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Methodological Heterogeneity and Discrepancies Due to External Quality Assessment Reference Materials in Natriuretic Peptide Measurements in Clinical Laboratories

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Introduction

Natriuretic peptides (NPs), particularly B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), have become indispensable biomarkers in the diagnosis, prognosis, and therapeutic monitoring of heart failure. Their integration into international clinical guidelines reflects their significant clinical utility in differentiating cardiac from non-cardiac causes of dyspnea, assessing disease severity, and predicting cardiovascular outcomes. Despite their widespread use, substantial analytical variability persists among clinical laboratories. A major contributor to this variability is methodological heterogeneity and the inconsistencies arising from external quality assessment (EQA) reference materials [1].

The measurement of natriuretic peptides is characterized by considerable assay diversity. Multiple commercial platforms employ different analytical principles, antibodies, calibration systems, and detection technologies. BNP assays typically target various epitopes on the BNP molecule, while NT-proBNP assays often utilize distinct antibody pairs recognizing different regions of the precursor fragment. These methodological differences influence assay sensitivity, specificity, and susceptibility to interference from circulating peptide fragments, post-translational modifications, and degradation products [1, 2].

Unlike many routine biochemical analytes, natriuretic peptides lack complete assay harmonization. Consequently, results generated by different analytical systems may not be directly comparable. A patient sample analyzed on two separate platforms may yield significantly different concentrations despite being derived from the same specimen. Such discrepancies create challenges in establishing universal clinical decision limits and complicate longitudinal patient monitoring when laboratory methods change [1, 3].

External quality assessment programs serve a critical role in evaluating laboratory performance and ensuring analytical quality. EQA schemes distribute standardized specimens to participating laboratories, allowing comparison of reported results against consensus values or assigned target concentrations. Ideally, EQA materials should behave identically to native patient samples across all analytical systems, a property known as commutability. However, this ideal is often difficult to achieve in natriuretic peptide testing [4].

One of the principal challenges involves the preparation and composition of EQA reference materials. Many EQA samples are manufactured using processed human serum, recombinant peptides, pooled plasma, or artificially supplemented matrices. Although these materials are designed to mimic clinical specimens, they may not fully replicate the molecular complexity of endogenous natriuretic peptides found in patient circulation. Differences in peptide stability, glycosylation patterns, degradation products, and protein binding characteristics can alter assay responses [3].

The lack of commutability of EQA materials may generate apparent discrepancies that do not accurately reflect true laboratory performance. Certain assay platforms may exhibit enhanced recovery or reduced detection of peptides within processed materials compared with native patient samples. Consequently, laboratories using specific analytical systems may appear biased in EQA evaluations despite producing clinically reliable patient results. Conversely, acceptable EQA performance may mask analytical limitations that become evident in real-world testing [5].

Another important factor is the absence of universally accepted higher-order reference measurement procedures for natriuretic peptides. In clinical chemistry, traceability to certified reference materials and reference methods forms the foundation of assay standardization. For BNP and NT-proBNP, such reference systems remain incompletely developed. Manufacturers therefore rely on proprietary calibration strategies, contributing further to inter-assay variability. When EQA programs employ materials

calibrated according to one analytical approach, laboratories using alternative methods may experience systematic deviations [1, 2, 5].

The issue is particularly significant in multicenter clinical studies and heart failure management programs. Clinical decision thresholds for BNP and NT-proBNP are often derived from studies using specific assay platforms. Applying identical cutoff values across laboratories employing different methodologies may lead to misclassification of patients. Variability introduced by non-commutable EQA materials may further obscure the interpretation of assay performance and inter-laboratory comparability [5].

Several studies have demonstrated that NT-proBNP assays generally exhibit better agreement than BNP assays due to greater standardization efforts. Nevertheless, clinically relevant differences remain. EQA reports frequently reveal substantial between-method variation even when within-method precision is acceptable. These findings highlight that analytical consistency within a laboratory does not necessarily guarantee comparability across institutions [5].

Addressing these challenges requires coordinated efforts among manufacturers, regulatory agencies, professional organizations, and EQA providers. The development of highly commutable reference materials derived from authentic patient specimens represents an important priority. Improved characterization of natriuretic peptide molecular forms and enhanced understanding of assay-specific epitope recognition may facilitate better calibration strategies. Furthermore, establishing internationally recognized reference measurement systems could substantially reduce inter-assay discrepancies [4, 5].

Clinical laboratories should remain aware of the limitations associated with natriuretic peptide measurements and EQA interpretation. Participation in EQA programs remains essential, but performance assessments should be evaluated in the context of assay methodology and material commutability. Laboratories should communicate assay-specific characteristics to clinicians, particularly when changing analytical platforms or interpreting serial patient results [1, 4].

In conclusion, methodological heterogeneity and discrepancies arising from EQA reference materials continue to represent significant challenges in natriuretic peptide testing. Differences in assay design, calibration approaches, and the commutability of quality assessment materials contribute to variability among laboratories. While natriuretic peptides remain invaluable biomarkers in cardiovascular medicine, ongoing standardization and harmonization efforts are necessary to ensure reliable, comparable, and clinically meaningful measurements across diverse laboratory settings [1-3, 5].

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