Plenary: Standardization of MR-based Biomarkers for Evidenced Based Medicine Across Institutions
"Frontiers in Body MRI: Qualitative to Quantitative"
2013 ISMRM Salt Lake City, Utah

Scott Reeder, MD, PhD
University of Wisconsin, Madison, WI

Target Audience: Radiologists, Clinicians, and Scientists interested in standardized and validated quantitative biomarkers applied to diseases of the abdomen.

In this lecture I will review some of the technical and clinical requirements needed to both develop and validate quantitative biomarkers that are appropriate for clinical care and multi-center clinical trials. This will be followed by examples of successful quantitative biomarkers and how they have met these requirements, as well as important biomarkers that have shown promise but have fallen short on translation into valid quantitative biomarkers. Finally this will be followed by a review of exciting new work from leading groups performing research on quantitative imaging biomarkers as applied to abdominal disease.

In the past 2-3 decades, there have been numerous quantitative MR biomarkers developed for a variety of disease including various abdominal diseases, particularly in the liver. Most validation studies have demonstrated excellent correlation, *i.e.*, technical accuracy between a measured parameter and a reference standard. Based on such evidence, investigators inccorectly conclude that since excellent correlation has been achieved that the biomarker has been fully validated. However, there are many other requirements that are needed in the validation of a quantitative biomarker. In addition to demonstrating ***accuracy***, *i.e.*, good correlation with an established reference standard, there are other important steps that must be taken. First, a biomarker must have ***clinical utility****, i.e.,* it must measure a clinical meaningful parameter that will be used for diagnosis, staging end, or treatment monitoring. It is essential that a biomarker be useful to physicians who are making diagnoses and treating patients. This is important for prognosis and treatment. Assuming that a biomarker has clinical utility and is accurate, it should also be ***precise***. Precision refers to the variability that occurs when a measurement is made multiple times. Precision, also known as repeatability, is extremely important for longitudinal measurements. The "error" or variability of he biomarker should be sufficiently low that meaningful changes in a physiological parameter can be detected. If the variability of a measurement exceeds the change that must be detected in a clinical meaningful way, the biomarker will not be valid. In addition to accuracy and precision, a biomarker should also be ***robust*** to changes in scan parameters. For example, if common scan parameters such as TR, TE, flip angle, spatial resolution, bandwidth, image orientation, etc. are changed, it is important that the same value of the biomarker be measured. In some circumstances it is possible to fix the standardized imaging parameters such that they can be used across all platforms, however this is not always possible and variations in scanner hardware performance, as well as other factors such as the patient's size or ability to hold their breath, will necessitate changes in the scan parameters. A robust biomarker is one that is insensitive to changes in these parameters. This is essential for both accurate and reproducible results across protocol, site, and manufacturer. ***Reproducibility*** refers to the variability of a quantitative biomarker across platforms, site, and/or MRI manufacturer. A biomarker that is reproducible across sites, platforms, and manufacturers will have tremendous clinical utility because it will allow for broad interpretation of the biomarker's results. By obtaining the same result on different systems and at different sites, this leads to tremendous opportunities for large-scale multi-site clinical trials and drug development as well as the ability to pool scientific data in meta-analyses. Should a quantitative biomarker meet all of these requirements then it has tremendous potential for

translation into a broadly applicable biomarker. Other features such as short scan time, insensitivity to artifacts and good image quality also contribute to these above parameters.

The abdomen is a highly diverse region of the body with numerous internal organs affecting multiple systems of the body including gastrointestinal, endocrine/metabolic, hematological, vascular and even musculoskeletal. There has been a tremendous amount of research in numerous organs including diffuse liver disease, malignancy, pancreatic disease, distribution of visceral versus subcutaneous fat in metabolic syndrome, inflammatory and malignant diseases of the small and large bowel as well as malignancies of the uterus and ovaries, prostate cancer, among others. There are a large number of quantitative imaging biomarkers that have been developed including the apparent diffusion coefficient measured by diffusion weighted imaging, proton density fat fraction (PDFF) measured by chemical shift encoded fat-water separation techniques, quantitative perfusion imaging with both arterial spin labeling (ASL) and dynamic contrast enhanced imaging. Examples of these include new methods for perfusion imaging in liver tumors, dynamic imaging of prostate cancer among others. Additional examples include emerging biomarkers of iron overload in the liver, pancreas, spleen and bone marrow. New biomarkers of liver fibrosis with diffusion weighted imaging, MR elastography and more recently cardiac gated-tagging methods have also shown great promise for the detection and staging of fibrosis and cirrhosis. Finally new quantitative biomarkers in 4D phase velocity imaging for examining the hemodynamics of vascular disease in the renal arteries, mesenteric vessels as well as the portal vein in patients with portal hypertension have shown exciting promise as quantitative biomarkers. A review of established and emerging biomarkers and some exciting new work from leading groups will be discussed in this lecture.