health outcomes. (e.g., end-of-life diseases, diseases with poor prognosis, diseases that affect offspring - "Cascade testing", avoiding a lengthy diagnostic odyssey) that would allow for future planning (e.g., signing advanced directives, spending time with family)

Value of knowing is a type of value proposition. The primary value proposition of majority of tests lies in their precision, promptness in facilitating clinical interventions, cost-effectiveness, or other factors driving efficiency. I don't think value of knowing test are anywhere as near as common, but I think that's a specific type of value proposition that needs to be considered.

Academic

Policy Recommendation 5

Support the use of various types of evidence such as real-world evidence when assessing the full value of diagnostics.

Quality of evidence

The current gold standard method to evaluate the value of an in-vitro diagnostic consists of a randomized controlled trial (RCT) that assigns patients to either a new test strategy arm or current best practice arm and provides evidence of the net benefits or harm of introducing a new test.[5] But RCTs have important, well-recognized, practical limitations in terms of number of questions that can be examined, sample size, length of follow-up, inclusion of a broadly representative population, generalizability, subgroup analyses and types of outcomes assessed.[37]

Hence, the VAF should allow for the inclusion of several types of evidence which, on their own or in combination, can serve as appropriate evidentiary support, including patient-centred and patient-generated data.[17] The assessment approach should allow a novel product with high expected value to be available for patient care while further evidence is generated, even if there is limited evidence at approval/ launch, preventing any delay in patient access to essential diagnostic technologies. This may require new ways of partnering to accumulate evidence and support adoption of the test or technology with the appropriate patient populations.[17]

Payers, who represent their covered population, can reward investment in diagnostic evidence. For example, variable and greater reimbursement for stronger evidentiary packages or by reimbursement conditional upon inclusion in a registry study or managed entry agreements like coverage with evidence development. These practices that reward evidence generation can encourage payers to accept higher diagnostic prices as a premium to reward value and support a regulated, but flexible market-oriented system to generate the appropriate evidence.[25]

Real world evidence

Real-world evidence (RWE) is defined as evidence generated from the analysis of real-world data. It can cover a large array of evidence types including disease epidemiology, health service research or causal estimation and can be generated from a large range of study designs and analytical methods (including quantitative and qualitative methods) depending on the research question or use case.[38]

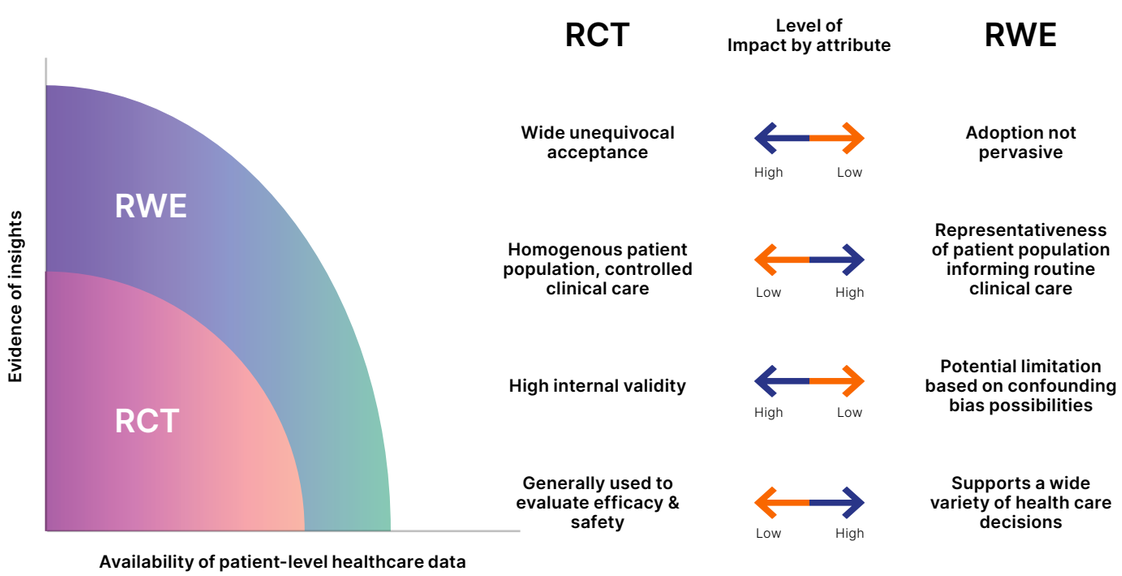
As mentioned earlier, the evidence from RCTs are limited, and so it is likely that there will be a greater dependence on “real world data” as an alternative, i.e., data collected from routine practice.[22]

Real-world evidence are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWE include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.[39] The ADHERE-AP is an example of a heart failure registry in the Asia-pacific region where RWE data can be obtained. It is an electronic web-based observational database of more than 10,000 patients hospitalized with a principal diagnosis of HF from 8 Asia-Pacific countries.[10]

Real-world data can improve our understanding of health and social care delivery, patient health and experiences, and the effects of interventions on patient and system outcomes in routine settings.[38] RWE could be used more routinely to fill evidence gaps and speed up patient access.[38] The use of RWE provides insights with fewer resources, lower costs, and a shorter amount of time than traditional RCTs.[40]

However, there are trade-offs that exist between RWE and evidence from RCTs.
These are described in Figure 7.

Figure 7: Trade-offs between RCTs and RWE studies



6. Conclusion and Way Forward

During the recently held 76th World Health Assembly in May 2023 in Geneva, member countries endorsed a resolution on strengthening diagnostic capacity, which would allow for the precise identification of diseases, and therefore the timely initiation of the correct treatments for better health outcomes.[1]

In the area of CVDs, there is a rising socioeconomic and clinical burden of HF and CAD within the APAC region. Patients are presenting with HF at a much younger age, where CAD has been identified as one of their top 3 co-morbidities. At least 1 in 5 people will develop HF in their lifetime and failing to receive appropriate and timely treatment can result in irreversible damage to their hearts.

Given the relatively younger demographic of heart failure patients in the Asia-Pacific region, the healthcare system bears a substantial burden due to these diseases. Heart failure in the Asia-Pacific region is estimated to incur an annual economic cost of $25 billion. Direct costs make up 48% ($12 billion) of this total, while indirect costs constitute the remaining 52% ($13 billion).[15]

Considering the above, cardiac biomarkers (IVDs) have proven to offer significant advantages to the care pathway of CAD/HF patients and all healthcare system stakeholders. This contribution can effectively alleviate the anticipated burden imposed by these diseases.

To fully tap into its potential, diagnostics require a distinct value assessment framework focused on capturing their complete value. This framework should be separate from drugs and medical devices, incorporate a broader range of value criteria, and be supported by sustainable funding. Furthermore, high-quality diagnostics should be available at all care levels to ensure patient access and enhance the overall quality of care.

The adoption and implementation phase of this comprehensive value assessment framework for in-vitro diagnostics will require a collaborative effort, drawing upon the involvement and dedication of governments, industry players, payers, and various other stakeholders operating within the healthcare system.[2]

Given the numerous benefits in-vitro diagnostics offer to patients, countries should provide sustainable funding and reimbursement for diagnostics to ensure that patients receive the best quality of care. If the adoption and implementation of the framework in each country progresses appropriately, the resolution recently passed by the 76th World Health Assembly regarding the enhancement of diagnostic capability will not only augment the significance of in-vitro diagnostics in healthcare provision but also facilitate global prioritization of patient care and enable them to lead healthier lifestyles.

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8. Appendix A: Proposed criteria for Diagnostic Value Assessment Framework

Our project synthesized the literature on existing diagnostic value assessment frameworks and their recommendations for a broad value assessment framework (VAF) that allows the full value of diagnostics to be captured. This study—carried out between October 2022 and March 2023—had two clearly defined stages, each with different methodological approaches:

i. Targeted systematic review, with the aim to identify current VAFs and their dimensions

ii. Ascertainment of the level of importance of different value criteria via one-on-one primary interviews with expert stakeholders within the APAC region as well as outside of APAC. For APAC region, the interviewees were from Australia, Korea Singapore, and Thailand. Stakeholders were asked to rate each criteria's importance on a scale of 0 to 10. (0 being irrelevant, 1 being the least important and 10 being the most important to be included in the VAF for diagnostics)

For the targeted systematic review, a scoping review of the literature to pick out value assessment frameworks or adaptations of generic value assessment frameworks targeted for the evaluation of diagnostic tests was conducted. Publications that described a value assessment framework (defined as a set of criteria or attributes that aid in defining the full value of diagnostics) targeted to assist in the decision-making process of diagnostic tests were included.

Criteria to be considered in a value assessment framework were identified and extracted from the literature review. An exhaustive set of criteria and sub criteria was first generated. Then, redundant and overlapping criteria were eliminated, resulting in the final list of key criteria.

Criteria	Sub-criteria	Description
Clinical Impact	**Test performance**	The diagnostic capacity of the test (i.e., the test's sensitivity, specificity, precision, and reproducibility) compared to current alternative tests.
	Impact on Clinical Management and decision-making	The ability of a test to inform an appropriate clinical decision, change clinical thinking, management, recommendations, and treatments received.
	Impact on clinical outcomes	The ability of the test to impact patient health outcomes. These patient health outcomes include outcomes resulting from various uses of the test (E.g.: tests used for screening, diagnostic, prognostic, monitoring, discharge planning, outpatient prognostication and patient management, triage, titration, and treatment purposes).
	Availability of alternative diagnostic technologies	The test identifies a health problem where there is currently no diagnostic technology available.
	Quality of Scientific evidence	The strength and reliability of the evidence (E.g.: from clinical studies, clinical trials, meta-analyses, linked evidence) provided in supporting the clinical claim of the test and the potential that different biases or systematic errors do not allow us to draw valid conclusions.
Safety	**Procedural safety**	The impact the test would have with regards to the safety during sample collection for the test (e.g., harms from biopsy or radiation, harms caused by insufficient training, lack of equipment maintenance).
	Consequences of wrong diagnosis	Undesirable consequences to the patient as a result of misdiagnosis from testing (false positives and false negatives).
	Reduction / Avoidance of adverse events	The impact the test would have on the reduction or avoidance of adverse events to improve patient safety and tolerability.
Economic Aspects	**Cost-effectiveness (Direct costs)**	Comparison between relative costs and outcomes (benefits) with the results of two or more alternatives. Direct costs are the monetary costs directly related to prevention, treatment and diagnosis of the disease. They're fees from services such as medical professionals, surgery, hospital stays, diagnostic tests like x-rays, ambulances, and medications.
	Cost-effectiveness (Indirect costs)	Indirect costs are also monetary costs; however, they are not directly related to treating the disease. They are about money loss due to being ill, especially as they may be too sick to work, and include: • For the individual: loss of income, employing someone to complete household tasks, travel costs related to treatment, such as taxi visits to the doctor. • For the community: loss of productivity in the workplace, Centrelink social security payments, less taxation revenue, people caring for the ill without being paid.
	Budget Impact – Govt perspective	A budget impact model (BIM) is used to estimate the likely change in expenditure to a specific budget holder resulting from a decision to reimburse a new healthcare intervention.
	Economic Impact (Direct costs) – Patient perspective	The impact the test would have on the patient's out-of-pocket expenses that result from outpatient and inpatient health services (E.g.: consultation visits, hospitalisation, medication).
	Economic Impact (Indirect costs) – Patient perspective	The impact the test would have on the patient and family's loss of productivity (E.g.: absenteeism, inability to work).
	Intangible economic Impact	Intangible costs are social, emotional, and human costs; they're not related to money. They are about the pain, grief and stress related to being ill or seeing a loved one ill. They involve the loss of quality of life, participation in social events, and self-esteem.
	Spill overs	Healthcare interventions that affect the well-being of the family and carers. The impact the test has on reducing the burden on the family and carer and in turn improving their health-related quality of life (HRQOL).
Organisational Aspects and Feasibility within the clinical pathway	**Impact on health services provision system**	The impact the test would have on the need for modifications of buildings, processes, logistics etc within the organisation providing health services. (E.g.: additional laboratory space required to place machines needed for the test
	Impact on hospital resources	The impact the test would have on the usage of hospital/ healthcare resources and efficiency. (E.g.: patient throughput, medical servicaaes, hospital personnel, readmissions, length of stay, turnaround time, need for repeated clinical GP or special consults, ability of individual to perform self-tests, at home tests).
	Impact on patient care pathway	The impact the test would have on the patient's time to access to the benefits. The impact the test would have in avoiding unnecessary studies and associated practices in the patient care pathway.
	Impact on healthcare providers	The impact the test would have on the decision-making efficiency of healthcare providers, allowing for better patient management.

Criteria	Sub-criteria	Description
Non-clinical Impact	Patient experience	Experience of patients who take the test (comfort, invasiveness, preparation, care) (E.g., cannula for CT scan, wound care from biopsies).
	Value of Knowing	Value of the information provided by the test in special situations which may not lead to any change in management of health outcomes. (e.g., end-of-life diseases, diseases with poor prognosis, diseases that affect offspring - "Cascade testing", avoiding a lengthy diagnostic odyssey) that would allow for future planning (e.g., signing advanced directives, spending time with family).
	Value of Hope	Value of the information provided by the test that would allow patients to take risks or pay for options with greater immediate mortality risk if there is a significant chance of increased long-term survival.
	Burden on family and caregivers	The impact the test would have on lowering the burden on the family or caregivers.
	Number of results associated with the test	Number of results associated with the sample (amount of information provided by the test with the sample obtained) (E.g.: one test run that can generate results on the levels of >2 cardiac biomarkers).
Equity	Test for neglected diseases	Impact of a test used for the diagnosis of neglected diseases (E.g.: Rare diseases with limited research in the field due to lack of funding (diseases that affect the poor).
	Test that addresses poor access to health services	Impact of a test contemplated for situations of poor access to health services. (E.g.: self-test that can be done anywhere like remote or regional areas far from a clinic).
Disease burden	Clinical burden	A test that addresses a HIGH / SIGNIFICANT clinical burden (morbidity and mortality) of a disease to society.
	Economic burden	A test that addresses a HIGH / SIGNIFICANT economic burden of a disease to society.
	Humanistic burden	A test that addresses a HIGH / SIGNIFICANT humanistic burden of a disease to society.
Severity of medical condition		A test that aids in reducing the severity of the patient's health condition.society.
Ethical and legal aspects		A test that considers the relevant social and moral norms and values that derive from the technology in question. (E.g.: Could the health technology have implications for matters of human dignity, stigma, privacy, or moral, religious, or cultural conviction or tradition?
Political aspects		Political importance of this health problem due to government and/or society 's perception. (E.g.: National health priorities such as Diabetes, Cancer, HIV, AIDS, Infant mortality. CVD etc). How important is a test that aids in a priority health problem in a country or health system?
Innovation		The impact the test has on the digitization, disruption, and transformation in health outcomes. Digitisation: Digitization involve setting up digital capabilities that support routine healthcare processes or services (E.g.: CT scans and MRIs). Disruption: Involves newer technologies that could change clinical decision making or inform clinical decision faster. Transformation: Involves transforming healthcare that allows healthcare professionals to deliver value-based care.
Ethical and legal aspects		Impact of the production, use or implementation of the test on the environment. (E.g., technology is associated with an increased or decreased generation of toxic waste).
Broader social Impact		Impact on other sectors beyond health, such as job creation, industrial promotion, technology transfer, and society as a whole.

9. Appendix B: Application of proposed value assessment framework for IVDs undergoing HTA assessment with CEA requirement

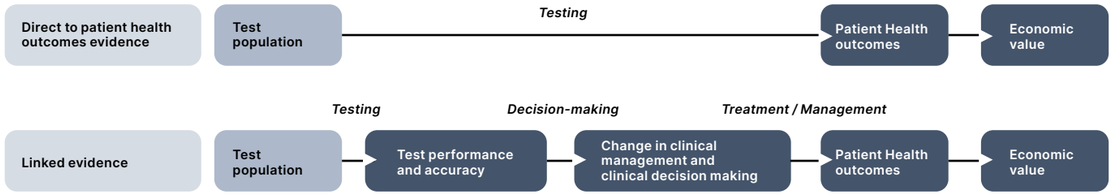
This paper recommends that HTA assessment should be applied wisely and appropriately, considering the investment of time, resources, and evidence-generation that a robust HTA process entails.

However, in a scenario where it is determined that a HTA assessment with cost-effectiveness analysis (CEA) requirement for the given diagnostic technology needs to be undertaken, this paper proposes a linked evidence approach, that can be considered by payers and HTA bodies. The linked evidence approach is an integrative framework, that narratively links evidence addressing key elements of the test-treatment pathway. Evidence of health outcomes can be demonstrated through this linked evidence approach, showing that a test changes clinical thinking, management recommendations and treatments received.[41] As direct trial evidence is often absent, this linkage approach maximizes the available information so that the likely impact of the new test on patient health outcomes can be determined.[42]

Australia developed its own guidance for the assessment of medical tests for reimbursement purposes in 2005, proposing a "linked evidence approach," which has subsequently been recommended in many international guidance documents (Figure B1).

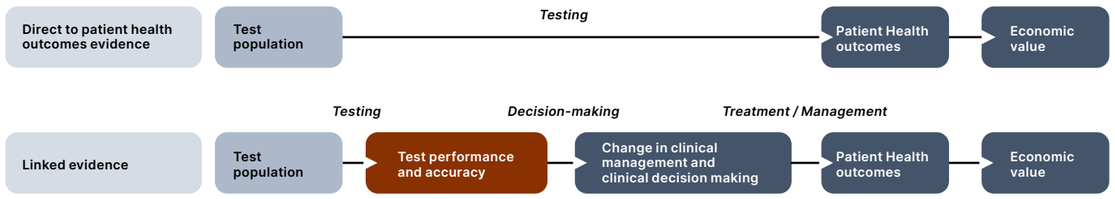
In the subsequent sections, we shall elucidate the manner in which the linked evidence approach can be employed in economic analyses with the objective of estimating a subsequent monetary value of diagnostics.

Figure B1: Direct to health outcomes vs linked evidence approach



> ***I believe that establishing a reliable system for assessing the strength and reliability of linked evidence is a vital task that requires substantial effort. Currently, such a system does not exist, but I emphasize its significance. Developing this system will undoubtedly pose significant challenges, therefore companies undertaking this endeavour will need to be adequately supported.***
>
> ***Academic***

Test performance



The first part of the linked evidence approach addresses the test performance and accuracy.

An important aspect when evaluating the accuracy of cardiac tests is understanding how the proposed test performs in comparison to other tests. Particularly, the reference gold standard test is of interest. The assessment should demonstrate how the proposed test classifies patients as either positive or negative, when compared to the results of another test. This can be achieved through a straightforward approach utilizing a 2-by-2 table, where the positive and negative outcomes for each test are outlined and compared.

The values within Table B1 can help to determine sensitivity, specificity, and predictive values of cardiac diagnostic tests.

Table B1: Diagnostic testing accuracy

	Disease present	Disease absent	
Positive (+) test	**True positive A**	**False positive B**	**Total test positives: A+B**
Negative (-) test	**False negative C**	**True negative D**	**Total test negatives: C+D**
	Total diseased: A+C	**Total normal: B+D**	**Total population: A+B+C+D**

The accuracy of a cardiac diagnostic test is primarily determined by its sensitivity and specificity (Table B2).[43] The positive predictive value determines, out of all the positive findings, how many are true positives. The positive predictive value indicates the proportion of true-positive findings among all positive results. Similarly, the negative predictive value indicates the proportion of true-negative findings among all negative results (Table B2). The positive and negative predictive values are influenced by the prevalence of the disease in the population. If the disease is highly prevalent, the positive predictive value will be higher, indicating that the test is more effective at confirming the presence of the disease. Conversely, the negative predictive value will be lower, suggesting that the test is less effective at ruling out the disease.[43]

Table B2: Test accuracy formulas and definitions

Terminology	Description
Sensitivity = A / (A + C)	The proportion of persons with a disease who are correctly identified by a screening test, that is, a test with a high sensitivity is useful for ruling out a disease if a person test negative.
Specificity = D / (B + D)	The proportion of persons without a disease who are correctly identified by a test. High specificity is important when the treatment or diagnosis is harmful to the patient.
Positive predictive value = A / (A + B)	The proportion of patients with positive test results who are correctly diagnosed.
Negative predictive value = D / (D + C)	The proportion of patients with negative test results who are correctly diagnosed.

The presence or absence of heart failure disease is confirmed with a gold or reference standard which is the highest quality established test for that disease. An illustrative example of 200 subjects given a new test and the presence of disease verified by a gold standard is shown in Table B3.

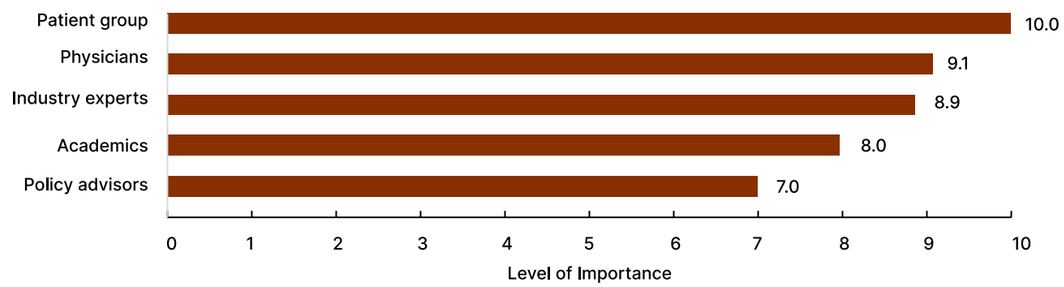
- A cardiac test with high sensitivity is useful to rule out a disease, in that a high sensitivity would indicate that a negative test is likely to not have a disease (a low C)
- A cardiac test with high specificity is useful to confirm a disease, in case there is little chance that a positive result will create a false positive (a low B).

Table B3: Test Accuracy Outcomes

	Disease present	Disease absent	
Positive (+) test	**True positive A - 75**	**False positive B - 15**	**Positive predictive value: 75 / 90 = 83.3%**
Negative (-) test	**False negative C - 25**	**True negative D - 85**	**Negative predictive value: 85 / 110 = 77.3%**
	Sensitivity: 75 / 100 = 75%	**Specificity: 85 / 100 = 85%**	**Total population: 200**

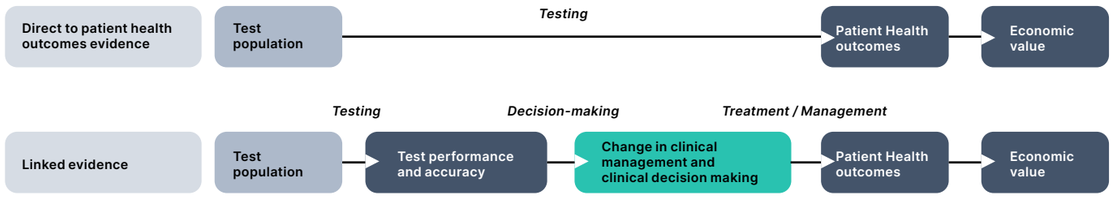
Figure B2 shows that the different groups stakeholders view test performance as a high or essential criterion to be included in the value assessment framework for diagnostics.

Figure B2: Test performance (specificity, sensitivity)



The diagnostic capacity of the test (i.e., the test's sensitivity, specificity, precision, and reproducibility) compared to current alternative tests.

Change in management and clinical decision making

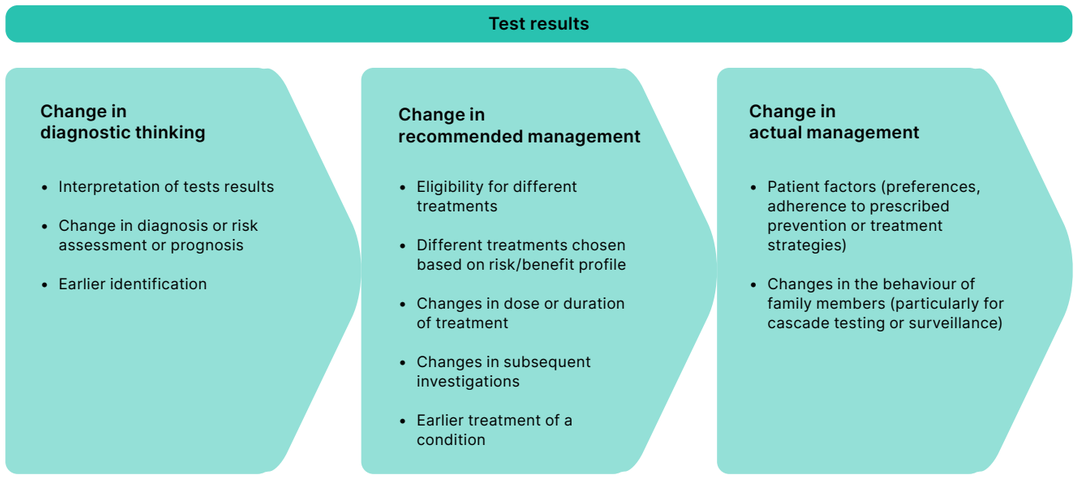


The impact of a test on health outcomes can only be achieved if the interpretation of the test result leads to a change in patient management.[45] For example, a cardiac biomarker may be used to diagnose the condition, measure disease severity, measure response to treatment, monitor patients over time or predict the prognosis.

The variety of uses of cardiac biomarkers means that the method of assessing the indirect impact on patient-relevant health outcomes needs to be flexible. For example, the availability of a new cardiac test may result in the same management decisions for patients, but at an earlier time point. In this circumstance, the comparative management strategies would be early versus late intervention. An early intervention would result in earlier treatment compared with waiting for a clinical diagnosis, resulting in improved patient outcomes.

Change in management involves several sequential steps as shown in Figure B3 below. Evidence may represent how a cardiac test result is interpreted (diagnostic thinking), what recommendations are made, and what is adopted by patients (i.e., the actual change in management).

Figure B3: Sequential steps involved in change in patient management



Source: MSAC Guidelines[41]

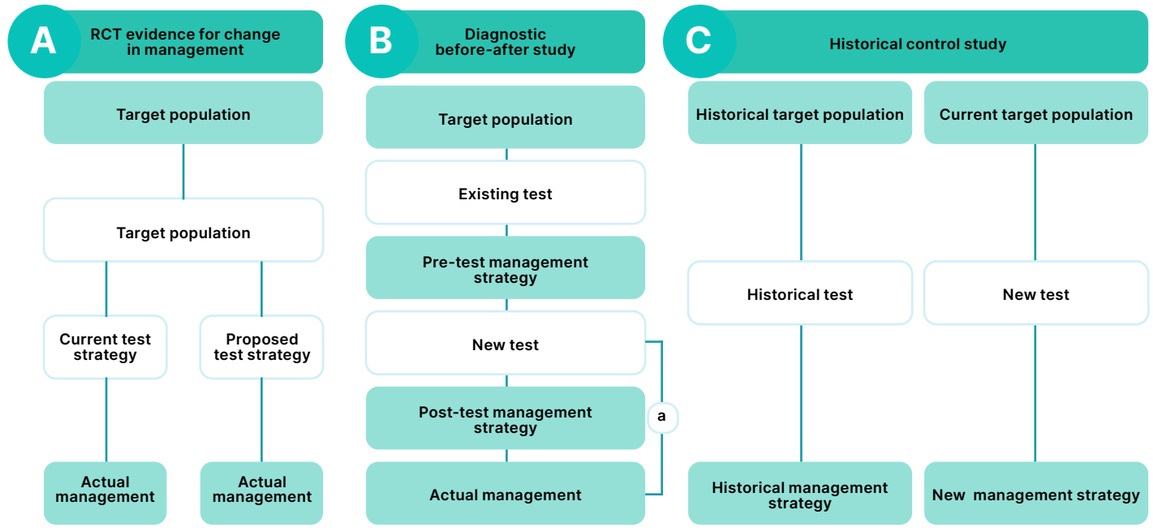
Change in management studies may be either experimental or observational (Figure B4).

Randomised trials (A): Contain less risk of bias and are suitable for all test types (e.g., replacement tests, add-on tests, triage tests).

Before and after studies (B): The most common design for change in management studies is the observational 'diagnostic before-after' study. This study design is useful when the test is an add-on to an existing test strategy, that is, the existing test strategy matches the 'before' component, and the proposed test strategy matches the 'after' component with the addition of the new cardiac test.[41]

Historical control studies (C): Another study design that may be informative for change in management outcomes is the historical control study, which reports practice prior to and after the introduction of the new cardiac test.

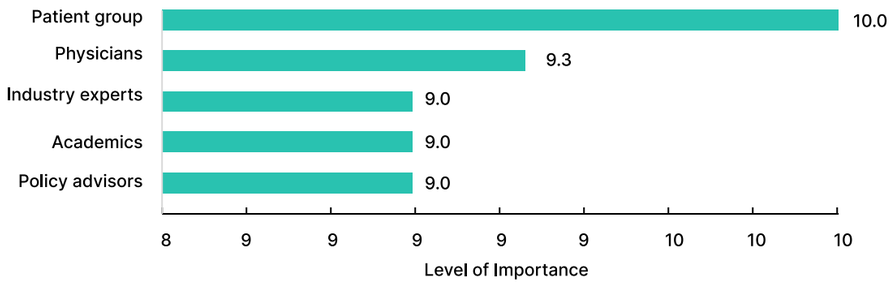
Figure B4: Change in management study designs



Source: MSAC Guidelines[42]

Figure B5 shows that the different groups of stakeholders view the impact on clinical management and decision-making as an essential criterion to be included in the value assessment framework for diagnostics, supporting secondary findings.

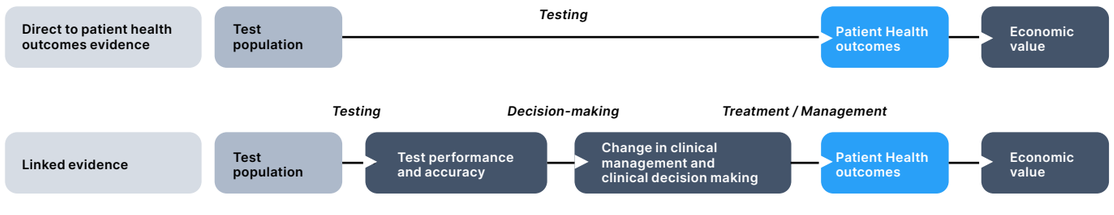
Figure B5: Clinical management and decision making



The ability of a test to inform an appropriate clinical decision, change clinical thinking, management, recommendations, and treatments received.

> ***When you adopt any technology for diagnostic, you want to make sure that it makes a difference in the patient care pathway. However, there are times where it may not affect patient outcomes. The impact of a diagnostic directly on patient outcomes is unlikely to exist without it having an impact on clinical decision-making first.***
>
> ***Policy Advisor***

Patient Outcomes

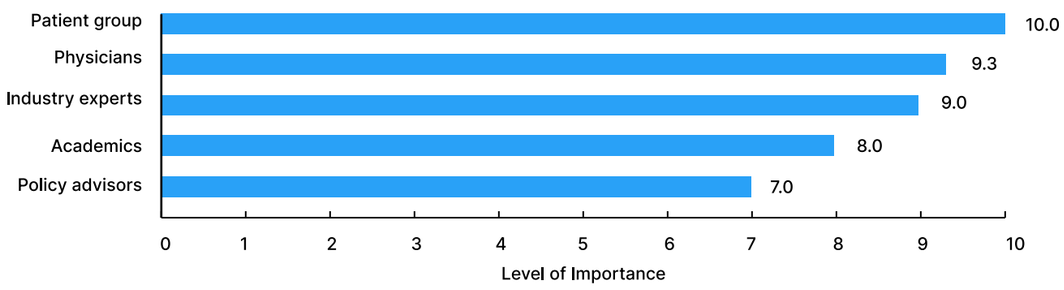


Patient outcome efficacy or clinical effectiveness is the factor that is of the greatest relevance to policy makers for public funding decisions, and to clinicians determining the best use of testing in managing their patients.[45]

Hence, in addition to assessing mortality and morbidity, it is crucial to consider the impact on the patient's functional status, quality of life, and economic outcomes (including direct and indirect medical costs and productivity effects) during the decision-making process. These considerations should encompass not only the patients themselves but also other relevant stakeholders such as family, employers, and society at large.[37]

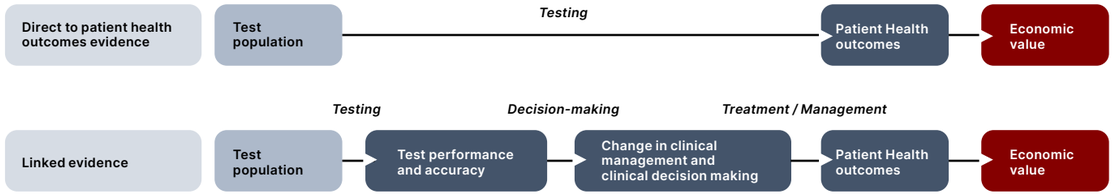
In accordance with the peer-reviewed literature, Figure B6 illustrates the perspective of all stakeholder groups interviewed during our research. They consistently regard the impact on clinical outcomes as a significant or crucial factor to be considered when developing the value assessment framework for diagnostics.

Figure B2: Test performance (specificity, sensitivity)



The ability of the test to impact patient health outcomes. These patient health outcomes include outcomes resulting from various uses of the test (E.g.: tests used for screening, diagnostic, prognostic, monitoring, discharge planning, outpatient prognostication and patient management, triage, titration, and treatment purposes).

Economic analysis



There 5 major types of economic evaluation methods with their strengths and drawbacks are outlined in Table B4 below. Apart from budget impact analysis, each of these analyses involves systematic identification and measurement of the costs and consequences of the interventions.

Table B4: Types of economic models

	Outcomes reported	Strengths	Weaknesses
Cost minimisation	• Direct costs • Potentially indirect costs	Easy to perform	Useful only if safety and effectiveness outcomes are known, or assumed to be equivalent or non-inferior for both interventions
Cost benefit	Costs and monetized benefits	Can be used within healthcare and across sections of the economy	Less commonly accepted by healthcare decision makers
Cost effectiveness	In clinical terms (events, life years gained	• Relevant for clinicians • Easily understandable	Cannot compare interventions across disease areas when using disease specific endpoints
Cost utility	Quality adjusted life years (QALY)	• Incorporates quality of life • Comparable across disease areas	• Requires evaluation of patient preferences • Can be difficult to interpret
Budget impact analysis	• Net costs • Cost savings	Measures affordability	No standard to evaluate the affordability of each intervention individually

One commonly utilized evaluation method by several HTA agencies is the cost-effectiveness analysis. This analysis employs a formula known as the incremental cost-effectiveness ratio (ICER). The ICER calculates the disparity in costs between two interventions and divides it by the discrepancy in health benefits, such as a life saved, avoidance of a heart attack, or gain in quality-adjusted life-year (QALY). Please refer to Figure B7 for a visual representation of this concept.

Figure B7: Formula to calculate the Incremental Cost Effectiveness Ratio (ICER)

$$ICER = \frac{\text{Incremental Cost}}{\text{Incremental Effectiveness}} = \frac{\text{Cost (A) - Cost (B)}}{\text{Benefit (A) - Benefit (B)}}$$

The total ***costs*** associated with a specific medical illness or condition include 3 major components[27]:

1. Direct costs
2. Indirect costs
3. Intangible costs (Quality of Life)

The benefits component encompasses the various potential intermediate value outcomes that cardiac biomarkers offer along the patient care pathway for coronary artery disease (CAD) and heart failure (HF) patients (Table 1). These outcomes can be effectively integrated into cost-effectiveness analyses.

Table B5, Table B6 and Table B7 show three simplified illustrative examples of how a stepwise addition of the costs of a cardiac diagnostic test, and other intermediate direct outcomes can be used to calculate an ICER. The intermediate direct outcomes used in the following ICER calculations include reduced ED visits and turnaround time.

Table B5 includes the costs of the novel and existing cardiac diagnostic test. With the novel cardiac test, we might assume there may be a 1.4% improvement in diagnostic accuracy for myocardial infarction episodes. Based on an estimated value of $200 for the novel cardiac test compared to $10 for the current test, a simplified illustrative example indicates that the incremental costs associated with the identification and potential avoidance of one additional myocardial infarction would amount to $13,571.

Table B5: ICER - cost of cardiac test only

	New test	Current test	Increment	ICER
Costs				
1. Cost of cardiac diagnostic test	$200	$10	$190	
Outcomes				
Correct myocardial infarction diagnosis	1	0.986	0.014	
Incremental costs to identify and potentially avoid 1 myocardial infarction				**$13,571**

Note the costs and outcome values are for illustrative purposes only.

In a second example, assume a cardiac diagnostic test demonstrated a 15% reduction in the costs for ED visits, hospitalisations and outpatient services in 60 days vs usual care.

By factoring in the 15% reduction in the cost of ED visits resulting from the new test at an assumed cost of $300 per day, Table B6 illustrates how the ICER, cost to identify and potentially avoid 1 additional myocardial infarction is reduced to $10,357.

Table B6: ICER - cost of cardiac test + reduction in ED visits

	New test	Current test	Increment	ICER
Costs				
1. Cost of cardiac diagnostic test	$200	$10		
2. Reduction in costs for ED visits	15%	0%		
a. Cost of ED visit (per day)	$300	$300		
b. Total cost due to ED visit	$255	$300		
Total costs	**$455**	**$310**	**$145**	
Outcomes				
Correct myocardial infarction diagnosis	1	0.986	0.014	
Incremental costs to identify and potentially avoid per 1 myocardial infarction				**$10,357**

Note the costs and outcome values are for illustrative purposes only.

In a third example, assume a cardiac diagnostic test reduced the ED turnaround time by 40 minutes, from an average of 6.3 hours to 5.6 hours. By incorporating this time saving into the cost effectiveness calculation, and by assuming an illustrative ED cost per hour of $50 in Table B6, the ICER is further reduced to $7,857.

Table B7: ICER - cost of cardiac test + reduction in visits to ED + reduction in turnaround time

	New test	Current test	Increment	ICER
Costs				
1. Cost of cardiac diagnostic test	$200	$10		
2. Reduction in costs for ED visits	15%	0%		
a. Cost of ED visit (per day)	$300	$300		
b. Total cost due to ED visit	$255	$300		
3. Turnaround time (hours)	5.6	6.3		
a. Cost per hour in ED	$50	$50		
b. Total costs incurred in the ED	$280	$315		
Total costs	**$735**	**$625**	**$110**	
Outcomes				
Correct myocardial infarction diagnosis	1	0.986	0.014	
Incremental costs to identify and potentially avoid per 1 myocardial infarction				**$7,857**

Note the costs and outcome values are for illustrative purposes only.

Calculating a cost per life year gained and cost per QALY

In a final example, let us consider the scenario where individuals at 50 years of age face a lifetime risk of death due to heart attack of 51.7%.[46] Additionally, there is a 1% increased risk of death in the next 12 months due to missed first diagnosis, and the decrement in quality of life resulting from heart failure is 0.10.

Applying these values to the ICER calculation presented in Table B8 using the same ICER formula in Figure B7, we find that the incremental cost per life year gained amounts to $21,277, and the cost per quality-adjusted life year (QALY) gained stands at $23,641

Table B8: Incremental costs per Life Year Gained (LYG) and Quality Adjusted Life Year Gained

	New test	Current test	Increment	ICER
Costs				
1. Cost of cardiac diagnostic test	$200	$10		
2. Reduction in costs for ED visits	15%	0%		
a. Cost of ED visit (per day)	$300	$300		
b. Total cost due to ED visit	$255	$300		
3. Turnaround time (hours)	5.6	6.3		
a. Cost per hour in ED	$50	$50		
b. Total costs incurred in the ED	$280	$315		
Total costs	**$735**	**$625**	**$110**	
Outcomes				
Correct myocardial infarction diagnosis	1	0.986	0.014	
Risk of death	0.517	0.51183	0.00517	
Incremental costs per Life Year Gained (LYG)				**$21,277**
Incremental costs per Quality Adjusted Life Year Gained (QALY)				**$23,641**

Note the costs and outcome values are for illustrative purposes only.

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