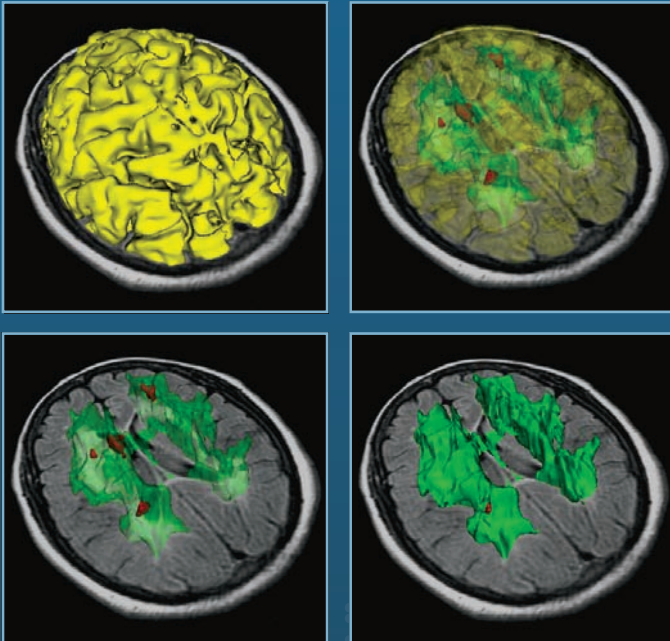


Image Analysis Capabilities

in Multiple Sclerosis (MS) Studies

For more than 2 decades, Magnetic Resonance Imaging (MRI) has played a major role in the evaluation of new therapeutic compounds in MS. The objective evaluation of MS Lesion Burden & Activity in longitudinal MRI datasets has been accepted by regulatory agencies both as primary and secondary efficacy endpoints. Furthermore, additional quantitative endpoints such as brain atrophy, Diffusion-Tensor Imaging (DTI) & Magnetization Transfer Imaging (MTI) have been introduced as Markers of Neurodegeneration and have shown tremendous value for investigating the long term efficacy of new disease-modifying therapies. This document provides a short overview of BioClinica's vision & capabilities for enabling such endpoints in MS trials.



ACHIEVING ACCURACY & REPRODUCIBILITY THROUGH MORE AUTOMATED PROCESSES

Accuracy & reproducibility are the most important requirements for a given quantitative analysis technique. The associated processes must be scalable for a successful deployment in the context of large multicenter trials. The biggest scientific & operational challenges consist in making use of the most advanced quantitative image processing techniques in a highly regulated environment (FDA's 21 CFR Part 11 & software validation guidelines). The complex nature of the quantitative endpoints usually requires the use of automated image processing capabilities, enabling high-throughput analysis. The proposed approaches must be robust enough for variations in image quality (especially in multicenter contexts, where different MRI manufacturers & models are used).

SITE STANDARDIZATION & QA / IMAGE QC

Maximizing the quality of MRI data, minimizing intra/inter-site variability, providing vendor & model-specific MRI acquisition parameter and the ongoing quality control of MRI data performed within short turnaround time are among the most crucial tasks to increase the accuracy & reproducibility of image processing techniques. Test MRI scans are used for site qualification and for monitoring potential system upgrades during the course of the study. Repeat scans may be requested whenever image quality is poor. Data collection can be expedited using electronic, web-based data upload capabilities (WebSend).

IMAGE PROCESSING FOR QUANTITATIVE ANALYSIS

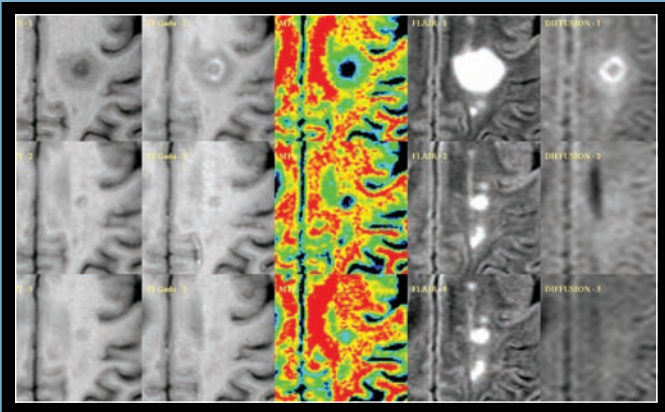
The following image processing modules can be used in MS trials:

- 3D image registration
- MRI signal intensity inhomogeneity correction
- Atlas-based segmentation
- Detection & Quantification of MS lesions:
 - Gadolinium-enhancing T1-weighted lesions
 - Hyperintense FLAIR/T2-weighted lesions
 - Hypointense T1-weighted lesions ("black holes")
- Automatic detection of New, Enlarging, Persisting lesions using 4D-Connectivity
- Fast localization of active lesions through the generation of "Difference" & "Jacobian" maps
- Automatic detection of Combined Unique Lesions
- Diffusion-Weighted Imaging (DWI)
- Diffusion-Tensor Imaging (DTI)
- Magnetization-Transfer Imaging (MTI)

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Global clinical trial solutions. Real-world results.

Image Analysis Capabilities

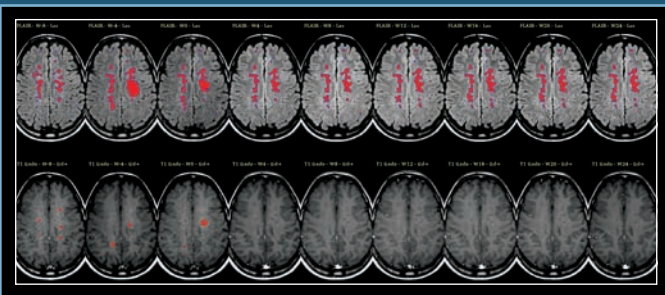
in Multiple Sclerosis (MS) Studies



3D image registration using Mutual Information

Rows: Baseline, M12 & M24 MRI scans of one MS patient

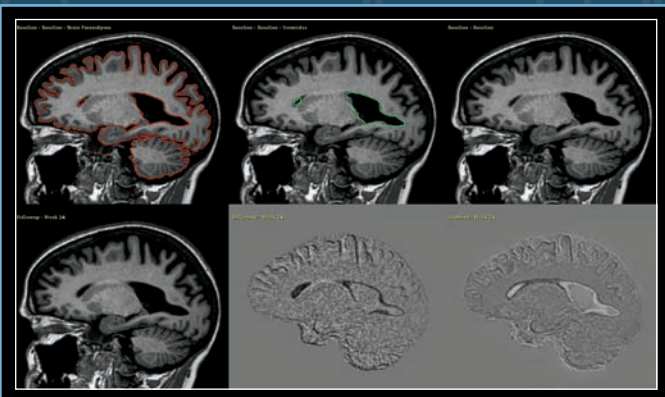
Columns: T1, Post-Gadolinium T1, MTR, FLAIR & DWI MRI sequences



MS lesions segmentation & quantification

Rows: FLAIR & Post-Gadolinium T1 MRI sequences

Columns: 9 consecutive MRI scans of one MS patient



Segmentation of brain parenchyma & lateral ventricles using atlas-based segmentation, Computation of longitudinal brain atrophy (difference & Jacobian maps are presented)

3D IMAGE REGISTRATION

All MRI sequences and timepoints are spatially registered with respect to a given reference MRI sequence. This is done at baseline, using a three-dimensional (3D) mutual information-based registration algorithm.

LESION QUANTIFICATION & TRACKING (4D-CONNECTIVITY)

An unsupervised 3D segmentation algorithm is used for the detection of MS lesions in FLAIR/T2 and gadolinium-enhancing T1-weighted sequences. The algorithm is based on Bayesian MRI signal intensity classification and Markov Random Field models. Segmentation consists in classifying image pixels in different anatomical classes (white matter, gray matter, cerebrospinal fluid and MS lesions) based on MRI intensity-based image features and spatial information such as connectivity and regularity. Each individual MS lesion will be quantified as a 4D object (3D + time) using a 4D-Connectivity algorithm. Once detected and delineated, MS lesions can be automatically counted and labeled in different categories using the 4D-Connectivity algorithm: New, Enlarging, Persisting, etc.

BRAIN & VENTRICULAR ATROPHY QUANTIFICATION

Several registration-based techniques can be used for the quantification of brain atrophy. The most commonly used techniques are **Tensor-Based Morphometry – Jacobian Integration (TBM - JI)** and **Boundary Shift Integration (BSI)**.

INDEPENDENT IMAGE REVIEW BY EXPERT NEURORADIOLOGISTS

Board-certified Neuroradiologists, who are highly specialized in MS & MRI independently assess both native and processed MRI data for the evaluation of eligibility and efficacy endpoints. The conduct of remote read sessions can significantly increase the efficiency of central reading activities while minimizing the inherent costs. The image evaluation results are made available at the sponsor's site in real-time. This is done to facilitate the tracking of operations and allowing fast decision making when it comes to patient monitoring in case of safety findings.

For any technical questions or software demonstration, please contact us at +1.267.757.3000 or info@bioclinica.com

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