The project aims to advance the measurability of disease progression at early stages of neurodegenerative diseases: Huntington's disease (HD), spinocerebellar ataxia (SCA) and motor neuron disease (MND). In order to unequivocally identify patients in early and even pre-symptomatic stages, we selected genetic neurodegenerative disorders with high penetrance. We will focus on repeat expansion disorders (REDs), characterized by dynamic expansion mutations. Prior studies suggest that quantitative measurements are essentialto detect subtle change reliably and determine change rates. Subtle speech impairment develops in the prodromal stages of REDs prior to the emergence of diagnostic motor signs. Therefore, quantitative analysis of speech alterations may represent an excellent candidate as a state and progression biomarker in several neurodegenerative disorders. *Acoustic speech analysis* is a reliable and sensitive method that objectively determines the degree of speech impairment. The study will define target acoustic parameters (TAPs) as potential state and progression biomarkers. The project aims to investigate speech changes in pre-symptomatic, prodromal, and manifested patients and their correlation to other quantitative motor measures of disease severity. We will establish the rate of change of quantitative speech parameters based on longitudinal analysis. Using a novel, interactive digital smartphone application, we will explore their robustness and reliability using hospital and home-based speech assessments. In addition, we will compare TAPs head-to-head with structural brain alterations (disclosed through magnetic resonance imaging (MRI) and atlas-based volumetry (ABV)) and a plasma-derived fluid candidate biomarker, NfL. To improve the understanding of underlying disease mechanisms, we will explore the impact of somatic expansion rates on these quantitative progression marker candidates. To this end, we will determine leukocytes/blood somaticexpansion indices (SEI) and estimate annual somatic expansion rates (SER). In a population carefully selected to display a broad range of SERs, we will correlate the rate of change of the quantitative traits with SERs. In addition, we will explore the responsiveness of quantitative progression marker (QPM) candidates in HD by taking advantage of ongoing clinical trials aimed at silencing the mutant huntingtin gene. This project will deliver experimental data to further qualify quantitative analysis of speech alterations, thus advancing the progression's measurability for the early stages of REDs. Furthermore, we will gain insights into mechanisms driving disease progression at early stages of REDs by relating change rates to somatic instability of repeat expansion and responsiveness to lowering the burden of mutant gene products.