Under the sponsorship of the Michael J Fox Foundation, since 2006 we have been engaged in a comprehensive survey of the CNS and PNS distribution of alpha-synuclein pathology (ASP) in subjects with Lewy body diseases (LBD). A necessary concurrent initiative has been to evaluate the sensitivity and specificity of immunohistochemical methods together with observer variability and accuracy. The first phase of work culminated in the Unified Staging System for Lewy Body Disorders (USSLB), as prior CNS LBD staging systems failed to classify large percentages of subjects and provided only ambiguous instructions for stage assignment. The olfactory bulb-only stage was identified as the probable first stage for all LBDs, with subsequent divergent pathways through the limbic brain regions for those destined for dementia with Lewy bodies (DLB) or Alzheimer’s disease with Lewy bodies, or through the brainstem for those destined for Parkinson’s disease (PD). The USSLB is suitable for staging all types of LBDs and is a significant predictor of both cognitive and motor dysfunction. The second phase established the PNS prevalence of ASP in LBDs. No subjects have had PNS pathology in the absence of CNS pathology, consistent with an initial localization in the CNS. Vagus nerve and sympathetic ganglia are the most likely PNS sites to be affected, followed by the gastrointestinal (GI) tract, with the latter having a rostrocaudal gradient of involvement. The submandibular gland (SMG) was identified as the most frequently affected GI location, and its suitability for needle biopsy prompted two studies with promising results in living PD subjects. As published studies from multiple different groups across the world were producing conflicting results for biopsies of skin, colon and other body regions, multi-center groups were established to conduct blinded-panel assessments of colon, skin and SMG ASP in both autopsy and biopsy tissue. Results from the colon autopsy group indicated that, with adequate tissue volumes and judge training, biopsies had potential for diagnostic usage but were severely limited by low submucosa volume. The S4 study, currently underway, is comparing sensitivity and specificity of ASP IHC in colon, skin and SMG biopsies from 60 PD and 20 control subjects. Judges received comprehensive training and will independently and blindly assess samples with final decisions based on majority opinion. If a biopsy site with sufficient sensitivity and specificity is identified, PNS ASP would be poised to become a useful biomarker for clinical trial molecular target engagement and subject selection.