

# Bulletin Technical

---

---

## Natriuretic peptide testing at the Pathology Center: NT-proBNP

**Beginning January 12, 2010 the Pathology Center will convert natriuretic peptide testing from BNP to NT-proBNP.**

**NOTE:** The laboratory will be reporting both BNP and proBNP at no extra charge to the patient, from **Jan. 12 through January** end, to assist clinician adaptation to the different values. During this time, physicians should be cautious about confusing the two assays, as their clinical cut point concentrations and patient results are different.

**Why change?** The Pathology Center instituted natriuretic peptide testing (BNP) seven years ago. Since then the medical literature has validated proBNP as an equally useful heart failure marker, and studies have established easy to use cutoffs to aid diagnosis of heart failure in the acutely dyspneic patient.

Thus, conversion of natriuretic peptide testing to proBNP will deliver the following benefits to our physicians, caregivers, clients, and laboratory:

- Equivalent performance (to BNP) for diagnosis of acute heart failure.
- No cutpoint adjustment required for impaired renal function, in the acutely dyspneic patient.
- No cutpoint adjustment required for obesity, in the acutely dyspneic patient
- Technologist time and labor cost savings.
- Elimination of an entire instrument platform.
- Specimen type (not unique) and improved stability.
- Leaner processes for natriuretic peptide and cardiac marker testing.
- Established medical decision cutpoints—functionally similar to BNP (see below) for acute dyspnea.
- Other local and national centers converting (for example, Mayo Clinic).
- Better prognostic performance (than BNP), for the interested clinician.

**Interpretation:** The following cutpoints for **diagnosis of acute heart failure** have been established via a multicenter international study:

- Less than 50 years old: >450 pg/mL
- 50-75 years old: >900 pg/mL
- Greater than 75 years old: >1800 pg/mL

For **exclusion of acute heart failure** (any adult age):

- Any age (adult): <300 pg/mL

These values are noted to remain valid in **obese** patients, and patient with **renal insufficiency**.

**Specimen Requirements:** 1 mL Serum (SST), Lithium Heparin Plasma, or EDTA plasma. Separate serum or plasma from cells ASAP. The sample is stable 4 days at 2-8° C or otherwise freeze sample. CPT (83880) and Charge will not change.

**Availability:** 24hours / 7days

**References:** Attached is a set of **FAQ's** developed from relevant literature to assist clinicians with this conversion.

**Questions:** Please contact Dr. Tom Williams, 402-354-4540

## FAQ's for natriuretic peptides (any, focusing on NT proBNP):

- **What is the number one use of natriuretic peptides today?**
  - 90% of BNP tests are performed (internationally) in the ED as an aid to diagnose heart failure.<sup>5</sup> The most widely accepted use for the BNP or NT-pro BNP is the evaluation of the acutely dyspneic patient.
- **What NT- pro BNP cut points should be used as an aid for the diagnosis or exclusion of heart failure in the acutely dyspneic patient?**
  - Those established by the International Collaborative of NT-proBNP (ICON) study<sup>2</sup>
  - They are used the same way as cutoffs for BNP: There is an exclusionary cutoff; and three age dependent inclusionary (diagnostic) cutoffs:
  - **To rule in** heart failure:

< 50 y/o	>450 pg/mL
50 – 75 y/o	>900 pg/mL
>75 y/o	>1800 pg/mL
  - **Conversely, to exclude AHF.....**  
Age independent, 98% neg. predictive value: <300 pg/mL.
- **What will the Pathology Center laboratory report contain besides the proBNP result?**
  - It will include “cut points” for diagnosis and exclusion of acute heart failure (from the ICON study—above), as well as a “reference range”.
- **How are the “reference range” and “cut point” different?**
  - **Reference range** describes test results recovered **only** from clinically perfectly normal subjects. Test results which have predictive value for heart failure are not offered.
  - **Cut point**, instead, represent medical decision points, which are based upon comparison of proBNP results from populations of **both** clinically normal and acute heart failure patients. Cut points, or medical decision points, optimized to aid the diagnosis or exclusion of acute heart failure for acutely dyspneic patients, are offered. This is similar to the approach used for BNP.
- **Is BNP or proBNP better for this use?**
  - “Some experts believe strongly about the superiority of either BNP or proBNP....the data however, show little advantage of one over the other.”<sup>1,5</sup>
- **Are BNP or NT proBNP helpful while a patient is in the hospital? Is there a reason to do these serially or “daily”?**
  - No. “Serial natriuretic peptide measurements are not recommended.”<sup>5</sup>
  - “We do not have sufficient data at this time... [for using] daily BNP to optimize heart failure management in the inpatient or outpatient setting.”<sup>5</sup>
- **Why do results from peptide markers done serially not help? How much change in the result is significant (for worsening or improving failure)?**
  - The most widely accepted use of natriuretic peptides is aiding diagnosis of AHF.
  - Serial testing (for example, daily) is hampered by very large intraindividual variations found in studying either normal patients or patients with stable chronic failure. Clinically meaningful changes found were 80% to 130%<sup>7</sup> (meaning the natriuretic peptide result needs basically halve or almost double to reflect a physiologic change with 95% confidence).
- **Can / how should the test be used in hospitalized patients?**
  - “[Admission and] Day of discharge ... measurements are of value. Heart failure patients do poorly after discharge when their BNP or proBNP have not fallen substantially.”<sup>5</sup>
  - “At MGH, we aim for at least a 30% reduction in the NT proBNP from the time of presentation to the time of discharge.”<sup>5</sup>
- **Does the natriuretic peptide result alone, in a given patient, predict the extent of failure (NYHA class)?**
  - No. There is enormous overlap in the class to class data.

- **What is known about BNP and pro BNP in renal disease? (CKD effects and clinical import of elevated values).**
  - Both increase significantly with renal insufficiency. <sup>3,5</sup>
  - "...increased BNP and NT-proBNP concentrations are predominantly related to and a result of the presence and extent of cardiac pathology rather than impaired renal clearance." <sup>1</sup>
  - The renal excretion of BNP and proBNP is the same. "Fractional excretion of both NT-proBNP and BNP remained equivalent across a wide span of age and renal function at 14-23%." <sup>3</sup>
  - "...[the] ... conclusion that NT proBNP was more 'dependent' on renal function...may have been related in part to a failure to account for the [low] upper limit of detection of first generation of the BNP assays." <sup>3</sup>
  - For BNP, "...a cutpoint of ~200 pg/mL is reasonable for those with renal disease." <sup>6</sup>
  - "Importantly, when using proBNP to evaluate a patient with dyspnea and impaired renal function, the recommended (ICON) cutpoints.....do not require further adjustment." <sup>3</sup> "In the unusual patient < 50 years old with chronic kidney disease, a cut point of 1200 pg/mL would be indicated." <sup>3</sup>
- **What about obesity?**
  - "BNP and proBNP may be 20% lower in the most obese subjects." <sup>5</sup>
  - For BNP, a very low cutoff (<50 pg/mL) should be used to r/o HF in obese patients
  - "With regard to NT proBNP, an analysis of the ICON study demonstrated that rule-out values remained robust irrespective of BMI." <sup>4</sup>
- **Is there a prognostic cutoff for bad prognosis for pro BNP in heart failure?**
  - "Around 5000 [appears] markedly prognostic ...for 60 day mortality in heart failure." <sup>5,4</sup>
  - Admission NT-proBNP concentration was so strongly predictive of short term mortality among our patients with AHF that [it]...overwhelmed the prognostic impact of other risk factors..., such as age or NYHA classification." <sup>4</sup>
- **What are some other health systems now using NTproBNP:**
  - Mayo Clinic, Stanford, Massachusetts General Hospital, locally Alegant.
- **What are the specimens suitable for testing proBNP?**
  - SST (red/black top) Lithium heparin (green top) or EDTA (purple top) plasma.
- **How often is the proBNP performed by the laboratory?**
  - ProBNP is available 24/7.

### **Take home messages:**

Do use NT proBNP to diagnose heart failure, in a patient dyspneic of uncertain etiology.

Do use the ICON study cutoffs (above) to interpret the test.

Don't serially (or daily) measure NT proBNP (or for that matter, BNP) in the hospital. There are no known indications for daily measurements according to the experts.

You may consider doing admission and discharge measurements if the patient is admitted for heart failure. A significant (30 – 40% decrease) portends a favorable course. No change in an elevated result is bad prognostically, in spite of what is seen clinically.

Marked obesity causes both BNP and proBNP to be lower. However, the ICON study cutoffs retained good performance for NT proBNP and you can still use them.

Renal failure causes both BNP and proBNP to increase. However, the ICON study cutoffs retained good clinical performance for NT proBNP and you can still use them.

**References:**

1. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Mueller T, Gegenhuber A, Poelz W, et al. Heart 2005;91:606-612.
2. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. The International Collaborative of NT-proBNP Study. Januzzi JL, van Kimmenade R, Lainchbury J, et al. European Heart Journal (2006) 27, 330-337. (A.K.A., "ICON" study)
3. Amino Terminal Pro-B type Natriuretic Peptide Testing in Renal Disease. DeFilippi C, van Kimmenade R, Pinto Y. American Journal of Cardiology 2008;101[suppl]:82A-88A.
4. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Bayes-Genis A, Lloyd-Jones D, et al. Archives of Internal Medicine 2007; 167:400-7.
5. The Editor's Roundtable: B-Type Natriuretic Peptide. Friedewald V, Burnett J, Januzzi J, Roberts W, et al. The American Journal of Cardiology. [www.AJConline.org](http://www.AJConline.org)
6. High Intraindividual Variation of BNP and proBNP in Patients with Stable Chronic heart Failure. Bruins S, et al. Clinical Chemistry 2004;50:2052-2058.
7. Only Large Reductions in Concentrations of Natriuretic Peptides Are Associated with Improved Outcome in Ambulatory Patients with Chronic Heart Failure. Miller W, et al. Clinical Chemistry 2009;55:78-84.