Surrogate markers are biomarkers intended to substitute for clinical end-points. This definition is applicable for both use in clinical practice of an individual patient, and for cross-sectional evaluation within clinical trials. Biomarkers can be subcategorised into those a) identifying disease susceptibility (DS), b) disease diagnosis (DD), c) disease course (DC), d) drug response prediction (DR), and drug monitoring (DM).

MRI is the only example of a biomarker that has reached surrogate status for the diagnosis of multiple sclerosis (MS) (McDonald criteria), based on its ability to detect and quantitate neuroinflammation, both acutely and longitudinally. The refinement of MRI diagnostic criteria led to a more reliable diagnosis of MS, specifically in early stages of disease. However, there is currently no other biomarker (imaging and from biofluids) that is sufficiently validated for a clinical endpoint. The absence of prognostic (as per disease course) and predictive (as per drug response related to efficacy and safety) biomarkers prevents the implementation of personalised health care for therapy of neurological disease, on the background of pathomechanistic heterogeneity and individual variability of the longitudinal outcome.

In the context of clinical trials this dilemma has become more pronounced with the impracticability of placebo-controlled trials and the need to use already registered therapies as comparators. This leads inherently to a smaller margin to detect differences of treatment effects. Trial cohorts and study duration have to be increased to demonstrate an incremental benefit of a novel compound over standard therapies, with the consequence of higher costs and operational challenges (e.g. patient recruitment).

Three fields of biomarker development needs can be identified in neurology:

- **a) impact of therapy on disease progression**
  MS compounds have become increasingly effective in suppressing relapses, while there is uncertainty about their value in preventing long-term disability. Clinical and MRI readouts have been of limited help to capture features of neurodegeneration as underlying mechanism of clinical progression,

- **b) predictive differentiation of responders vs. non-responders**
  The introduction of many new compounds gives patients and physicians in theory the potential to optimise therapy along individual needs. However, this advantage cannot be fully exploited, as there are no markers established to predict individual response, leaving physicians for the coming future only with the choice of trial and error. Accordingly, in clinical drug development we will remain with the use of ‘average response’ measures as read-outs for clinical efficacy,

- **c) tools for monitoring drug effects and safety risks**
  New MS drugs such as FTY720 and various monoclonal antibodies do not allow to measure therapy-relevant pharmacodynamic and pharmacokinetic effects in plasma/serum, leading to uncertainty regarding optimal dose and dose interval. Further, many of those compounds have more severe side effects as compared to standard therapies; some of them are of idiosyncratic nature. Both features represent a challenge for the successful pursuit of clinical trials.

We will discuss novel imaging techniques that may be able to address questions around neurodegeneration, both from the mechanistic aspect and for longitudinal quantitation. A second focus will be on connecting biofluid markers and imaging findings (‘imaging genomics’) that allow refining disease endophenotypes.