I. Aetna considers measurement of plasma brain natriuretic peptide (BNP) medically necessary to differentiate dyspnea due to heart failure from pulmonary disease.

II. Aetna considers serial measurements of plasma BNP and/or its inactive metabolite, N-terminal pro-BNP (NT-proBNP), experimental and investigational for all other indications, including any of the following, because the clinical value of their measurements for these indications has not been established.

- As a cardiovascular biomarker in healthy normal subjects; or
- As a prognostic biomarker for the presence of diastolic dysfunction related to anemia in persons with sickle cell disease (NT-proBNP only); or
- As a prognostic biomarker for the risk of incident of type 2 diabetes; or
- As a prognostic marker for individuals with structural congenital heart disease; or
- For detecting early cardiac dysfunction in
individuals with tetralogy of Fallot; or

- For determining prognosis of members after an acute coronary syndrome episode; or
- For determining prognosis of members with chronic heart failure; or
- For diagnosing cardio-embolic stroke; or
- For diagnosing Kawasaki disease; or
- For diagnosing patent ductus arteriosus; or
- For guiding statin decisions for members with heart failure; or
- For guiding the initiation of thrombolytic therapy in members with acute pulmonary embolism; or
- For identifying individuals at risk of developing abnormal brain aging; or
- For identifying stress-induced myocardial ischemia; or
- For managing (diagnostic, prognostic and therapeutic) members with chronic renal failure; or
- For monitoring the effectiveness of therapy for members with congestive heart failure; or
- For prediction of fatal outcome after stroke; or
- For prediction of outcome in congenital diaphragmatic hernia; or
- For prediction of the occurrence of atrial fibrillation after cryptogenic stroke or after thoracic surgery; or
- For pre-operative cardiac risk assessment in non-cardiac surgery (e.g., predicting adverse cardiovascular outcomes following non-cardiac surgery); or
- For routine evaluation of dyspnea, other than where necessary to distinguish heart failure from pulmonary disease; or
- For risk stratification of individuals with aortic stenosis; or
- For screening unrecognized left ventricular dysfunction; or
- For titrating therapy for members with chronic
heart failure.

See also CPB 0709 - Nesiritide (Natrecor) (.../700_799/0709.html).

Background
This policy is based in part upon American College of Cardiology/American Heart Association (ACC/AHA)'s 2005 Guideline Update on the Management of Chronic Heart Failure in the Adult (Hunt et al, 2005).

Plasma brain natriuretic peptide (BNP) is a 32-amino acid polypeptide that contains a 17-amino acid ring structure common to all natriuretic peptides. The cardiac ventricles are the major source of plasma BNP. This circulating peptide has been used as a marker to assist in the diagnosis of congestive heart failure. In general, plasma BNP levels correlate positively with the degree of left ventricular dysfunction, but they are sensitive to other biological factors such as age, sex, and diastolic dysfunction. Plasma BNP levels greater than 100 pg/ml are reported to support a diagnosis of abnormal or symptomatic heart failure.

The ACC/AHA practice guidelines on heart failure (Hunt et al, 2005) stated the following conclusions about the clinical utility of BNP: “Measurement of B-type natriuretic peptide (BNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. (Level of Evidence: A).”

The guidelines stated, however, that “[t]he value of serial measurements of BNP to guide therapy for patients with HF is not well established. (Level of Evidence: C).”

The guidelines explained that serum BNP levels have been shown to parallel the clinical severity of heart failure in broad populations (Hunt et al, 2005). Levels are higher in hospitalized patients and tend to decrease during aggressive therapy for decompensation. The guidelines stated, however, that it can
not be assumed that BNP levels can be used effectively as targets for adjustment of therapy in individual patients. The guidelines explained that many patients taking optimal doses of medications continue to show markedly elevated levels of BNP, and some patients demonstrated BNP levels within the normal range despite advanced heart failure (HF). The guidelines concluded that the use of BNP measurements to guide the titration of drug doses has not been shown to improve outcomes more effectively than achievement of the target doses drugs shown in clinical trials to prolong life. The guidelines noted that ongoing trials will help to determine the role of serial BNP measurements in both diagnosis and management of heart failure.

Regarding the use of BNP to assess prognosis, the guidelines stated that elevated BNP levels predict higher risk of heart failure and other events after myocardial infarction, whereas marked elevation in BNP levels during hospitalization for heart failure may predict re-hospitalization and death (Hunt et al, 2005). The guidelines concluded, however, that “the BNP measurement has not been clearly shown to supplement careful clinical assessment.”

Thus, measurement of plasma BNP may be medically necessary to differentiate dyspnea due to heart failure from pulmonary disease in the urgent care setting. The value of measurements of BNP for the routine (non-urgent) diagnosis or for the management of patients with heart failure has not been established.

A 2005 technology assessment of BNP for the diagnosis and management of congestive heart failure by the Institute for Clinical Systems Improvement stated that “BNP testing is useful as an adjunct to other clinical tools for differentiating cardiac (congestive heart failure [CHF]) causes from other causes of dyspnea presenting in the emergency department or urgent care setting.” The ICSI technology assessment stated that, in particular, the diagnosis of CHF is highly unlikely in patients with normal BNP levels. The ICSI technology assessment states that
care should be taken when measuring BNP within 2 to 4 hours after the onset of acute symptoms as false negatives may occur. The ICSI technology assessment concluded that there are no data to support the use of BNP in the general screening of asymptomatic populations for CHF, and thus BNP testing should not be used for this purpose. The ICSI technology assessment also concluded that the utility of BNP as a tool to optimize management of heart failure or measure treatment response has yet to be defined. “Serial testing of BNP levels has not been shown to have clinical utility” (ICSI, 2005).

In a review on the use of BNP as a potential marker of acute coronary syndromes, Body and Roberts (2006) stated that the clinical bottom line is that BNP shows promise as an early cardiac marker and may enhance prognostic stratification. Negative-predictive value and positive-predictive value may be unacceptably low to enable use as a sole cardiac marker. Incorporation into a multi-marker strategy and serial estimations may be necessary.

Sohne and associates (2006) determined the predictive value of elevated BNP levels for early recurrent venous thromboembolism with or without fatal outcome in hemodynamically stable patients with acute pulmonary embolism (PE). In addition, these researchers evaluated the potential clinical consequences of initiating thrombolytic therapy based on the BNP levels alone. A nested case-control study was performed within the framework of a large randomized-controlled trial totaling 2,213 hemodynamically stable patients with confirmed acute, symptomatic PE. A total of 90 patients experienced a fatal or non-fatal recurrent venous thromboembolism during the first 3 months of follow-up (cases); 297 patients with uneventful follow-up served as controls. Blood for BNP levels was obtained at referral and assayed in a central laboratory. Cases had significantly higher mean baseline BNP levels ($p = 0.0002$). The odds ratio (OR) for every logarithmic unit increase in BNP concentration was 2.4 (95% confidence interval [CI]: 1.5 to 3.7). A BNP cut-off level of 1.25 pmol/L [the optimal point on the receiver-operating
characteristic curve] was associated with a sensitivity and specificity of 60% and 62%, respectively. In theory, for every patient correctly receiving thrombolytic therapy at this cut-off, 16 patients will receive this therapy unnecessarily. These investigators concluded that BNP level at presentation is significantly associated with early (fatal) recurrent venous thromboembolism in hemodynamically stable patients with acute PE. However, this relationship appears clinically insufficient to guide the initiation of thrombolytic therapy.

The Agency for Healthcare Research and Quality's assessment on testing for BNP and the N-terminal fragment of B-type natriuretic peptide (NT-proBNP) in the diagnosis and prognosis of heart failure (Balion et al, 2006) stated that these natriuretic peptides can be used to rule out heart failure in patients being seen in emergency rooms, specialized clinics, and primary care settings. It also noted that there were few studies that examined B-type natriuretic peptides in populations without known heart failure. All but a single study suggested that measurements of these biomarkers are inaccurate to be an effective screening test for unrecognized left ventricular dysfunction.

Although several studies have addressed the use of biomarkers -- particularly BNP and NT-proBNP -- in populations with heart failure (HF), integrating these markers into clinical care has been controversial. The National Academy of Clinical Biochemistry (NACB) convened a committee to develop practice guidelines for the use of biomarkers for screening, diagnosis, prognostication, and treatment of HF (Tang et al, 2007). Some of the key points of this practice guideline are as follows:

- Although natriuretic peptide levels, including longitudinal measurements, may be useful for additional risk stratification in some patients, routine use solely for HF risk stratification is discouraged (Class III recommendation).
- Natriuretic peptide levels may be influenced by several patient factors, including age, sex, renal function, thyroid function, anemia, and body habitus. Importantly, obese
persons tend to have lower natriuretic peptide levels than do non-obese persons.
- Natriuretic peptide levels should not replace standard clinical assessment tools, such as echocardiography (Class III recommendation).
- Normal BNP and NT-proBNP ranges vary according to the assay used and the characteristics of the control population. The assay commonly used for research produces systematically lower measurements than do commercial assays.
- The committee made only one Class I recommendation for the clinical use of natriuretic peptides: to exclude or confirm the diagnosis of HF in patients with ambiguous signs and symptoms in the acute setting. Such an application in the non-acute setting received a Class IIa recommendation for lack of studies.
- The routine use of natriuretic peptides in the initial evaluation of patients with suspected HF, for guiding therapy in patients with established HF, and for screening purposes is also discouraged (Class III recommendations).

Thus, available data support relatively few strong recommendations for the clinical use of natriuretic peptide measurements in patients with HF, other than adjunctive use for diagnosis in the acute care setting. Until more evidence is available on how these cardiac biomarkers should be integrated into clinical care, their routine use in the diagnosis, treatment, and screening of HF is not warranted.

Rottlaender et al (2008) stated that several factors (e.g., age, sex, obesity as well as chronic renal failure) have to be considered in the interpretation of natriuretic peptides, which may support diagnostics of HF in patients with unexplained dyspnea. However, cardiac biomarkers should not be used to replace conventional clinical evaluation. The use of natriuretic peptides for screening asymptomatic populations is inappropriate. A BNP-guided titration of HF medication is not yet warranted. Brain natriuretic peptide testing may be used only in selected situations for risk stratification since the
prognostic value is still limited by a lack of clear usefulness in guiding clinical management. The authors concluded that measurements of natriuretic peptides are at present largely an addition in the diagnosis of acute HF, as long as possible errors in interpretation are taken into account.

Mark and colleagues (2007) stated that premature cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal failure. Natriuretic peptides, specifically BNP, are released from the heart in response to chamber distension and thus increased in the presence of volume expansion and cardiac overload. Their physiological role is to cause vasodilatation and promote natriuresis to maintain volume homeostasis. However, the diagnostic role of serum BNP levels in patients with advanced renal dysfunction remains to be defined. This is in agreement with the observation of Rosner (2007) who noted that the diagnostic utility of BNP in end-stage renal disease is limited.

Pfisterer et al (2009) stated that it is unclear if intensified HF therapy guided by N-terminal BNP is superior to symptom-guided therapy. In a randomized, controlled multi-center study, these investigators compared 18-month outcomes of N-terminal BNP-guided versus symptom-guided HF therapy. A total of 499 patients aged 60 years or older with systolic HF (ejection fraction less than or equal to 45 %), New York Heart Association (NYHA) class of II or greater, prior hospitalization for HF within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal were included in this trial. The study had an 18-month follow-up and was conducted at 15 outpatient centers in Switzerland and Germany. Interventions were up-titration of guideline-based treatments to reduce symptoms to NYHA class of II or less (symptom-guided therapy) and BNP level of 2 times or less the upper limit of normal and symptoms to NYHA class of II or less (BNP-guided therapy). Primary outcomes were 18-month survival free of all-cause hospitalizations and quality of life as assessed by structured validated questionnaires. Heart failure therapy guided by N-terminal BNP and symptom-guided therapy resulted in
similar rates of survival free of all-cause hospitalizations (41 % versus 40 %, respectively; hazard ratio [HR], 0.91 [95 % CI: 0.72 to 1.14]; p = 0.39). Patients' quality-of-life metrics improved over 18 months of follow-up, but these improvements were similar in both the N-terminal BNP-guided and symptom-guided strategies. Compared with the symptom-guided group, survival free of hospitalization for HF, a secondary end point, was higher among those in the N-terminal BNP-guided group (72 % versus 62 %, respectively; HR, 0.68 [95 % CI: 0.50 to 0.92]; p = 0.01). Heart failure therapy guided by N-terminal BNP improved outcomes in patients aged 60 to 75 years but not in those aged 75 years or older (p < 0.02 for interaction). The authors concluded that HF therapy guided by N-terminal BNP did not improve overall clinical outcomes or quality of life compared with symptom-guided treatment.

Schneider et al (2009) noted that BNP is used to diagnose HF, but the effects of using the test on all dyspneic patients is uncertain. In a randomized, single-blind trial, these researchers evaluated if BNP testing alters clinical outcomes and health services use of acutely dyspneic patients. Patients were blinded to the intervention, but clinicians and those who assessed trial outcomes were not. A total of 612 consecutive patients who presented with acute severe dyspnea were included in this study (n = 306 for BNP testing; n = 306 for no testing). Primary outcome measures included admission rates, length of stay, and emergency department medications; secondary outcomes were mortality and re-admission rates. There were no between-group differences in hospital admission rates (85.6 % [BNP group] versus 86.6 % [control group]; difference, -1.0 percentage point [95 % CI: -6.5 to 4.5 percentage points]; p = 0.73), length of admission (median of 4.4 days [inter-quartile range, 2 to 9 days] versus 5.0 days [inter-quartile range of 2 to 9 days]; p = 0.94), or management of patients in the emergency department. Test discrimination was good (area under the receiver-operating characteristic curve, 0.87 [CI: 0.83 to 0.91]). Adverse events were not measured. The limitations of this study were that most patients were very short of breath and required hospitalization; the findings might not apply for
evaluating patients with milder degrees of breathlessness. The authors concluded that measurement of BNP in all emergency department patients with severe shortness of breath had no apparent effects on clinical outcomes or use of health services. It does not improve admission or discharge decisions or improve initial treatment planning. The findings do not support routine use of BNP testing in all severely dyspneic patients in the emergency department.

Karthikeyan and colleagues (2009) performed a systematic review and meta-analysis to determine if pre-operative BNP (i.e., BNP or N-terminal pro-B-type natriuretic peptide [NT-proBNP]) is an independent predictor of 30-day adverse cardiovascular outcomes after non-cardiac surgery. These investigators employed 5 search strategies (e.g., searching bibliographic databases), and included all studies that assessed the independent prognostic value of pre-operative BNP measurement as a predictor of cardiovascular complications after non-cardiac surgery. These researchers determined study eligibility and conducted data abstraction independently and in duplicate. They calculated a pooled odds ratio using a random effects model. A total of 9 studies met eligibility criteria, and included a total of 3,281 patients, among whom 314 experienced 1 or more peri-operative cardiovascular complications. The average proportion of patients with elevated BNP was 24.8 % (95 % CI: 20.1 % to 30.4 %; I(2) = 89 %). All studies showed a statistically significant association between an elevated pre-operative BNP level and various cardiovascular outcomes (e.g., a composite of cardiac death and non-fatal myocardial infarction; atrial fibrillation). Data pooled from 7 studies demonstrated an odds ratio (OR) of 19.3 (95 % CI: 8.5 to 43.7; I(2) = 58 %). The pre-operative BNP measurement was an independent predictor of peri-operative cardiovascular events among studies that only considered the outcomes of death, cardiovascular death, or myocardial infarction (OR: 44.2, 95 % CI: 7.6 to 257.0, I(2) = 51.6 %), and those that included other outcomes (OR: 14.7, 95 % CI: 5.7 to 38.2, I(2) = 62.2 %); the p value for interaction was 0.28. The authors concluded that these results suggested that an
elevated pre-operative BNP or NT-proBNP measurement is a powerful, independent predictor of cardiovascular events in the first 30 days after non-cardiac surgery.

In an editorial that accompanied the afore-mentioned paper, Bolliger et al (2009) stated that the study by Karthikeyan et al provided evidence for a high prognostic potential of NPs in patients scheduled for non-cardiac surgery. However, studies to evaluate if specific NP-based treatment modifications will result in improved outcome of surgical patients still need to be performed. Should future studies find outcome relevance of such a concept, NPs will be indeed the magic bullet of pre-operative risk optimization. So far, however, they are interesting and promising tools for risk stratification that requires further evaluation.

Cleland et al (2009) examined if plasma NT-proBNP a marker of cardiac dysfunction and prognosis measured in CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) could be used to identify the severity of HF at which statins become ineffective. In CORONA, patients with HF, reduced left ventricular ejection fraction, and ischemic heart disease were randomly assigned to 10 mg/day rosuvastatin or placebo. The primary composite outcome was cardiovascular death, non-fatal myocardial infarction, or stroke. Of 5,011 patients enrolled, NT-proBNP was measured in 3,664 (73 %). The mid-tertile included values between 103 pmol/L (868 pg/ml) and 277 pmol/L (2,348 pg/ml). Log NT-proBNP was the strongest predictor (per log unit) of every outcome assessed but was strongest for death from worsening HF (HR: 1.99; 95 % CI: 1.71 to 2.30), was weaker for sudden death (HR: 1.69; 95 % CI: 1.52 to 1.88), and was weakest for athero-thrombotic events (HR: 1.24; 95 % CI: 1.10 to 1.40). Patients in the lowest tertile of NT-proBNP had the best prognosis and, if assigned to rosuvastatin rather than placebo, had a greater reduction in the primary end point (HR: 0.65; 95 % CI: 0.47 to 0.88) than patients in the other tertiles (heterogeneity test, p = 0.0192). This reflected fewer athero-thrombotic events and sudden deaths with rosuvastatin. The authors concluded that patients
with HF due to ischemic heart disease who have NT-proBNP values less than 103 pmol/l (868 pg/ml) may benefit from rosuvastatin.

In an editorial that accompanied the study by Cleland et al, Daniels and Barrett Connor (2009) stated that clinical practice guidelines recommend that statins be prescribed to patients with ischemic heart disease, but do not make HF a consideration. If these findings are confirmed in other studies, NP levels may have a new application in guiding statin decisions for HF patients.

In a meta-analysis, Porapakkham and associates (2010) examined the overall effect of BNP-guided drug therapy on cardiovascular outcomes in patients with chronic HF. These researchers identified randomized controlled trials (RCTs) by systematic search of manuscripts, abstracts, and databases. Eligible RCTs were those that enrolled more than 20 patients and involved comparison of BNP-guided drug therapy versus usual clinical care of the patient with chronic HF in an outpatient setting. Eight RCTs with a total of 1,726 patients and with a mean duration of 16 months (range of 3 to 24 months) were included in the meta-analysis. Overall, there was a significantly lower risk of all-cause mortality (relative risk [RR], 0.76; 95 % CI: 0.63 to 0.91; p = 0.003) in the BNP-guided therapy group compared with the control group. In the subgroup of patients younger than 75 years, all-cause mortality was also significantly lower in the BNP-guided group (RR, 0.52; 95 % CI: 0.33 to 0.82; p = 0.005). However, there was no reduction in mortality with BNP-guided therapy in patients 75 years or older (RR, 0.94; 95 % CI: 0.71 to 1.25; p = 0.70). The risk of all-cause hospitalization and survival free of any hospitalization was not significantly different between groups (RR, 0.82; 95 % CI: 0.64 to 1.05; p = 0.12 and RR, 1.07; 95 % CI: 0.85 to 1.34; p = 0.58, respectively). The additional percentage of patients achieving target doses of angiotensin-converting enzyme inhibitors and beta-blockers during the course of these trials averaged 21 % and 22 % in the BNP group and 11.7 % and 12.5 % in the control group, respectively. The authors
concluded that B-type natriuretic peptide-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care, especially in patients younger than 75 years. A component of this survival benefit may be due to increased use of agents proven to decrease mortality in chronic HF. However, there does not seem to be a reduction in all-cause hospitalization or an increase in survival free of hospitalization using this approach.

Eurlings et al (2010) examined if management of HF guided by an individualized NT-proBNP target would lead to improved outcome compared with HF management guided by clinical assessment alone. A total of 345 patients hospitalized for decompensated, symptomatic HF with elevated NT-proBNP levels at admission were included. After discharge, patients were randomized to either clinically-guided outpatient management (n = 171), or management guided by an individually set NT-proBNP (n = 174) defined by the lowest level at discharge or 2 weeks thereafter. The primary end point was defined as number of days alive outside the hospital after index admission. Management of HF guided by this individualized NT-proBNP target increased the use of HF medication (p = 0.006), and 64 % of HF-related events were preceded by an increase in NT-proBNP. Nevertheless, HF management guided by this individualized NT-proBNP target did not significantly improve the primary end point (685 versus 664 days, p = 0.49), nor did it significantly improve any of the secondary end points. In the NT-proBNP-guided group mortality was lower, as 46 patients died (26.5 %) versus 57 (33.3 %) in the clinically-guided group, but this was not statistically significant (p = 0.206). The authors concluded that serial NT-proBNP measurement and targeting to an individual NT-proBNP value did result in advanced detection of HF-related events and importantly influenced HF-therapy, but failed to provide significant clinical improvement in terms of mortality and morbidity.

In an editorial that accompanied the afore-mentioned study by Eurlings et al, Troughton et al (2010) stated that “further data
are needed from more robust, adequately powered trials with hard clinical outcomes and from a meta-analysis utilizing individual patient data (rather than summary grouped data) before guidelines can confidently endorse a biomarker-guided strategy ... Whether the biomarker-guided strategy is applicable to elderly patients and those with heart failure and preserved left ventricular ejection fraction remains unclear and needs further evaluation”. Furthermore, Kim and Januzzi (2011) noted that “although evidence is increasing that NP-guided outpatient management of HF may improve clinical outcomes, more information is needed before adoption of such an approach, which is currently being tested in clinical trials”.

Previous studies reported that plasma NT-proBNP has prognostic value for cardiovascular events in the general population even in the absence of HF. It is unclear if NT-proBNP retains predictive value in healthy normal subjects. McKie and associates (2010) determined the prognostic value of plasma NT-proBNP for death and cardiovascular events among subjects without risk factors for HF, which the authors termed healthy normal. These investigators identified a community-based cohort of 2,042 subjects in Olmsted County, Minnesota. Subjects with symptomatic (stage C/D) HF were excluded. The remaining 1,991 subjects underwent echocardiography and NT-proBNP measurement. These researchers further defined healthy normal (n = 703) and stage A/B HF (n = 1,288) subgroups. Healthy normal was defined as the absence of traditional clinical cardiovascular risk factors and echocardiographic structural cardiac abnormalities. Subjects were followed for death, HF, cerebrovascular accident, and myocardial infarction with median follow-up of 9.1, 8.7, 8.8, and 8.9 years, respectively. NT-proBNP was not predictive of death or cardiovascular events in the healthy normal subgroup. Similar to previous reports, in stage A/B HF, plasma NT-proBNP values greater than age-/sex-specific 80th percentiles were associated with increased risk of death, HF, cerebrovascular accident, and myocardial infarction (p < 0.001 for all) even after adjustment for clinical risk factors and structural cardiac abnormalities. The authors concluded that these findings do
not support the use of NT-proBNP as a cardiovascular biomarker in healthy normal subjects.

Nadir and colleagues (2011) noted that studies in victims of sudden cardiac death and those surviving a cardiac arrest have confirmed that extent of coronary artery disease is similar in those with and without angina, suggesting that it is the presence of myocardial ischemia rather than associated symptoms that determine the prognosis. Experimental models show that hypoxic myocardial tissue results in production of extra BNP, suggesting that BNP could potentially serve as a biomarker of myocardial ischemia. These investigators performed a meta-analysis of the studies that link BNP to inducible myocardial ischemia as indicated by non-invasive stress tests. Values of true-positive, false-positive, true-negative, and false-negative were calculated from the reported sensitivity, specificity, disease prevalence, and total number of patients studied. A total of 16 studies reporting data on 2,784 patients across 14 study populations were included in the final analysis. Mean age of participants was 55 to 69 years and 55 % to 90 % were men. Pooled sensitivity and specificity of BNP for detection of stress-induced myocardial ischemia were 71 % (95 % CI: 68 to 74) and 52 % (95 % CI: 52 to 54), respectively. Pooled diagnostic odds ratio was 3.5 (95 % CI: 2.46 to 5.04) and summary receiver operating characteristic curve revealed an area under the curve of 0.71 +/- 0.02 (mean +/- SE). The authors concluded that this meta-analysis suggests that an increased BNP level can identify inducible ischemia as detected by standard non-invasive stress tests. They stated that this raises the possibility of a whole new role for BNP in the diagnosis and management of myocardial ischemia.

Pfister et al (2011) noted that genetic and epidemiological evidence suggests an inverse association between BNP levels in blood and risk of type 2 diabetes (T2D), but the prospective association of BNP with T2D is uncertain, and it is unclear whether the association is confounded. In a prospective, case-cohort study, these researchers analysed the association
between levels of the NT-proBNP in blood and risk of incident T2D and genotyped the variant rs198389 within the BNP locus in 3 T2D case-control studies. They combined their results with existing data in a meta-analysis of 11 case-control studies. Using a Mendelian randomization approach, these investigators compared the observed association between rs198389 and T2D to that expected from the NT-proBNP level to T2D association and the NT-proBNP difference per C allele of rs198389. In participants of this case-cohort study who were free of T2D and cardiovascular disease at baseline, these researchers observed a 21% (95% CI: 3% to 36%) decreased risk of incident T2D per 1 standard deviation (SD) higher log-transformed NT-proBNP levels in analysis adjusted for age, sex, body mass index, systolic blood pressure, smoking, family history of T2D, history of hypertension, and levels of triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. The association between rs198389 and T2D observed in case-control studies (odds ratio= 0.94 per C allele, 95% CI: 0.91 to 0.97) was similar to that expected (0.96: 0.93 to 0.98) based on the pooled estimate for the log-NT-proBNP level to T2D association derived from a meta-analysis of the authors' study and published data (hazard ratio = 0.82 per SD, 0.74 to 0.90) and the difference in NT-proBNP levels (0.22 SD, 0.15 to 0.29) per C allele of rs198389. No significant associations were observed between the rs198389 genotype and potential confounders. The authors concluded that these findings provided evidence for a potential causal role of the BNP system in the etiology of T2D. They stated that further studies are needed to investigate the mechanisms underlying this association and possibilities for preventive interventions.

In a single-center, retrospective study, Takatsuki et al (2012) examined if NT-proBNP was a biomarker of clinical, laboratory, and echocardiographic abnormalities in children with homozygous sickle cell disease. This study consisted of analysis of data from November 2007 to December 2010. These investigators correlated serum NT-proBNP with clinical and laboratory findings, echocardiographic data, and NYHA functional class. NT-proBNP levels from 42 children (median
age of 9 years; 52 % female) had significant correlations with hemoglobin \( r = -0.63, p < 0.05 \), and echocardiographic measurements including tricuspid regurgitant velocity \( r = 0.46, p < 0.05 \), lateral E' \( r = -0.52, p < 0.05 \), and lateral E/E' ratio (an indicator of left ventricular filling pressures and is used in the assessment of diastolic dysfunction) \( r = 0.60, p < 0.05 \), suggesting diastolic dysfunction. In addition, NT-proBNP levels increased from NYHA functional class I to class III and had a significant linear correlation with the NYHA functional class \( r = 0.69, p < 0.05 \). The authors concluded that NT-proBNP correlated with low hemoglobin and tissue Doppler data as indicators of diastolic dysfunction. Elevated NT-proBNP may be a prognostic biomarker for the presence of diastolic dysfunction related to anemia in children with sickle cell disease. The findings of this small, retrospective study need to be validated by well-designed studies.

Lin and colleagues (2012) noted that novel biomarkers of myocardial ischemia and inflammatory processes have the potential to improve diagnostic accuracy of acute coronary syndrome (ACS) within a shorter time interval after symptom onset. These researchers reviewed the recent literature and evaluated the evidence for use of novel biomarkers in diagnosing ACS in patients presenting with chest pain or symptoms suggestive of cardiac ischemia to the emergency department or chest pain unit. A literature search was performed in MEDLINE, EMBASE, Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED for studies from 2004 to 2010. They used the inclusion criteria: (i) human subjects, (ii) peer-reviewed articles, (iii) enrolled patients with ACS, acute myocardial infarction or undifferentiated signs and symptoms suggestive of ACS, and (iv) English language or translated manuscripts. Two reviewers conducted a hierarchical selection and assessment using a scale developed by the International Liaison Committee on Resuscitation. Out of a total 3,194 citations, 58 articles evaluating 37 novel biomarkers were included for final review. A total of 41 studies did not support the use of their respective biomarkers; 17 studies supported the use of 5 biomarkers, particularly when
combined with cardiac-specific troponin: heart fatty acid-binding protein, ischemia-modified albumin, B-type natriuretic peptide, copeptin, and matrix metalloproteinase-9. The authors concluded that in patients presenting to the emergency department with chest pain or symptoms suggestive of cardiac ischemia, there is inadequate evidence to suggest the routine testing of novel biomarkers in isolation. Moreover, they stated that several novel biomarkers have the potential to improve the sensitivity of diagnosing ACS when combined with cardiac-specific troponin.

Eindhoven et al (2012) stated that BNP and NT-proBNP are well-established markers for heart failure in the general population. However, the value of BNP as a diagnostic and prognostic marker for patients with structural congenital heart disease (CHD) is still unclear. These investigators evaluated the clinical utility of BNP in patients with CHD. They executed a PubMed literature search and included 49 articles that focused on complex congenital heart defects such as tetralogy of Fallot, systemic right ventricle, and uni-ventricular hearts. Data on BNP measurements and cardiac function parameters were extracted. In all patients after correction for tetralogy of Fallot, BNP levels were elevated and correlated significantly with right ventricular end-diastolic dimensions and severity of pulmonary valve regurgitation. Patients with a systemic right ventricle had elevated BNP levels, and positive correlations between BNP and right ventricular function were seen. In patients with a uni-ventricular heart, elevated BNP levels were observed before completion of the Fontan circulation or when patients were symptomatic; a clear association between BNP and NYHA functional class was demonstrated. The authors concluded that this review showed an overall increase in BNP values in complex CHD, although differences between types of congenital heart anomaly are present. As BNP values differ widely, conclusions for individual patients should be drawn with caution. They stated that further investigation with sequential BNP measurement in a large, prospective study is warranted to elucidate the prognostic value of BNP assessment in patients with CHD.
Eindhoven et al (2014) determined the value of NT-proBNP in adults with ToF and established its relationship with echocardiography and exercise capacity. Electrocardiography, detailed 2D-echocardiography and NT-proBNP measurement were performed on the same day in 177 consecutive adults with ToF (mean age of 34.6 ± 11.8 years, 58 % male, 89 % NYHA I, 29.3 ± 8.5 years after surgical correction); 38 % of the patients also underwent a cardiopulmonary-exercise test. Median NT-proBNP was 16 [IQR 6.7 to 33.6] pmol/L, and was elevated in 55 %. NT-proBNP correlated with right ventricular (RV) dilatation ($r = 0.271, p < 0.001$) and RV systolic dysfunction ($r = -0.195, p = 0.022$), but more strongly with LV systolic dysfunction ($r = -0.367, p < 0.001$), which was present in 69 patients (39 %). Moderate or severe pulmonary regurgitation was not associated with higher NT-proBNP. Tricuspid and pulmonary regurgitation peak velocities correlated with NT-proBNP ($r = 0.305, p < 0.001$ and $r = 0.186, p = 0.045$, respectively). Left ventricular twist was measured with speckle-tracking echocardiography in 71 patients. An abnormal LV twist (20 patients, 28 %) was associated with elevated NT-proBNP ($p = 0.030$). No relationship between NT-proBNP and exercise capacity was found. The authors concluded that NT-proBNP levels were elevated in more than 50 % of adults with corrected ToF, while they were in stable clinical condition. Higher NT-proBNP is most strongly associated with elevated pulmonary pressures, and with LV dysfunction rather than RV dysfunction. They stated that NT-proBNP has the potential to become routine examination in patients with ToF to monitor ventricular function and may be used for timely detection of clinical deterioration.

García-Berrocoso et al (2013) measured the association of BNP and NT-proBNP with all-cause mortality after stroke, and evaluated the additional predictive value of BNP/NT-proBNP over clinical information. Suitable studies for meta-analysis were found by searching MEDLINE and EMBASE databases until October 26, 2012. Weighted mean differences measured effect size; meta-regression and publication bias were assessed. Individual participant data were used to estimate effects by
logistic regression and to evaluate BNP/NT-proBNP additional predictive value by area under the receiver operating characteristic curves, and integrated discrimination improvement and categorical net re-classification improvement indexes. Literature-based meta-analysis included 3,498 stroke patients from 16 studies and revealed that BNP/NT-proBNP levels were 255.78 pg/ml (95% CI: 105.10 to 406.47, p = 0.001) higher in patients who died; publication bias entailed the loss of this association. Individual participant data analysis comprised 2,258 stroke patients. After normalization of the data, patients in the highest quartile had doubled the risk of death after adjustment for clinical variables (NIH Stroke Scale score, age, sex) (odds ratio 2.30, 95% CI: 1.32 to 4.01 for BNP; and odds ratio 2.63, 95% CI: 1.75 to 3.94 for NT-proBNP). Only NT-proBNP showed a slight added value to clinical prognostic variables, increasing discrimination by 0.028 points (integrated discrimination improvement index; p < 0.001) and reclassifying 8.1% of patients into correct risk mortality categories (net re-classification improvement index; p = 0.003). Neither etiology nor time from onset to death affected the association of BNP/NT-proBNP with mortality. The authors concluded that BNPs are associated with post-stroke mortality independent of NIH Stroke Scale score, age, and sex. However, their translation to clinical practice seems difficult because BNP/NT-proBNP add only minor predictive value to clinical information. Thus, although this association was statistically significant, these biomarkers did not lead to better prediction of death than clinical information alone.

Hijazi et al (2013) assessed the prognostic value of NT-proBNP in patients with atrial fibrillation (AF) enrolled in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial, and the treatment effect of apixaban according to NT-proBNP levels. In the ARISTOTLE trial, 18,201 patients with AF were randomized to apixaban or warfarin. Plasma samples at randomization were available from 14,892 patients. The association between NT-proBNP concentrations and clinical outcomes was evaluated using Cox proportional hazard models, after adjusting for established cardiovascular
risk factors. Quartiles of NT-proBNP were: Q1, less than or
equal to 363 ng/L; Q2, 364 to 713 ng/L; Q3, 714 to 1,250 ng/L;
and Q4, greater than 1,250 ng/L. During 1.9 years, the annual
rates of stroke or systemic embolism ranged from 0.74 % in the
bottom NT-proBNP quartile to 2.21 % in the top quartile, an
adjusted HR of 2.35 (95 % CI: 1.62 to 3.40; p < 0.0001). Annual
rates of cardiac death ranged from 0.86 % in Q1 to 4.14 % in
Q4, with an adjusted HR of 2.50 (95 % CI: 1.81 to 3.45; p <
0.0001). Adding NT-proBNP levels to the CHA2DS2VASc score
improved C-statistics from 0.62 to 0.65 (p = 0.0009) for stroke
or systemic embolism and from 0.59 to 0.69 for cardiac death
(p < 0.0001). Apixaban reduced stroke, mortality, and bleeding
regardless of the NT-proBNP level. The authors concluded that
NT-proBNP levels are often elevated in AF and independently
associated with an increased risk of stroke and mortality. They
stated that NT-proBNP improved risk stratification beyond the
CHA2DS2VASc score and might be a novel tool for improved
stroke prediction in AF. The effectiveness of apixaban
compared with warfarin is independent of the NT-proBNP level.

In a prospective study, Rodriguez-Yanez et al (2013) examined if
pro-BNP levels in the acute phase of stroke predict the
development of AF in patients with cryptogenic stroke.
Demographic data, medical history, and stroke characteristics
were assessed at admission. A blood sample was obtained
within the first 24 hours from stroke onset to determine pro-
BNP levels. Patients were followed by a neurologist at 3 and 6
months and later by a primary care physician for 2 years to
evaluate the development of AF. A total of 1,050 patients with
ischemic stroke were evaluated – 372 patients (35 %) had
cryptogenic stroke. A total of 108 patients were excluded from
the study, so 264 patients were valid for the analysis. Atrial
fibrillation was detected in 15 patients (5.6 %) during the
follow-up. Patients who developed AF were older, had
hypertension more frequently, and showed higher levels of
pro-BNP. In the logistic regression model, these researchers
found that pro-BNP greater than or equal to 360 pg/ml was the
only variable independently associated with the risk of
developing AF (OR 5.70, 95 % CI: 1.11 to 29.29, p = 0.037). The
authors concluded that pro-BNP greater than or equal to 360 pg/ml increases by 5-fold the possibility of detecting AF during follow-up in patients with cryptogenic stroke. They stated that pro-BNP levels of greater than or equal to 360 pg/ml determine during the acute phase of cryptogenic stroke may be useful to identify patients at risk of AF during the 2 years after the stroke. The drawbacks of this study included (i) there were no data regarding the left atrial size of left ventricular ejection fraction, which are independent risk factor for AF development, (ii) there was no information about treatment before admission that could affect pro-BNP levels, and (iii) these researchers did not examine the temporal profile of pro-BNP, and some studies found that pro-BNP levels decrease in the days following a stroke.

Roldan et al (2014) stated that oral anti-coagulation is highly effective in reducing stroke and mortality in AF. Several risk stratification schemes have been developed using clinical characteristics. Elevated levels of NT-proBNP are important markers of increased mortality and morbidity in CHF and general community population. These investigators evaluated the predictive value of NT-proBNP levels in an unselected real-world cohort of anti-coagulated patients with AF. These researchers studied 1,172 patients (49 % male; median age of 76 years) with permanent AF who were well-stabilized on oral anti-coagulation (international normalized ratio, 2.0 to 3.0). Plasma NT-proBNP levels were quantified at baseline. These researchers recorded thrombotic and vascular events, mortality, and major bleeding. The best cut-off points were assessed by receiver-operating characteristic curves. Median levels (interquartile range) of NT-proBNP were 610 (318 to 1,037) pg/ml. Median follow-up was 1,007 (806 to 1,279) days. On multi-variate analysis, high NT-proBNP was significantly associated with the risk of stroke (HR, 2.71; p = 0.001) and composite vascular events (acute coronary syndrome or acute heart failure; HR, 1.85; p = 0.016), as well as a significant association with mortality (adjusted HR, 1.66; p = 0.006). No association with bleeding was found (p = 0.637). The integrated discrimination improvement (IDI) analysis demonstrated that
NT-proBNP improved the CHF, Hypertension, Age greater than or equal to 75 (doubled), Diabetes mellitus, Stroke (doubled)-Vascular disease and Sex category (female); CHA2DS2-VASc score for predicting embolic events (relative IDI, 2.8 %; p = 0.001) and all-cause death (relative IDI, 1.8 %; p = 0.001). The authors concluded that in real-world cohort of anti-coagulated patients with AF, NT-proBNP provided complementary prognostic information to an established clinical risk score (CHA2DS2-VASc) for the prediction of stroke/systemic embolism. Moreover, they stated that NT-proBNP was also predictive of all-cause mortality, suggesting that this biomarker may potentially be used to refine clinical risk stratification in anti-coagulated patients with AF.

Balion et al (2014) stated that BNP/NT-proBNP measurement has not gained widespread use for the management of patients with HF despite several RCTs. These investigators performed a systematic review addressing the question of whether patients with HF benefit from BNP-assisted therapy or intensified therapy compared with usual care. Relevant RCTs were selected by searching Medline, Embase, AMED, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL for English-language articles published from 1980 to 2012. Selected studies required patients to be treated for chronic HF with medical therapy based on BNP/NT-proBNP or usual care. There were no restrictions except that BNP/NT-proBNP measurement had to be done by an FDA-approved method. A total of 9 RCTs were identified with 2,104 patients with study duration that ranged from 3 to 18 months. Overall, there was a wide variation in study design and how parameters were reported including patient selection, baseline characteristics, therapy goals, BNP/NT-proBNP cut-point, and outcome types. Meta-analysis was not appropriate given this study heterogeneity. The strength of evidence for the outcome of mortality, reported in 7 studies, was found to be low due to inconsistency and imprecision. The authors concluded that the findings of this systematic review showed that the evidence is of low quality and insufficient to support the use of BNP/NT-proBNP to guide
HF therapy. They stated that further trials with improved
design are needed.

**Diagnosis of Cardio-Embolic Stroke:**

Yang et al (2014) performed a systematic review and meta-
analysis to evaluate the value of BNP in differentiating cardio-
embolic (CE) stroke from other subtypes of ischemic stroke.
These investigators searched the EMBASE, MEDLINE, and
Cochrane databases and reference lists of relevant articles
published in April 2013. They selected original studies
reporting the performance of BNP or NT-proBNP in diagnosing
CE stroke and summarized test performance characteristics
using forest plots, hierarchical summary receiver operating
characteristic curves, and bivariate random-effect models. Data
from 2,958 patients with ischemic stroke were retrieved from
16 studies. Of these, 1,024 (34.6 %) patients had a final
diagnosis of CE stroke. Overall, the mean diagnostic OR (DOR)
of BNP for CE stroke was 15.8 (95 % CI: 9.92 to 25.20). Even
after adjustment for multiple clinical predictors, serum
natriuretic peptide levels showed a strong association with CE
stroke (pooled adjusted DOR, 12.7; 95 % CI: 7.32 to 22.0). The
sensitivity and specificity of BNP for CE stroke were 0.78 (95 %
CI: 0.71 to 0.87) and 0.83 (95 % CI: 0.77 to 0.87), respectively. A
single BNP-negative result may be sufficient to exclude a
diagnosis of CE stroke in low-prevalence (less than 20 %)
settings. Subgroup analysis showed that NT-proBNP had a
slightly higher specificity (0.87; 95 % CI: 0.77 to 0.93) and better
capability for exclusion diagnosis. There was a lack of
homogeneity in the timing of measurement and BNP assay
method. The authors concluded that BNP has reasonable
accuracy in the diagnosis of CE stroke and may be a useful
marker for the early detection in patients who may benefit
from preventive anti-coagulation therapy.

An UpToDate review on “Clinical diagnosis of stroke subtypes”
(Caplan, 2015a) does not mention the use of measurement of
plasma brain natriuretic peptide as a diagnostic tool.
Furthermore, an UpToDate review on “Overview of the
evaluation of stroke” (Caplan, 2015b) states that “Other potential indicators that may predict which patients have or are likely to develop atrial fibrillation include determination of the left atrial appendage ejection fraction by transesophageal echocardiography and demonstration of an atrial fibrillation phenotype on left atrial appendage pulse wave Doppler even when the surface ECG shows normal sinus rhythm. In addition, measurements of B-type (brain) natriuretic protein (BNP) and the N-terminal fragment of BNP indicate that these values are elevated in patients with atrial fibrillation who have cardiogenic embolism, even in those with normal ventricular function, when compared with patients who have non-cardiogenic stroke. These measurements in patients with normal cardiac ventricular function might identify those who have intermittent atrial fibrillation or are prone to develop it. Further research is needed to confirm whether these indicators are clinically useful”.

Llombart et al (2015) noted that increased blood levels of BNP/NT-proBNP have been repeatedly associated with cardio-embolic stroke. These investigators evaluated their clinical value as pathogenic biomarkers for stroke through a literature systematic review and individual participants’ data meta-analysis. They searched publications in PubMed database until November 2013 that compared BNP and NT-proBNP circulating levels among stroke causes. Standardized individual participants’ data were collected to estimate predictive values of BNP/NT-proBNP for cardio-embolic stroke. Dichotomized BNP/NT-proBNP levels were included in logistic regression models together with clinical variables to assess the sensitivity and specificity to identify cardio-embolic strokes and the additional value of biomarkers using area under the curve and integrated discrimination improvement index. From 23 selected articles, these researchers collected information of 2,834 patients with a defined cause; BNP/NT-proBNP levels were significantly elevated in cardio-embolic stroke until 72 hours from symptoms onset. Predictive models showed a sensitivity greater than 90 % and specificity greater than 80 % when BNP/NT-proBNP were added considering the lowest and
the highest quartile, respectively. Both peptides also increased significantly the area under the curve and integrated discrimination improvement index compared with clinical models. Sensitivity, specificity, and precision of the models were validated in 197 patients with initially undetermined stroke with final pathogenic diagnosis after ancillary follow-up. The authors concluded that natriuretic peptides are strongly increased in cardio-embolic strokes. Moreover, they stated that future multi-center prospective studies comparing BNP and NT-proBNP might aid in finding the optimal biomarker, the best time-point, and the optimal cut-off points for cardio-embolic stroke identification.

*Diagnosis of Patent Ductus Arteriosus:*

Farombi-Oghuvbu et al (2008) noted that BNP is a marker for ventricular dysfunction secreted as a pre-prohormone, proBNP, and cleaved into BNP and a biologically inactive fragment, NT-proBNP. Little is known about the clinical usefulness of NT-proBNP in preterm infants. These researchers evaluated the usefulness of plasma NT-proBNP in diagnosing hemodynamically significant patent ductus arteriosus (hsPDA) in neonates and examined some factors that might affect this.

Infants born at less than 34 weeks' gestational age (GA) and less than 2 kg birth weight (BW) were prospectively enrolled within 6 to 12 hours of birth. Plasma NT-proBNP levels were measured on days 1, 3, 5 and 10 with simultaneous echocardiography done to detect hsPDA and assess ventricular function.

Significant PDA was diagnosed by large ductal flow with left to right shunt on color Doppler, measuring greater than 1.6 mm on 2-dimensional echocardiography, along with clinical features of PDA. A total of 49 infants were analyzed. Median GA was 30 weeks (range of 24 to 33) and median BW 1,220 g (range of 550 to 1,950). Eighteen infants with hsPDA had higher day 3 plasma NT-proBNP values (median of 32,907 pg/ml; range of 11,396 to 127,155) (p < 0.001) than controls (median of 3,147 pg/ml; range of 521 to 10,343). Infants who developed sepsis had higher day 10 plasma NT-proBNP levels. Area under receiver operator characteristic curve for detection of hsPDA, by day 3
NT-proBNP value, was significant 0.978 (95 % CI: 0.930 to 1.026). NT-proBNP was predictive of hsPDA (sensitivity 100 %; specificity 95 %) at a cut-off value of 11,395 pg/ml. The authors concluded that plasma NT-proBNP level on day 3 is a good marker for hsPDA in preterm infants; serial measurements of NT-proBNP may be useful in assessing the clinical course of PDA.

Kulkarni et al (2015) stated that echocardiogram is the gold standard for the diagnosis of hsPDA in preterm neonates. A simple blood assay BNP or NT-proBNP may be useful in the diagnosis and management of hsPDA. These researchers determined the diagnostic accuracy of BNP and NT-proBNP for hsPDA in preterm neonates and explored heterogeneity by analyzing subgroups. The systematic review was performed as recommended by the Cochrane Diagnostic Test Accuracy Working Group. Electronic databases, conference abstracts, and cross-references were searched. These investigators included studies that evaluated BNP or NT-proBNP (index test) in preterm neonates with suspected hsPDA (participants) in comparison with echocardiogram (reference standard). A bivariate random effects model was used for meta-analysis, and summary receiver operating characteristic curves were generated. A total of 10 BNP and 11 NT-proBNP studies were included. Studies varied by methodological quality, type of commercial assay, thresholds, age at testing, gestational age, and whether the assay was used to initiate medical or surgical therapy. Sensitivity and specificity for BNP at summary point were 88 % and 92 %, respectively, and for NT-proBNP they were 90 % and 84 %, respectively. The authors concluded that studies evaluating the diagnostic accuracy of BNP and NT-proBNP for hsPDA varied widely by assay characteristics (assay kit and threshold) and patient characteristics (gestational and chronological age); therefore, generalizability between centers is not possible. They recommended that BNP or NT-proBNP assays be locally validated for specific patient population and outcomes, to initiate therapy or follow response to therapy.
Furthermore, an UpToDate reviews on “Pathophysiology, clinical manifestations, and diagnosis of patent ductus arteriosus in premature infants” (Phillips, 2015) states that “Biomarkers, especially B-type natriuretic peptide (BNP) or the inactive N-terminal pro-BNP, which has a longer half-life, have been proposed as useful in the diagnosis and management of PDA. However, the sensitivity and specificity of these tests vary in different populations and sites and further study is needed to identify their role in the diagnosis of PDA”.

Diagnosis of Kawasaki Disease:

In a systematic review and meta-analysis, Lin and colleagues (2015) examined the diagnostic value of serum BBNP in acute Kawasaki disease (KD). A systematic literature search strategy was designed and carried out using Medline, Embase and the Cochrane Library from inception to December 2013. These investigators also performed manual screening of the bibliographies of primary studies and review articles, and contacted authors for additional data. They included all BNP and NT-proBNP assay studies that compared pediatric patients with KD to patients with febrile illness unrelated to KD. These researchers excluded case reports, case series, review articles, editorials, congress abstracts, clinical guidelines and all studies that compared healthy controls. The performance characteristics of BNP were summarized using forest plots, hierarchical summary receiver operating characteristic (ROC) curves and bivariate random effects models. The authors found 6 eligible studies including 279 cases of patients with KD and 203 febrile controls; 6 studies examined NT-proBNP and 1 examined BNP. In general, NT-proBNP is a specific and moderately sensitive test for identifying KD. The pooled sensitivity was 0.89 (95 % CI: 0.78 to 0.95) and the pooled specificity was 0.72 (95 % CI: 0.58 to 0.82). The area under the summary ROC curve was 0.87 (95 % CI: 0.83 to 0.89). The positive likelihood ratio (LR+ 3.20, 95 % CI: 2.10 to 4.80) was sufficiently high to be qualified as a rule-in diagnostic tool in the context of high pre-test probability and compatible clinical symptoms. A high degree of heterogeneity was found using the
Cochran Q statistic. The authors concluded that current evidence suggested that NT-proBNP may be used as a diagnostic tool for KD; NT-proBNP had high diagnostic value for identifying KD in patients with protracted undifferentiated febrile illness. Moreover, they stated that prospective large cohort studies are needed to help determine best cut-off values and further clarify the role of NT-proBNP in the diagnosis of KD.

Identification of Individuals at Risk of Developing Abnormal Brain Aging:

In a cross-sectional study, Sabayan et al (2015) examined the independent association of serum NT-proBNP with structural and functional features of abnormal brain aging in older individuals. This study was based on the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, and these investigators included 4,029 older community-dwelling individuals (born 1907 to 1935) with a measured serum level of NT-proBNP. Outcomes included parenchymal brain volumes estimated from brain MRI, cognitive function measured by tests of memory, processing speed, and executive functioning, and presence of depressive symptoms measured using the Geriatric Depression Scale. In a sub-study, cardiac output of 857 participants was assessed using cardiac MRI. In multi-variate analyses, adjusted for socio-demographic and cardiovascular factors, higher levels of NT-proBNP were independently associated with lower total (p < 0.001), gray matter (p < 0.001), and white matter (p = 0.001) brain volumes. Likewise, in multivariate analyses, higher levels of NT-proBNP were associated with worse scores in memory (p = 0.005), processing speed (p = 0.001), executive functioning (p < 0.001), and more depressive symptoms (p = 0.002). In the sub-study, the associations of higher NT-proBNP with lower brain parenchymal volumes, impaired executive function and processing speed, and higher depressive symptoms were independent of the level of cardiac output. The authors concluded that higher serum levels of NT-proBNP, independent of cardiovascular risk factors and a measure of cardiac function, are linked with alterations in brain structure and function. Moreover, they stated that the
roles of natriuretic peptides in the process of brain aging need to be further elucidated. They noted that further research is needed to elucidate mechanisms underlying this association and to clarify whether measurement of NT-proBNP can be a tool to identify older individuals at high risk of developing abnormal brain aging.

*Prediction of the Occurrence of Atrial Fibrillation after Thoracic Surgery:*

In a systematic review and meta-analysis, Simmers et al (2015) examined if elevated pre-operative BNP measurements are an independent predictor of AF in patients having thoracic surgery. Embase, Ovid Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ProQuest Dissertations and Theses A&I databases were searched for all studies of non-cardiac thoracic surgery patients in whom a pre-operative NP was measured up to 1 month before surgery, and that measured the incidence of post-operative AF. Studies were included regardless of their language, sample size, publication status, or study design. Study quality was evaluated using the Newcastle Ottawa Scale. The combined incidence of post-operative AF was 14.5 % (n = 108/742), and the NP thresholds used to predict AF varied among studies. An elevated pre-operative NP measurement was associated with an OR of 3.13 (95 % CI: 1.38 to 7.12; I2 = 87 %) for post-operative AF, with the sensitivity analysis reporting an OR of 9.51 (95 % CI: 4.66 to 19.40; I2 = 0). The authors concluded that patients with an elevated pre-operative NP measurement were at an increased risk of post-operative AF. They stated that there may be value in incorporating NP measurement into existing AF risk prediction models.

*Prediction of Outcome in Congenital Diaphragmatic Hernia:*

Snoek et al (2016) stated that biomarkers may be helpful in prediction of outcomes of infants with congenital diaphragmatic hernia (CDH). The predictive value of high-sensitivity troponin T and NT-proBNP was investigated in
128 infants with CDH. After correction for multiple testing, these biomarkers did not predict severe pulmonary hypertension, death, need of extra-corporeal membrane oxygenation, or broncho-pulmonary dysplasia.

Risk Stratification of Individuals with Aortic Stenosis:

Lindman et al (2015) examined if multiple biomarkers of cardiovascular stress are associated with mortality in patients with aortic stenosis (AS) undergoing aortic valve replacement (AVR) independent of clinical factors. From a prospective registry of patients with AS, a total of 345 participants who were referred for and treated with AVR (trans-catheter [n = 183] or surgical [n = 162]) were included. A total of 8 biomarkers were measured on blood samples obtained prior to AVR: growth differentiation factor 15 (GDF15), soluble ST2 (sST2), NT-proBNP, galectin-3, high-sensitivity cardiac troponin T, myeloperoxidase, high-sensitivity C reactive protein and monocyte chemotactic protein-1. Biomarkers were evaluated based on median value (high versus low) in a Cox proportional hazards model for all-cause mortality and a parsimonious group of biomarkers selected. Mean follow-up was 1.9 ± 1.2 years; 91 patients died. Three biomarkers (GDF15, sST2 and NT-proBNP) were retained in the model. One-year mortality was 5 %, 12 %, 18 % and 33 % for patients with 0 (n = 79), 1 (n = 96), 2 (n = 87) and 3 (n = 83) biomarkers elevated, respectively (p < 0.001).

After adjustment for the Society of Thoracic Surgeons (STS) risk score, a greater number of elevated biomarkers was associated with increased mortality (referent: 0 elevated): 1 elevated (HR 1.47, 95 % CI: 0.60 to 3.63, p = 0.40), 2 elevated (HR 2.89, 95 % CI: 1.24 to 6.74, p = 0.014) and 3 elevated (HR 4.59, 95 % CI: 1.97 to 10.71, p < 0.001). Among patients at intermediate or high surgical risk (STS score greater than or equal to 4), 1-year and 2-year mortality rates were 34 % and 43 % for patients with 3 biomarkers elevated versus 4 % and 4 % for patients with 0 biomarkers elevated. When added to the STS score, the number of biomarkers elevated provided a category-free net re-classification improvement of 64 % at 1 year (p < 0.001). The association between a greater number of elevated biomarkers
and increased mortality after valve replacement was similar in the trans-catheter and surgical AVR populations. The authors concluded that the findings of this study demonstrated the potential utility of multiple biomarkers to aid in risk stratification of patients with AS. Moreover, they stated that further studies are needed to evaluate their utility in clinical decision-making in specific AS populations.

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Amendment to
Aetna Clinical Policy Bulletin Number: 0618
Brain Natriuretic Peptide Testing

There are no amendments for Pennsylvania Medicaid.

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