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Elecsys® ProBNP Immunoassay for the Diagnosis of Congestive Heart Failure

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This *Horizon scanning report* was prepared by Dr Petra Bywood, Ms Tracy Merlin, Dr Annette Braunack-Mayer, and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Department of Public Health, Mail Drop 511, University of Adelaide, Adelaide, South Australia, 5005.

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Introduction

The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the introduction and use of the Elecsys® proBNP immunoassay (Register ID no 000087).
Roche Diagnostics provide a fully automated immunoassay for the detection and quantitation of NT-proBNP, the N-terminal fragment of brain natriuretic peptide (BNP), in plasma and serum. NT-proBNP is a direct marker of ventricular dysfunction in patients with suspected heart failure. It is offered through public and private pathology laboratories and sometimes as a point-of-care service. It is currently in use in Australia.
This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of Elecsys® proBNP immunoassay, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.
This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the Elecsys® proBNP immunoassay.

Background

Description of the technology

The procedure

Brain (or B-type) natriuretic peptide (BNP) is a cardiac neurohormone released as pre-proBNP, which is cleaved enzymatically to the active hormone, BNP (77-108), and the inactive N-terminal proBNP (NT-proBNP, 1-76) fragment (McCullough & Sandberg 2003). The main stimulus for the constitutive release of pre-proBNP from cardiac myocytes is cardiac wall stretch resulting from fluid overload. Under pathologic conditions, BNP is synthesised rapidly in the ventricles and/or atrium. The function of the natriuretic peptides is to protect the cardiovascular system from the effects of chronic volume overload by inducing vasodilation, sodium excretion, and diuresis, thereby lowering blood volume and blood pressure (Azzazy & Christenson 2003).

BNP and NT-proBNP have been proposed as diagnostic and prognostic biomarkers for heart failure in clinical practice and BNP testing has been described as the most significant advance in the diagnosis of heart failure since the introduction of echocardiography (Maisel 2003).

BNP assays
The first immunoradiometric assays (IRMA) for BNP required large sample volumes of plasma, involved a frequently imprecise extraction step, and took up to three days to complete (Azzazy & Christenson 2003). The development of automated BNP assays, such as the Biosite Triage® BNP assay, solved many of the limitations of these first generation assays.

BNP levels are known to increase with advancing age, renal failure, myocardial infarction, and acute coronary syndrome. In patients presenting with dyspnoea, CHF is usually absent at BNP levels <100 pg/ml, possibly occurs between 100-500 pg/ml, and is probable at levels >500 pg/ml (McCullough & Sandberg 2003). Although elevated BNP levels (>100 pg/ml) may be present in other conditions, such as cor pulmonale, lung cancer and pulmonary embolism, usually it is not elevated to the same extent as in patients with CHF. The consistency of findings in a range of studies suggests that measures of BNP may be accurate enough to distinguish non-cardiogenic from cardiogenic pulmonary oedema to the extent that it may decrease unnecessary invasive procedures, such as use of a hemodynamic catheter (Maisel 2003).

NT-proBNP assays

More recently, measurement of NT-proBNP has been proposed as an ideal cardiac biomarker for the detection of impaired ventricular function as it satisfies several important criteria. It appears to be well-characterised, cardiac specific, easy to measure accurately and precisely (coefficient of variation ≤6.1%), and more stable in circulating blood compared to BNP (Collinson et al 2004; Seino et al 2004; Yeo et al 2003).

The Elecsys® 1010, 2010, and E170 analysers (Roche Diagnostics) are the subject of this Horizon Scanning report. They measure NT-proBNP in serum and plasma, and are small, medium, and high-throughput systems, respectively. The Elecsys® 1010 model, a rapid-response, point-of-care system, is illustrated in Figure 1. This two-site assay uses two polyclonal antibodies, one labelled with biotin and the other with a ruthenium complex, that bind to NT-proBNP to form a sandwich (Lainchbury et al 2003). Streptavidin-coated microparticles are added to form a biotin-streptavidin complex, which enables detection and quantitation of NT-proBNP by chemiluminescence.

Figure 1. The Modular E170, the most current Elecsys® platform
(Printed with permission: Roche Diagnostics)

The assay takes less than 20 minutes to complete and Roche Diagnostics claim total assay precision ranges from 1.8% at 800 pmol/L to 2.7% at 20.7 pmol/L, and a detection limit of 0.6 pmol/L. Cross-reactivity with other natriuretic peptides (BNP, proANP1, CNP2) and the renin-angiotensin system were <0.001%.

The Christchurch Cardio-Endocrine Group makes several recommendations for interpretation of the assay – see Appendix B (Christchurch Cardio-Endocrine Group 2003).

[1] ANP = atrial natriuretic peptide
[2] CNP = C-type natriuretic peptide

Most studies have shown that NT-proBNP concentrations rise with age and some have shown higher levels in women compared to men (Collinson et al 2004; McDonagh et al 2004). McCullough et al suggest that, due to age-dependent changes in NT-proBNP levels, two cutoff points for the detection of CHF are necessary - 125 pg/ml in patients under 75 years of age and 450 pg/ml in those over 75 years (McCullough & Sandberg 2003). NT-proBNP levels between 125-450 pg/ml in the elderly are non-diagnostic and would require more information.

Intended purpose

The Elecsys® proBNP immunoassay is proposed primarily as an aid in diagnosing heart failure. It is used for risk stratification - i.e. for patients who have established symptoms - and to determine which patients require echocardiograms (Hobbs 2002). Those diagnosed with heart failure would still receive an echocardiogram, but the potential cost saving from avoiding unnecessary echocardiograms, electrocardiograms or chest X-rays in borderline cases may be considerable.
Increasing evidence also suggests the natriuretic peptides are an accurate marker for prognosis and, therefore, may be a useful tool for triaging patients. Higher BNP elevation appears to correlate with more severe heart failure and poorer prognosis (Maisel 2003). For example, in patients hospitalised with CHF, failure of NT-proBNP to drop during hospitalisation or at discharge predicted high mortality rates (Hartmann et al 2004).
NT-proBNP may be useful for guiding treatment, screening for left ventricular dysfunction and transplant rejection, predicting patients with acute pulmonary embolism, diagnosing diastolic dysfunction, and aiding in hospital discharge decisions (Peterson 2003).
Future investigations may be undertaken on the use of NT-proBNP for selecting patients in need of more aggressive blood pressure reduction and for monitoring antihypertensive therapy.

Clinical need and burden of disease

Congestive heart failure (CHF), which is a general term that encompasses the broad classification of heart failure, occurs when the heart is unable to pump blood adequately to the rest of the body. Typically the left ventricle fails to pump blood effectively, causing backflow and accumulation of fluid in the lungs or legs (oedema). The heart muscles may fail to contract normally and expel sufficient blood (systolic heart failure) or they may fail to relax and fill normally (diastolic heart failure). Characterised by marked breathlessness (dyspnoea) with activity and while lying flat, the causes of CHF include chronic hypertension, cardiomyopathy, valvular heart disease, or myocardial infarction.

Heart failure as a principal diagnosis accounted for approximately 41,874 hospitalisations and 2,612 deaths in Australia during the period 2001-2002 (AIHW 2004). The number of public hospital separations for patients with congestive heart disease or left ventricular failure was 28,113 and 12,648 respectively in 2001-2002 (AIHW 2004). People over the age of 75 are the key target group as illustrated by the sharp rise in heart failure-related deaths in people aged over 75 years (Figure 2). In addition, prevalence of heart failure increases from 1% in 50-59 year-olds to 50% in people aged 85 years and older, and hospitalisation rates for heart failure are three times higher among people aged 75-84 years than in the 65-75 year group (AIHW 2003; Krum 2001). Based on overseas findings, it is predicted that 300,000 people have chronic heart failure in Australia (about 4% of the population over 45 years of age), and 30,000 new cases are diagnosed each year (Krum 2001).

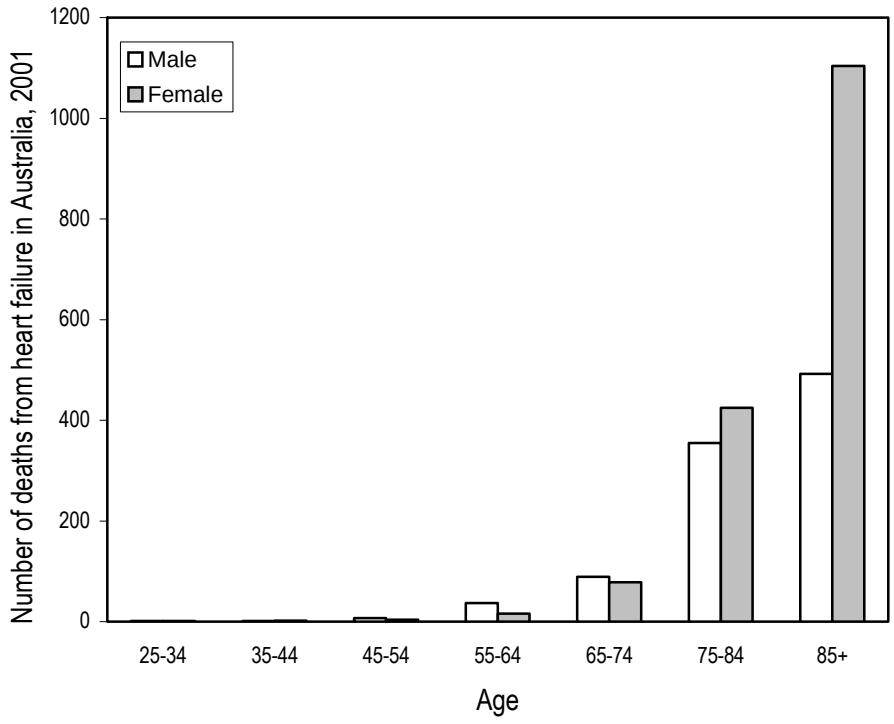

Figure 2. Number of deaths from heart failure in Australia (2001) by age group

In New Zealand, heart failure as a principal diagnosis accounted for approximately 7,074 public hospital separations and 361 deaths during the period 2000-2001[3]. The number of public hospital separations for patients with congestive heart disease or left ventricular failure was 4,892 and 2,026 respectively in 2000-2001 (personal communication Chris Lewis [4]).

The ageing population, improved survival after coronary events, and increasing incidence of diabetes and obesity may underlie the growing incidence and prevalence of CHF (AIHW 2003; Kenchaiah et al 2002). Survival rates for heart failure patients in Australia are unavailable. However, international data from the Framingham longitudinal cohort study suggest that CHF is 'highly lethal' having a 5-year mortality rate of 59% in males and 45% of females with heart failure between 1990 and 1999 (Levy et al 2002).

Initial diagnosis of CHF is often challenging, relying mainly on clinical physical examination and personal history, and rates of misdiagnosis may range from 25-50% (Bayes-Genis et al 2004; Hobbs et al 2002). For example, approximately 20% of dyspnoeic patients labelled with asthma or emphysema are ultimately correctly diagnosed as having CHF (McCullough & Sandberg 2003). Although echocardiography offers an effective semi-objective measure of heart structure and function, it is not always available, particularly in the primary health care setting. Accurate diagnosis is crucial for deciding the correct course of action, since early treatment can improve patient outcomes by preventing or retarding disease progression. In addition, patients would greatly benefit from a diagnostic assay that was non-invasive, available at the point of care, and provided rapid results.

Stage of development

In Australia, natriuretic peptide assays such as the Elecsys® proBNP assay, do not require listing by the Therapeutic Goods Administration of Australia[5], and are widely used in diagnostic laboratories (Personal communication, Roche representative). Although the National Heart Foundation and Cardiac Society of Australia & New Zealand acknowledge that measuring BNP (and NT-proBNP) levels is a highly sensitive and specific method for testing for heart failure, and relate to the severity of heart failure, risk of hospitalisation and survival, their use is not yet standard clinical practice (NHF & CSANZ 2002).

Overseas, the United States Food and Drug Administration granted approval for the Biosite Triage® immunoassay test in 2000 and the Elecsys® proBNP test in 2002 for the diagnosis of congestive heart failure (CHF). Additionally, the Elecsys® proBNP test has been approved for risk stratification in CHF and in acute coronary syndrome (ACS) since 2003 (Roche Diagnostics 2002). The Elecsys® proBNP assay has been available since 2002 in Europe and since 2003 in Japan (Roche Diagnostics 2002). In the United Kingdom, BNP and NT-pro-BNP are recommended as a screening test to 'rule out' heart failure (Department of Health's Heart Team 2003).

[3] Total population in New Zealand was 4,058,921 as at June 16, 2004. Source: Statistics New Zealand.
[4] Chris Lewis, Information Analyst, New Zealand Health Information Service.
[5] Articles, or classes of articles, that are declared not to be medical devices include "diagnostic goods for in vitro use" (Source: Therapeutic Goods Administration, Australia. *Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2004*).

Existing comparators

A patient is diagnosed with CHF when three conditions are satisfied simultaneously. These include a clinical history or signs consistent with heart failure, such as dyspnoea and oedema, normal or near-normal systolic function, and evidence of abnormal diastolic relaxation. Establishing left ventricular diastolic dysfunction is the most definitive condition and is best determined by measuring the ratio of early to late or atrial ventricular filling velocity using echocardiography.

Diagnostic clinical evaluation

The most common method of diagnosing heart failure is by clinical examination which includes the patient's medical history and physical examination, including observation, palpation, and auscultation. The World Health Organization criteria (Table 1) may be used to assess the possible diagnosis of heart failure. The subjective nature of a diagnosis, made on clinical features alone, is a weakness of this method. Clinical evaluation may be used in conjunction with objective tests, including electrocardiograms (ECGs), chest X-rays, and echocardiography when available (NHF & CSANZ 2002). Although ECGs, which may exclude left ventricular systolic dysfunction, and chest X-rays, which may detect the presence of cardiac enlargement and pulmonary congestion, are useful in identifying the cardiac abnormalities, the abnormalities in CHF are often non-specific (NHF & CSANZ 2002; Remme & Swedberg 2001). Laboratory investigations (e.g. blood count, creatinine, urinalysis) are also part of a routine diagnostic evaluation for CHF.

Table 1 Modified World Health Organization criteria for assessment of possible chronic heart failure, 1995 (Krum et al 2001)

Symptoms	Dyspnoea, chronic fatigue, oedema, and exercise intolerance
Signs	Third or fourth heart sounds, heart murmur, cardiomegaly, pulmonary crackles, raised jugular venous pressure, and dependent oedema
Causative factors	Angina, previous myocardial infarction, hypertension, valvular heart disease/rheumatic fever, and cardiomyopathy
Possible CHF is considered if patients have:	• 2 symptoms • > 2 signs • > 1 symptom and > 1 sign, or • > 1 symptom and > 1 causative factor

CHF cannot be diagnosed or excluded reliably on the basis of clinical examination alone. Approximately 25-50% of patients presenting at the emergency department with decompensation symptoms, such as dyspnoea and oedema, are misdiagnosed (Bayes-Genis et al 2004). Although incorrect treatment due to misdiagnosis may alleviate the patient's symptoms, it may obscure an underlying problem that worsens over time. This is particularly relevant in the elderly population who are most at risk of heart failure and in whom multiple diseases are common (Remme & Swedberg 2001).

The "gold standard" objective measurement of ventricular function for all patients with suspected CHF is the transthoracic echocardiogram (de Denus et al 2004). Echocardiography utilises ultrasound to image the heart and surrounding tissues, providing structural and functional information. Left ventricular ejection fraction (LVEF) is the key parameter for distinguishing patients with cardiac systolic dysfunction from those with preserved systolic function (Remme & Swedberg 2001). The transthoracic echocardiogram is a painless, non-invasive procedure that takes between 15 to 30 minutes, and involves the patient lying still on their back on the examination table with their chest exposed. The radiologist or technician applies gel onto the skin to allow the transducer to slide against the skin, emitting ultrasound waves that bounce back, or 'echo' off the structures of the heart (Penn State College of Medicine 2004).

Despite the need for accurate diagnoses many physicians, particularly in primary care, rely on clinical grounds alone since access to echocardiograms is often limited, interpretation requires the services of an experienced cardiologist, and patients with dyspnoea find it difficult to lay down long enough for an echocardiogram (Hobbs 2002).

In a Tasmanian study, only 34% of patients who had a classification of CHF (as identified by the International Classification of Disease coding system) had documentary evidence of an echocardiogram (Boyles et al 2004). In the Australian Cardiac Awareness Survey and Evaluation (CASE) study, it was noted that of the 4,807 patients who met the diagnostic criteria for CHF, only 466 (9.7%) underwent echocardiogram investigation, and of these, 108 showed left ventricular or diastolic dysfunction. Despite this objective evidence, only 77 of the 108 patients with ventricular dysfunction were diagnosed by their general practitioners as having CHF (Krum et al 2001).

Although clinical evaluation and complementary tests may aid in diagnosis, a definitive positive test is frequently elusive. For example, a normal left ventricular ejection fraction, measured by echocardiography, does not rule out cardiac failure due to diastolic dysfunction.

BNP assays

Measurement of serum or plasma BNP is being used increasingly in the clinical setting. In addition to ECG and X-ray examination, the Task Force of the European Society of Cardiology included the BNP assay in the first step of the algorithm for the diagnosis of heart failure (Figure 4) (Remme & Swedberg 2001). The Triage® BNP assay is the most widely used form of the BNP antibody test and is increasingly being used in Australia.

The FDA-approved Biosite Triage® BNP assay is a point-of-care fluorescence immunoassay for quantitative assessment of BNP in whole blood or plasma EDTA6 samples. Dao et al (Dao et al 2001) were the first to use the rapid BNP assay in a clinical setting. Two hundred and fifty patients who presented to the emergency department with dyspnoea (shortness of breath) were assessed and

[6] EDTA = ethylene diamine tetra acetate is a chemical that binds to metal ions to control unwanted reactions with ions during a laboratory process

diagnosed according to standard criteria (medical history, physical examination, blood tests, and X-rays) as having high or low probability of congestive heart failure (CHF). Patients with a confirmed diagnosis of CHF had a significantly higher mean concentration of serum BNP (1076±138 pg/ml) compared to those diagnosed with pulmonary disease (38±4 pg/ml, $p<0.001$).

Similarly, measures of serum BNP (Biosite Triage® BNP assay) were used to differentiate between patients with CHF and those without CHF in a recent large multi-centre study of 1586 patients who presented to the emergency department with acute dyspnoea (Maisel 2003). Results showed that CHF patients had mean BNP levels of 675±450 pg/ml while non-CHF patients had mean BNP levels of 110±225 pg/ml. The diagnostic accuracy of BNP was 83.4% for a cut-off point of 100 pg/ml BNP, and the negative predictive value of BNP was 96% for levels less than 50 pg/ml. It was reported that adding BNP levels to clinical judgement would have improved diagnostic accuracy from 74% to 81% (McCullough et al 2002). The high sensitivity and negative predictive value of BNP testing makes it a reliable test to rule out heart failure with a high degree of certainty. Also, if a higher threshold (BNP value) is used for testing, it is more likely the test will have improved specificity and higher positive predictive value. Subsequently, a clinically-validated algorithm for CHF diagnosis has been introduced into many emergency departments in the USA (Figure 3).

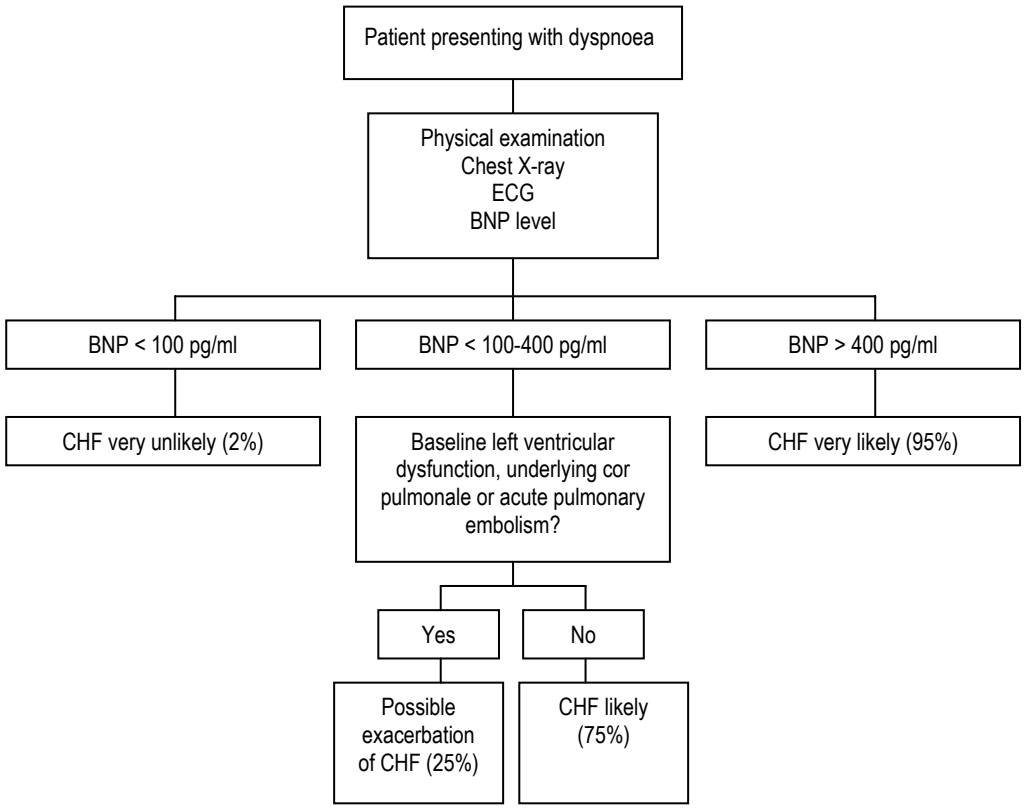

Figure 3. Algorithm for using BNP levels in the emergency department (Maisel 2003)

It has also been suggested that BNP measures may be used as a surrogate for the New York Heart Association (NYHA – see Appendix B) classification for CHF (Peterson 2003).

Recent studies have suggested that NT-proBNP may be more accurate at detecting left ventricular dysfunction than BNP, as NT-proBNP is more stable and has a longer half life than BNP (Pfister et al 2004). Synthetic BNP is also used as a treatment for heart failure, and therefore measuring BNP may not allow the physician to differentiate between elevated BNP due to drug treatment or due to ventricular dysfunction (Roche Diagnostics 2002). Many physicians elect to use the analyser-based Roche Elecsys® proBNP as it fulfils the same role and is less expensive than the point-of-care Triage® BNP test (Peterson 2003). In addition, the Elecsys® proBNP assay has the advantage of being fully automated, which reduces the technologist's time and minimises human error.

Clinical Outcomes

Diagnostic Accuracy

Elecsys® proBNP vs diagnostic clinical evaluation (echocardiography)

Six studies evaluated the diagnostic performance of the NT-proBNP assay (Elecsys®) at detecting CHF. The better quality study (Hobbs et al 2002), which was conducted in consecutive patients from the general population, yielded high sensitivity (100%) and moderate specificity (70%) for the NT-proBNP assay. Using a cut-off level of 304.5 pg/ml NT-proBNP, the high negative predictive value (100%) indicated that a negative test result effectively ruled out heart failure for these patients. The positive predictive value was poor (7%) but this is of less concern as the test is considered as primarily a screening tool, rather than a diagnostic tool. All patients with positive test results would go on to further testing. Diagnostic accuracy was also determined in consecutive patients from three high-risk groups – those with existing heart failure, at risk of heart failure, or prescribed diuretics. As expected, due to the relationship between disease prevalence and positive predictive value, the assay had higher positive predictive values for the higher risk groups. The negative predictive value in these groups was similar to that in the general population and remained high (97-100%).

Three average quality exploratory cohort studies assessed the ability of Elecsys® proBNP to predict CHF in patients at risk of CHF (Bayes-Genis et al 2004; Nielsen et al 2004; Pfister et al 2004). NT-proBNP cut-off values varied widely in these studies but results were largely similar – high negative predictive values and low positive predictive values – excepting the study by Bayes-Genis (2004). In this study, patients were selected on the basis of acute dyspnoea, NYHA classification (see Appendix B), and in an Emergency setting. The higher positive predictive value probably reflects the CHF risk status of these patients (spectrum effect). Measures of NT-proBNP levels also increased the combined power of medical history, symptoms, X-ray and laboratory results (Bayes-Genis et al 2004). This study also showed that changes in NT-proBNP values occur over time and NT-

proBNP may be a valuable marker to monitor the response to therapy during hospitalisation.

Multiple logistic regression analysis, which was adjusted for the higher levels of NT-proBNP in women and the increase in concentration of NT-proBNP with advancing age, showed that NT-proBNP was an independent predictor of CHF in a large sample of patients pooled from three European population-based studies of left ventricular dysfunction (McDonagh et al 2004).

All studies showed significantly higher concentrations of NT-proBNP in patients with confirmed CHF compared to those with dyspnoea of a non-cardiac origin (Bayes-Genis et al 2004; Nielsen et al 2004), with levels of NT-proBNP proportional to the degree of disease severity (Pereira-Barretto et al 2003). Consistently high negative predictive values for both men and women (Nielsen et al 2004), and in more severe classes of CHF (Pfister et al 2004), were evident in all studies. Diagnostic accuracy, measured by ROC curve analysis, ranged between 0.80 and 0.97, depending on the threshold level of NT-proBNP.

Overall, the main value of this test lies in its high negative predictive value, making it a good rule-out test for the exclusion of heart failure. This is likely to reduce the need for echocardiography in approximately 50% of patients (Nielsen et al 2004). Results from Bayes-Genis (2004) also suggest that testing is most likely to be accurate for patients at high risk of CHF, presenting in an Emergency setting.

Table 2. Elecsys® pro-BNP vs diagnostic clinical evaluation

Study	Level and quality of evidence	Study design	Population	Outcomes		
Hobbs et al (2002)	1b	Cross-classification of patients by NT-proBNP and clinical examination (history, ECG, echocardio-graphy) Independent and blinded assessment of results	591 patients randomly selected from 4 target groups 1. general population >45 years 2. patients with existing heart failure 3. patients on diuretics 4. patients at high risk of heart failure		General population [95% CI]	Existing CHF [95% CI]
				NT-proBNP cut-off	304.5 pg/ml	304.5 pg/ml
				Diagnostic accuracy, AUC	0.92 [0.82-1.0]	0.80 [0.72-0.88]
				Sensitivity, %	100 [65-100]	100 [92-100]
				Specificity, %	70 [65-75]	18 [10-29]
				PPV, %	7 [3-14]	39 [28-49]
				NPV, %	100 [99-100]	100 [78-100]
					Diuretics [95% CI]	At risk of CHF [95% CI]
				Diagnostic accuracy, AUC	0.97 [0.76-0.99]	0.84 [0.76-0.93]
				Sensitivity, %	93 [66-100]	100 [72-100]
				Specificity, %	40 [28-52]	44 [35-54]
				PPV, %	23 [13-36]	12 [5-21]
				NPV, %	97 [83-100]	100 [96-100]
Nielsen et al (2004)	2b	Exploratory cohort study	345 consecutive patients referred to clinic with dyspnoea		Men	Women
				NT-proBNP cutoff	93 pg/ml	135.3 pg/ml
				Diagnostic accuracy AUC [95% CI]	0.93 [0.89-0.97]	0.90 [0.84-0.97]
				Sensitivity	96%	94%
				Specificity	67%	69%
				PPV	57%	48%
				NPV	97%	97%
Pfister et al (2004)	2b	Exploratory cohort study	339 consecutive hospital in-patients undergoing diagnostic cardiac catheter-isation	*Elecsys® proBNP (n=339)*		
					Severe systolic	Systolic	Diastolic /systolic
				NT-proBNP cutoff	368.7 pg/ml	152.4 pg/ml	103.5 pg/ml
				Sensitivity	91.7%	90.3%	88.5%
				Specificity	60.8%	37.2%	37.8%
				PPV	15%	28%	63%
				NPV	99%	93%	74%
McDonagh et al (2004)	2b	Exploratory cohort study	3051 patients pooled from 3 population-based studies	NT-proBNP cutoff - females	< 70 years = 88 pg/ml > 70 years = 123 pg/ml		
				NT-proBNP cutoff - males	< 70 years = 49 pg/ml > 70 years = 67 pg/ml		
				Diagnostic accuracy, AUC	0.85		
				Sensitivity	75%		
				Specificity	79%		
				PPV	10%		
				NPV	99%		

Bayes-Genis et al (2004)	2b	Exploratory cohort study	89/100 patients with acute dyspnoea, consecutively recruited in an emergency department - NYHA class III[a]	Diagnostic accuracy, AUC [95% CI]	0.96 [0.92-1.0]	
				NT-proBNP cutoff	253.7 pg/ml	972.6 pg/ml
				Sensitivity	98.6%	91.4%
				Specificity	46.7%	93.3%
				PPV	89.7%	98.5%
				NPV	100%	70.0%
				Accuracy	90.6%	91.8%
				Changes in NT-proBNP levels over time, mean pg/ml±SD		
					Admission	24 hours	7 days
				Ventricular dysfunction	7780±1184	7112±1243	4381±888
				Normal ventricular function	427±127	499±152	245±68
Groenning et al (2004)	3b	Non-consecutive study	372 patients recruited from general practices 70% response rate		LVEF ≤ 40%	LVEF ≤ 50%
				NT-proBNP cutoff	902.4 pg/ml	615.7 pg/ml
				Diagnostic accuracy, AUC	0.94	0.77
				Sensitivity	92%	65%
				Specificity	86%	80%
				PPV	11%	20%
				NPV	100%	97%

[a] NYHA classifications – see Appendix B; AUC = area under the receiver-operator characteristics curve; CHF = chronic heart failure; ECG = electrocardiogram; LVEF = Left ventricular ejection fraction; NPV = negative predictive value; PPV = positive predictive value

Elecsys® pro-BNP vs BNP assays

Six studies evaluated the effectiveness of the Elecsys® pro-BNP assay and alternative BNP assays in detecting cardiac failure. Three studies included patients and disease-free healthy subjects (Mueller et al 2004; Prontera et al 2004; Seino et al 2004), while two other studies examined the assays in patients only (Lainchbury et al 2003; Pfister et al 2004). The sensitivity of the latter studies may be affected by spectrum bias and the specificity is unreliable when the control group is selected to be disease-free. Despite this, similar results were found in all studies. Studies reported significantly higher NT-proBNP and BNP levels in patients compared to healthy controls ($p<0.001$) and the magnitude of elevation of NT-proBNP and BNP was proportional to the degree of cardiac failure according to the clinical classification of NYHA. That is, the higher the NYHA grade, the higher the mean level of plasma natriuretic peptide. Levels of NT-proBNP were consistently correlated with levels of BNP, irrespective of the BNP assay utilised.

The best quality study (Mueller et al 2004) evaluated the diagnostic utility of NT-proBNP (Elecsys®) compared to BNP (Bayer) assays to identify patients with structural heart disease in the presence or absence of symptoms. The key finding from this study was that both assays were equally effective in detecting structural heart disease in patients with symptoms of heart failure, whereas NT-proBNP was significantly more accurate than BNP at detecting the disease in asymptomatic patients ($p=0.009$). The mechanism is thought to relate to a greater proportional rise in NT-proBNP at an earlier stage of the disease. Diagnostic accuracy, as measured

by ROC analysis, indicated that Elecsys® was significantly better than the BNP IRMA assay ($p<0.001$) in discriminating affected patients from healthy subjects, particularly when only patients with mild disease severity were considered (Prontera et al 2004). Similarly, Seino et al (2004) found little difference between NT-proBNP and BNP in the more severe class of heart failure (LVEF <40%), but NT-proBNP proved to be more accurate than BNP for those with less severe heart failure (LVEF <50%, AUC 0.82 vs 0.79).

Lainchbury et al (2003) also compared the commercially available point-of-care NT-proBNP (Elecsys®) and BNP (Biosite Triage®) assays with locally developed and validated radioimmunoassays for NT-proBNP and BNP in patients with dyspnoea (Lainchbury et al 2003). All assays were closely correlated (r values ranged from 0.90 to 0.97) and were significantly predictive of a final diagnosis of CHF ($p<0.005$). However, testing of study populations that comprise symptomatic patients with known or high likelihood of cardiac failure (Lainchbury et al 2003; Pfister et al 2004) is prone to the spectrum effect. The estimated sensitivity and specificity of the diagnostic tests can only be generalised to similar high-risk patient groups.

The clear separation between normal and abnormal values makes NT-proBNP very useful in the clinical setting and results from these studies suggest that NT-proBNP may be a more discerning marker than BNP for asymptomatic patients.

Table 3. Elecsys® proBNP vs BNP assay systems

Study	Level and quality of evidence	Study design	Population	Outcomes		
Mueller et al (2004)	1b	Cross-classification of patients by NT-proBNP and BNP and clinical examination (history, ECG, X-ray, echocardio-graphy) Independent and blinded assessment of results	157 consecutive patients admitted for extensive cardiac evaluation and 23 consecutive patients with symptomatic heart failure	*Prediction of symptomatic structural heart disease* [a]		
					Elecsys® proBNP 211 pg/ml	Bayer BNP 113 pg/ml
				Diagnostic accuracy AUC [95% CI]	0.92 [0.87-0.95]	0.93 [0.88-0.96]
				Sensitivity	93%	81%
				Specificity	82%	96%
				Prediction of asymptomatic structural heart disease [a]		
					Elecsys® proBNP 70.2 pg/ml	Bayer BNP 13.4 pg/ml
				Diagnostic accuracy AUC [95% CI]	0.84 [0.77-0.90]	0.74 [0.65-0.81]
				Sensitivity	80%	75%
				Specificity	77%	64%
Lainchbury et al (2003)	2b	Exploratory cohort study	205 patients presenting to the emergency department with dyspnoea		Elecsys® proBNP 2875 pg/ml	Biosite Triage® BNP 208 pg/ml
				AUC	0.89	0.89
				Sensitivity	80%	94%
				Specificity	87%	70%
				PPV	76%	61%
				NPV	89%	96%
				Overall accuracy[b]	85%	78%
Pfister et al (2004)	2b	Exploratory cohort study	149/339 consecutive hospital in-patients undergoing diagnostic cardiac catheterisation	*Diagnostic accuracy for identifying left ventricular dysfunction (n=149)*		
					Elecsys® pro-BNP AUC [95% CI]	Shionoria BNP, AUC [95% CI]
				Severe systolic[c]	0.87 [0.77-0.96]	0.87 [0.75-1.00]
				Systolic[c]	0.72 [0.62-0.81]	0.72 [0.62-0.82]
				Diastolic/ Systolic[c]	0.74 [0.66-0.82]	0.71 [0.63-0.80]
Prontera et al (2004)	2b	Exploratory cohort study	193 consecutive patients with cardiac myopathy 85 healthy subjects		Elecsys® proBNP 2456 pg/ml	BNP IRMA 117.5 pg/ml
				Normal subjects vs all patients		
				Diagnostic accuracy AUC [95% CI]	0.96 [0.93-0.98]	0.92 [0.89-0.95]
				Sensitivity	92%	81%
				Specificity	93%	94%

				Normal subjects vs patients with mild heart failure (NYHA I & II) [d]		
				Diagnostic accuracy AUC [95% CI]	0.93 [0.89-0.97]	0.87 [0.81-0.91]
				Sensitivity	87%	78%
				Specificity	94%	87%
Fischer, (2001)	3b	Non-consecutive study	100 patients with suspected CHF 50 healthy subjects		Elecsys® proBNP 845.7 pg/ml	Shionoria BNP 346.6 pg/ml	Biosite Triage® BNP 450.6 pg/ml
				Diagnostic accuracy AUC [95% CI]	0.86 [0.77-0.94]	0.88 [0.80-0.95]	0.91 [0.83-0.98]
				Sensitivity	90%	80%	93%
				Specificity	66%	79%	79%
Seino et al (2004)	4	Diagnostic case-control study	105 consecutive patients with chronic heart failure 67 normal healthy controls		Elecsys® proBNP 695 pg/ml	Shionoria BNP 135 pg/ml
				Diagnostic accuracy AUC LVEF<40%	0.75	0.77
				Diagnostic accuracy AUC LVEF<50%	0.82	0.79
				Sensitivity	85%	72%
				Specificity	73%	73%

[a] adjusted for age, sex and renal function; [b] Overall accuracy of the test = the proportion of patients correctly classified as having heart failure or not; [c] Severity classification: Severe systolic = ejection fraction < 40%; Systolic = ejection fraction < 60%; Diastolic/systolic = ejection fraction <60% and left ventricular end-diastolic pressure > 16 mmHG; [d] NYHA classifications – see Box 2; AUC = area under the receiver-operator characteristics curve; CHF = chronic heart failure; ECG = electrocardiogram; LVEF = Left ventricular ejection fraction; IRMA – immunoradiometric assay; NPV = negative predictive value; PPV = positive predictive value

Effectiveness

There was limited information available on whether the use of Elecsys® proBNP assays changed management of the patient by the physician, or impacted on patient health outcomes.

One good quality randomised controlled trial examined the effectiveness of heart failure pharmacotherapy guided by plasma concentrations of NT-proBNP (Troughton et al 2000). Hospitalised heart failure patients were randomised to receive treatment guided by patients' plasma NT-proBNP levels or standard clinical assessment alone. Patients were assessed every three months and at additional visits as required. Treatment targets, which correspond to clinically compensated heart failure, were plasma NT-proBNP <200 pmol/l for the NT-proBNP group and Heart Failure Score <2[7] for the clinical group. If targets were not achieved, drug therapy was intensified according to a predetermined stepwise protocol and reassessed at 2-week intervals until targets were met. As shown in

[7] Standardised Heart Failure Scoring system: decompensated heart failure is indicated by a total score ≥ 2 according to a list of 10 possible symptoms with values between 0.5 and 1.0.

Table 4, fewer cardiovascular events (19), including death, hospital admission, or heart failure, occurred in the patients receiving treatment guided by NT-proBNP levels compared to those receiving treatment according to the standard clinical assessment (54, p=0.02). Changes in all other parameters, including LVEF, quality of life, heart failure scores, and adverse events (e.g. rate of cough or symptomatic hypotension) were similar for both groups.

Table 4. Effectiveness of treatment for CHF guided by NT-proBNP plasma concentrations

Study	Level and quality of evidence	Study design	Population	Outcomes				
Troughton et al (2000)	II	RCT	69 patients admitted to hospital with decompensated heart failure	*Change in NT-proBNP levels, pmol/l* [a]				
				Clinical		NT-proBNP		Relative change
				Before After	% change	Before After	% change	
				251 248	-1.2%	217 138	-36.0%	30.3%
				Change in LVEF over 3 months, %				
				+5.3±1.8		+8.3±2.2		P=0.23
				Cardiovascular-related events, deaths, and hospital admissions				
				54		19		P=0.02

[a] Treatment target NT-proBNP = < 200 pmol/l

Several studies, which were conducted in a variety of settings and populations, investigated the utility of NT-proBNP as a tool for risk stratification and prognosis (Bettencourt 2004; Galvani et al 2004; Hartmann et al 2004; James et al 2003; Jernberg et al 2004; Kirk et al 2004; Richards et al 2003). All studies confirmed that NT-proBNP is a strong independent predictor of mortality and that NT-proBNP testing is helpful for identifying patients at greatest risk who would benefit most from early intervention and/or referral to specialist services.

Safety

None of the studies reported on safety considerations associated with the use of natriuretic peptide assays compared to echocardiography. Since the NT-proBNP assay is more accessible and results are obtained more rapidly than echocardiography, the main safety concern is the proportion of false positives and negatives that occur.

One study, which compared the Elecsys® proBNP and Bayer BNP assays, found more false positives in the NT-proBNP assay compared to the BNP assay (Mueller et al 2004). It is not clear how quickly echocardiography would follow the initial assay and allay the anxiety of patients. More importantly, however, fewer asymptomatic patients were missed by the NT-proBNP test compared to the BNP test.

Three studies reported false positive and/or negative rates for the Elecsys® proBNP assay. Overall false negative rates were low and most of these were for patients with borderline NT-proBNP levels, who were on heart disease medication that lowered NT-proBNP levels, or in patients who had left ventricular function assessments that were close to the lower limit of normal values (Groenning et al

2004; McDonagh et al 2004). Evidence suggests that heart failure patients with lower NT-proBNP have a good prognosis even in the absence of treatment (Troughton et al 2000).

Table 5. False positives and false negatives

Study	Level and quality of evidence	Study design	Population	Outcomes
Mueller et al (2004)	1b	Cross-classification of patients by NT-proBNP and BNP and clinical examination (history, ECG, X-ray, echocardio-graphy) Independent and blinded assessment	157 consecutive patients admitted for extensive cardiac evaluation and 23 consecutive patients with symptomatic heart failure	*Detection of structural heart disease in symptomatic patients* Elecsys®-proBNP / Bayer BNP False positive: 10.6% / 2.8% False negative: 5% / 5% *Detection of structural heart disease in asymptomatic patients* False positive: 11.7% / 9.5% False negative: 8% / 13.1%
McDonagh et al (2004)	2b	Exploratory cohort study	3051 patients pooled from 3 population-based studies	False negative: 10% of dyspnoeic subgroup (n=221)
Bayes-Genis et al (2004)	2b	Exploratory cohort study	89/100 patients with acute dyspnoea, consecutively recruited in an emergency department - NYHA class III[a]	False positive: 19.1% False negative: 1.1%
Groenning et al (2004)	3b	Non-consecutive study	372 patients recruited from general practices 70% response rate	False positive: 13.7% False negative: 0.15%

[a] NYHA classifications – see Box 2; ECG = electrocardiogram

Potential Cost Impact

Cost Analysis

Reports on the extent of economic burden of heart disease in Australia vary substantially. It was estimated in 1993/1994 that the direct costs to the health care system from patients with chronic heart failure was $411 million per annum, including $140 million per annum for hospital costs and $135 million per annum for nursing home costs (Krum 2001). A more recent report estimated that the total cost of hospitalisation for congestive heart failure in Australia in 2000 would have been $840 million, and the total direct costs in excess of $1 billion (Stewart et al 2003). The number of claims processed by the HIC for the Medical Benefit Schedule number 55113 (echocardiograph for the investigation of symptoms or signs of cardiac failure) was 237,106 for the period July 2002- June 2003. The

Medicare Benefits Schedule fee for this procedure is $230. At present there is no rebate available in Australia for the Triage® BNP test, but many organisations (both public and private) are promoting this test, which is provided by fee-for-service (approximately $30/test) (Personal communication, Triage Product Manager).

There is no available evidence of cost-effectiveness of NT-proBNP testing in an Australian setting. In a community-based study in Glasgow, Nielsen et al (2003) determined that screening high-risk patients by BNP testing before echocardiography could have reduced the cost per case detected of left ventricular dysfunction by 26% for the cost ratio of 1:20 (BNP:echocardiogram) (Nielsen et al 2003). Given the prevalence of CHF disease, and therefore the proportion of patients investigated for CHF disease, this cost reduction is not inconsiderable. The Elecsys® proBNP immunoassay 1010 and 2010 are capable of assessing 58 and 86 samples per hour, respectively (Roche Diagnostics 2002). The Elecsys 1010 costs approximately A$50,000.

Ethical Considerations

Informed Consent

Patients offered NT-proBNP testing should be informed of both the potential benefits and the limitations of negative and positive test results. Translating negative and positive predictive values into language meaningful to patients is necessary, yet challenging. In particular, patients may have difficulty in understanding that a positive test result is *not* likely to indicate CHF.

Harms and Benefits

The key diagnostic benefit of the NT-proBNP assay centres on the capacity of this test to rule out CHF, thereby eliminating the need to undergo more expensive and possibly uncomfortable echocardiography. The principal drawback of this test is the consistently low positive predictive values reported in studies of diagnostic accuracy, which indicate that a positive test result correctly identifies only a small proportion of patients who have CHF and, therefore, a large proportion of patients will have false positive results. It is important that guidelines are formulated regarding the diagnostic and treatment pathway, or algorithm, to be used on the finding of a positive test result.

Patients who have a positive result are likely to accrue a number of harms for little gain. In hospital settings, the harms are likely to be limited to increased anxiety while patients wait for the results of subsequent echocardiography. Substantial problems may arise for patients if the NT-proBNP test is made available as a test in the primary health care setting. If a patient tests positive, some general practitioners may not refer the patient for echocardiography, instead treating the patient for CHF when the true cause of their symptoms (and high NT-proBNP levels) lies elsewhere. This may result in significant harm to the patient. That is, inappropriate treatment may delay correct treatment of or exacerbate the undiagnosed condition, or mask symptoms as the condition worsens.

Access Issues

The Elecsys® proBNP immunoassay is currently in widespread use across Australia (Roche representative, personal communication). As NT-proBNP requires renal clearance, the NT-proBNP test is a less reliable marker of CHF in patients with coexisting chronic kidney disease (McCullough & Sandberg 2003). For these patients, the BNP assays may be superior, or patients should be referred directly to echocardiography services. In addition, since the technology entails a blood test, its use will be limited for a small proportion of patients who reject blood testing on religious grounds.

NT-proBNP testing, through the analyser-based or the point-of-care system, may be accessed more easily than the current echocardiography services, which are limited in some settings. However, in light of the potential for harm described above and the lack of information on the impact of NT-proBNP testing in a community setting, its use in the primary care setting and in rural and remote areas should be considered with caution.

Training

The Elecsys® proBNP assay is an automated platform that is compatible with routine laboratory testing, requiring minimal technologist time (<20 minutes for the point-of-care system), and no specific training requirements (Roche representative, personal communication).

Clinical Guidelines

The current recommendations from the National Heart Foundation and the Cardiac Society of Australia and New Zealand (NHF & CSANZ 2002) for diagnostic investigation of CHF in Australia are listed in Table 6.

Table 6. Recommendations for diagnosis of Chronic Heart Failure (NHF & CSANZ 2002)

Recommendation	Level of Evidence
All patients with suspected CHF should be considered for an objective measurement of ventricular function, preferably by transthoracic echocardiogram	EO
Coronary angiography should be considered in CHF patients with a history of exertional angina or suspected ischaemic LV dysfunction	EO
Haemodynamic measurements may be particularly helpful in patients with refractory CHF, recurrent diastolic CHF or in whom the diagnosis of CHF is in doubt	EO
Endomyocardial biopsy may be indicated in cardiomyopathy with recent onset of symptoms, where CAD has been excluded by angiography, or where systolic ventricular dysfunction is suspected	EO
Nuclear cardiological testing, stress echocardiography and Positron Emission Tomography can all be used to assess reversibility of ischaemia and viability of myocardium in CHF patients with myocardial dysfunction and coronary disease.	EO
Thyroid function tests should be considered, especially in older patients who develop atrial fibrillation, and who have pre-existing heart disease.	EO

EO= expert opinion

Although there is no provision for NT-proBNP in the current Australian clinical practice guidelines, they can be adapted readily to incorporate the new technology as shown in the algorithm developed by the Task Force for the diagnosis and treatment of CHF in Europe (Remme & Swedberg 2001) (Figure 4).

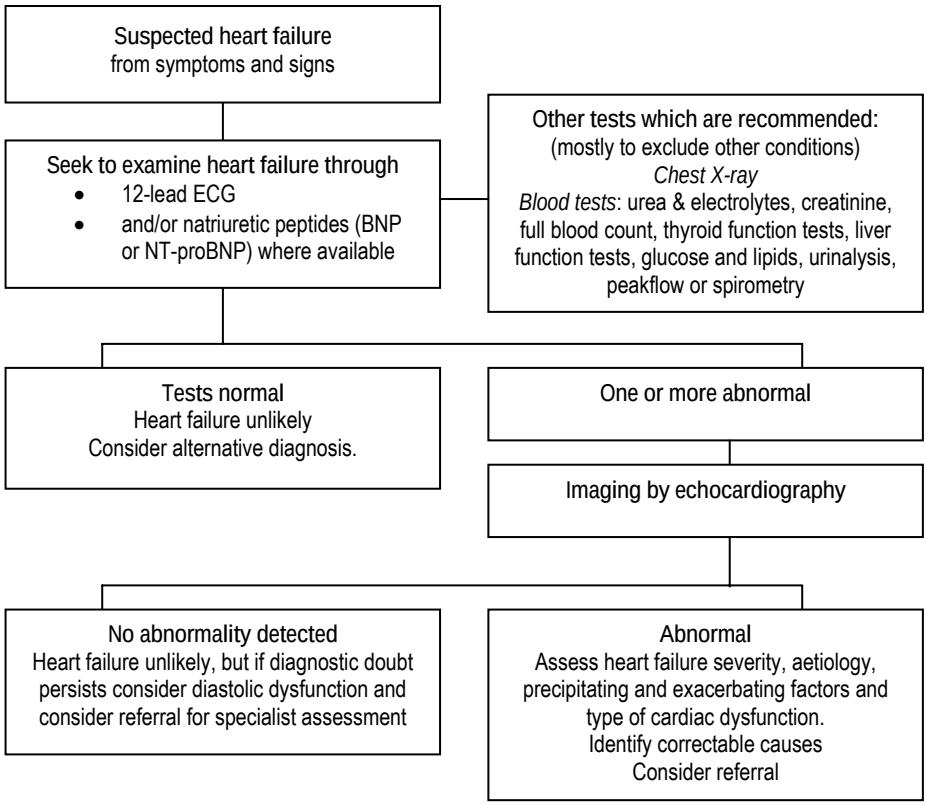

Figure 4. Algorithm summarising recommendations for the diagnosis of heart failure (Remme & Swedberg 2001)

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology. Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the Elecsys® proBNP immunoassay, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy Used for the Report

The medical literature (Table 7) was searched utilising the search terms outlined in Box 1 to identify relevant studies and reviews, until June 2004. In addition, major international health assessment databases were searched.

Table 7. Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK). • Medical Device Alert Safety warnings • Device evaluations • Diagnostic imaging review • Disability equipment assessments	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health. • Manufacturer and User facility Device Experience (MAUDE). MAUDE data represents reports of adverse events involving medical devices. • PreMarket Approvals database	http://www.fda.gov/cdrh/databases.html

Box 1. Search terms utilised

Search terms
MeSH
Congestive heart failure
Text words
Elecsys*, pro-BNP, NT-proBNP, BNP, natriuretic peptide, heart failure, ventricular dysfunction
Limits
Human, English

Availability and Level of Evidence

Twelve studies for assessment of diagnostic accuracy were included in this report. All were classified according to the levels of evidence for assessing diagnostic accuracy (Table 8) (Phillips et al 2001). Two level 1b, six level 2b, two level 3b, and one level 4 studies were included for assessment. Four of these studies (1 level 1b, 2 level 2b, and 1 level 3b) also provided data on safety considerations.

One level II study was assessed for effectiveness according to the designated levels of evidence described in Table 9 (NHMRC 1999).

Table 8. Levels of evidence for assessing diagnosis[a]

Level of evidence	Study design
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Validating** cohort study with good† reference standards; or CDR tested within one clinical centre
1c	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of Level ≥2 diagnostic studies
2b	Exploratory** cohort study with good† reference standards; CDR after derivation, or validated only on split-sample§ or databases
2c	n/a
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

[a] (Phillips et al 2001). SR = systematic review; CDR = clinical decision rule - these are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category; RCT = randomised controlled trial; n/a = not applicable. * Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level. ** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. † Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. †† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. § Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 9. Designations of levels of evidence[a]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a] Modified from (NHMRC 1999)

Sources of Further Information

No trials or other sources of information have been identified.

Conclusions

Congestive heart failure (CHF), which occurs when the heart fails to fill normally or to expel blood effectively, is characterised by breathlessness and oedema. CHF is a major health problem in Australia, accounting for more than 2,500 deaths and over 40,000 hospitalisations per year. Echocardiography, the 'gold standard' diagnostic technique for CHF, provides detailed information on ventricular function and structure and is a safe, relatively non-invasive method for detecting ventricular dysfunction. However, it is not always available and patients frequently find it uncomfortable to lay flat during the procedure.

The Elecsys® proBNP immunoassay is a fully automated diagnostic assay that detects the protein molecule NT-proBNP in the blood. NT-proBNP is the inactive fragment of the cardiac neurohormone, BNP, which is released in response to cardiac distension. Levels of NT-proBNP in blood and plasma increase proportionally with disease severity and NT-proBNP has been proposed as a diagnostic indicator for heart failure.
Importantly, as symptoms of CHF are also present in other conditions and misdiagnosis is common, the NT-proBNP assay allows clinicians to rapidly differentiate between heart failure and other conditions, such as pulmonary oedema.

Six studies investigated the diagnostic accuracy of the Elecsys® proBNP immunoassay compared to standard clinical assessment, including echocardiography. The most salient finding from these studies was that NT-proBNP testing has high negative predictive value (>92%), making it an excellent rule-out test in suspected cases. Patients suspected of having heart failure can then be selected for further investigation by echocardiography or other tests on the basis of having an elevated plasma concentration of NT-proBNP. If concentrations are normal, it is likely that symptoms (dyspnoea, oedema) are due to other causes. The added value of an objective measure of NT-proBNP is that it identifies those at greatest risk of future serious cardiovascular events, including death. Normal concentrations of NT-proBNP virtually excludes diagnosis of CHF. Cardiologists may prefer echocardiography, which requires high-level interpretative skills, as it provides more detailed information on cardiac structure and function. Typically, however, it is the non-cardiologist in the emergency department or primary care setting who must decide which patients to refer for echocardiography. An accurate and relatively quick rule-out test would decrease unnecessary echocardiography. Based on current findings, the NT-proBNP test could play a role in pre-screening patients for echocardiography.

Six studies, which compared the Elecsys® proBNP assay with BNP assays, showed similar results, with sensitivity and diagnostic accuracy equivalent for both NT-proBNP and BNP assays. However, the NT-proBNP appeared to be more accurate than BNP in detecting CHF in asymptomatic patients, and in those with less severe CHF, suggesting NT-proBNP may be a more discerning diagnostic marker at an earlier stage of the disease.

In contrast to the high negative predictive values reported in all studies, the positive predictive value was poor, except in higher risk groups. This makes the NT-proBNP test less valuable in determining, with certainty, which patients have CHF. Importantly, this has ethical implications concerning possible inappropriate treatment of patients with CHF medication when their high plasma NT-proBNP is due to other causes. Diagnosis of CHF on the basis of a positive NT-proBNP test should always be confirmed by echocardiography.

Evidence of the effectiveness of the Elecsys® proBNP assay was limited to one good quality randomised controlled trial, which showed that patient mortality was significantly reduced when pharmacotherapy was guided by monitoring levels of plasma NT-proBNP, as opposed to Heart Failure score (clinical judgement), during follow-up visits.

In terms of safety, four studies reported the false positive and false negative rates in diagnosing CHF using the NT-proBNP assay. Overall, false negative rates were low and occurred predominantly in patients on medication that lowered NT-proBNP levels, or in those with borderline NT-proBNP levels. However, evidence indicates that patients with lower NT-proBNP have good prognosis, even if their treatment is delayed. There were no reports of physical adverse events as a consequence of NT-proBNP testing.

Currently Elecsys® proBNP is used in hospital settings across Australia. Although the available evidence indicates its usefulness as a rule-out test for CHF, positive results should be interpreted with caution, requiring echocardiographic confirmation of CHF before providing treatment. Furthermore, the lack of good quality studies in a community setting limit speculation on the impact of primary care NT-proBNP testing on patient outcomes.

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Appendix A

Profiles of the studies included for assessment for the safety and effectiveness of Elecsys® NT-proBNP immunoassay in the diagnosis of congestive cardiac failure.

Level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
2b	(Bayes-Genis et al 2004)	Barcelona, Spain	Exploratory cohort study	89 patients with symptoms of acute dyspnoea 52/89 (58.4%) with decompensated heart failure 22/89 (24.7%) had masked heart failure 15/89 (16.9%) had normal ventricular function Age range 40-88 years	NT-proBNP levels- sensitivity, specificity, PPV, NPV, diagnostic accuracy (AUC)	7 days
1b	(Hobbs et al 2002)	Birmingham, United Kingdom	Cross-classification study (subset of ECHOES community cohort study)	591 consecutively screened patients 307 general population 103 with existing diagnoses of HF 87 taking diuretics 133 high risk for HF Mean age 65.8 ± 10.7 years	NT-proBNP, sensitivity, specificity, PPV, NPV, diagnostic accuracy (AUC)	Not stated
2b	(Lainchbury et al 2003)	Christchurch, New Zealand	Exploratory cohort study	205 patients with dyspnoea 70/205 (34%) with HF 135/205 (66%) without HF Median age 70± 14 years	NT-proBNP vs BNP levels-sensitivity, specificity, PPV, NPV, diagnostic accuracy (AUC)	Not stated

2b	(McDonagh et al 2004)	Copenhagen, Denmark North Glasgow, Scotland Augsburg/ Regensburg, Germany	Exploratory cohort study	3051 patients pooled from 3 population-based studies Age range 25-89 years	NT-proBNP levels, sensitivity, specificity, PPV, NPV, diagnostic accuracy (AUC) Safety	Not stated
1b	(Mueller et al 2004)	Linz, Austria	Cross-classification study	180 patients 157 consecutive patients admitted for cardiac evaluation 23 consecutive patients with symptomatic HF 42/180 without HF 39/180 with HF stage A 56/180 with HF stage B 43/180 with HF stage C	NT-proBNP vs BNP levels-sensitivity, specificity, diagnostic accuracy (AUC), LVEF	Not stated
2b	(Pfister et al 2004)	Cologne, Germany	Exploratory cohort study	339 consecutive patients with suspected cardiovascular disease Median age 66 years, range 24-88 years	NT-proBNP vs BNP levels, sensitivity, specificity, PPV, NPV, diagnostic accuracy (AUC)	Not stated
2b	(Prontera et al 2004)	Pisa, Italy	Exploratory cohort study	193 consecutive patients with chronic cardiomyopathy Mean age 64.4 ±12.3 years 85 healthy subjects Mean age 52.3 ± 12.0 years	NT-proBNP, BNP & ANP levels, sensitivity, specificity, diagnostic accuracy (AUC)	Not stated
2b	(Seino et al 2004)	Tokyo, Japan	Exploratory cohort study	67 healthy controls 105 consecutive patients with CHF Mean age 64.4 ±18.7 years	NT-proBNP vs BNP levels, LVEF, sensitivity, specificity, diagnostic accuracy (AUC)	Not stated

II	(Troughton et al 2000)	Christchurch, New Zealand	Randomised controlled trial	69 patients: 33 received N-BNP testing Mean age 68 years 36 received clinical assessment alone Mean age 72 years	Cardiovascular events: death; hospital admissions; heart failure; acute coronary syndrome; cerebrovascular accident/transient ischaemic attack; peripheral vascular event; arrhythmia; syncope N-BNP score LVEF Quality of Life (Minnesota) Functional capacity	≥ 6 months

PPV = positive predictive value, NPV = negative predictive value, AUC = area under the curve, LVEF = left ventricular eject fraction, HF = heart failure, ANP = atrial natriuretic peptide, BNP = brain natriuretic peptide

Appendix B

Box 2. Functional classifications of patients for severity of heart failure

Class	Killip Classification (Canada)	New York Heart Association Classification (USA)
I	No symptoms with normal activities, clear lungs	Normal daily activity does not initiate symptoms
II	Normal activities initiate symptoms, but subside with rest	Normal activities initiate symptoms, but subside with rest
IIA	Crackles (<1/3)	*Slight limitation of physical activity = IIs (modified NYHA, Seino et al, 2004)*
IIB	Crackles (>1/3)	*Moderate limitation of physical activity = IIm (modified NYHA, Seino et al, 2004)*
III	Symptoms on minimal activity or rest/pulmonary oedema	Minimal activity initiates symptoms; patient is usually symptom-free at rest
IV	Cardiogenic shock	Any type of activity initiates symptoms and symptoms persist while at rest

Box 3. Recommendations for interpretation of Elecsys® proBNP immunoassay results

- Normal range in healthy subjects is <40 pmol/l (<338 pg/ml)
- Values greater than 220 pmol/l (1860 pg/ml) strongly suggest heart failure in the newly symptomatic (breathless) patient
- In between these levels, heart failure is still possible, but all clinical information must be taken into account. NT-proBNP may be elevated by renal failure, atrial fibrillation,, valve disease, after myocardial infarction, in the elderly and with severe renal impairment. NT-proBNP may be decreased by hypothyroidism, treatment with diuretics, vasodilators and ACE-inhibitors
- Use of serial measurements to adjust therapy for heart failure (rather than single tests for diagnosis) is experimental. Such repeat measures should generally be no more frequent than 2-3 weeks apart in ambulatory outpatients undergoing changes in treatment.