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Diagnostic Biomarkers in Large Animals

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A biomarker is a defined characteristic that is considered as an indicator of biologic or pathologic processes, or responses to an exposure or therapeutic intervention. There is an explosive growth in the number and scope of biomarker knowledge in veterinary medicine indicating a highly positive outlook for biomarker researchers and developers. Use of biomarkers for diagnosis or in delivering appropriate treatment is not a new concept. Ancient Indians (circa 400–500 A.D.) who were aware of diabetes, tested for diabetes, which they called "honey urine" by determining if ants were attracted to a person's urine. Today without biomarkers, the study of biology and medicine would be impossible. Biomarkers can be anatomical, histological, imaging, genes, mRNA, proteins, metabolites, etc. Biomarkers are classified as prognostic and predictive biomarkers. Prognostic biomarkers are any measurement associated with clinical outcome in the absence of therapy, or with the application of a standard therapy that all patients are likely to receive. Predictive biomarkers are any measurement associated with response or lack of response to a particular therapy, where response can be defined using any of the clinical endpoints commonly used in clinical trials. A biomarker should be reliable, quantitative, fully validated, cost efficient, and non-invasive with high diagnostic sensitivity and specificity. Most likely the use of multiple biomarkers is required to obtain high sensitivity and specificity. There are several applications for biomarkers including for prognosis/diagnosis of disease, staging of disease (severity), monitoring/predicting drug toxicity, monitoring/predicting drug response, establishing disease risk and for clinical trial design, patient selection and stratification: responders/non-responders.

There are challenges in employing biomarkers. Application of the analyte, in context as a biomarker, requires deep biologic understanding of where the biomarker arises and is applied, test system, species, or patient, the kinetics and regulation of the biological response, the sensitivity and specificity of the analyte as a biomarker, and other complex biologic factors. It also requires understanding of the assay used to measure, and sources of pre-analytical, analytical, or post analytical variation that can influence quantitation and interpretation.

The emphasis now would be placed on biomarker assay development and method validation to eliminate the failure of biomarkers that occur in the clinic as a result of poor assay choice and the lack of robust validation. The biomarker method validation process begins with choosing the right assay, followed by developing this assay into a validated method. The appropriate choice of assay depends on the application of the biomarker and the limitations of the respective technology. Various types of assays can be used in the biomarker method validation process and range from the relatively low technology end such as immunohistochemistry

(IHC) to immunoassays to the high technology end including platforms for genomics, proteomics, and multiplex ligand-binding assays.

Biomarker validation is the process of assessing the assay performance characteristics. A biomarker is validated if it can be measured in a test system with well-established performance characteristics and if evidence for its clinical significance has been established. The two types of validation of biomarker assay are analytical and clinical validation. Analytical validation steps vary with technology, quantitative or qualitative, setting of use (e.g., marketed vs. single laboratory service, GLP vs. non-GLP) and should capture all steps from specimen preparation to final result. Analytical validation process includes sample type, collection, preparation, and reference material (preanalytical phase), standard (calibration) curve assessment, precision assessment (intra- and inter-assay), repeatability, reproducibility, diagnostic specificity (cross-reactivity), accuracy (spike/recovery), analytical sensitivity (limits of quantitation), dilution linearity, sample stability and interference studies. The clinical validation is to show the test result correlates with the expected clinical presentation.

Diagnostic biomarkers are important because diagnosis is the foundation of therapy. Biomarkers as quantitative measures allow one to diagnose and assess the disease process and monitor response to treatment. In this review several diagnostic biomarkers in large animals are discussed. These biomarkers are cardiac injury biomarkers including cardiac troponin I (cTnI), cardiac troponin T (cTnT), and atrial and brain natriuretic peptides (NT-proANP and NT-proBNP); skeletal muscle injury biomarkers including skeletal troponin I (sTnI), fatty acid binding protein 3 (FABP3), and myosin light chain 3 (Myl3); renal injury biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), cystatin C and symmetric dimethylarginine (SDMA); and vascular injury biomarkers including angiopoietin-2 (Ang 2).