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Research Summary

A major barrier to delivery of effective treatment for NPC disease has been significant delays in diagnosis (> 5 years) due to the lack of an inexpensive, reliable and easy to use test for diagnosis. We have developed a highly sensitive and specific clinical diagnostic assay for NPC disease based on an oxysterol biomarker. This assay is at various stages of implementation in over two-dozen laboratories worldwide and is replacing filipin staining of fibroblasts as the diagnostic standard. Our continued biomarker efforts have led to discovery of an even more sensitive blood marker that may have significant advantages over the oxysterol marker, including ease of detection and simplification of the diagnostic assay. The latter will help with dissemination of the assay into clinical laboratories and accelerate adoption of this new blood test. This new blood marker also has significant potential to facilitate development of a newborn screen. A newborn screen would enable for the first time routine initiation of drug therapy in pre-symptomatic NPC patients, the group that would benefit the most from early medical treatment.

We have developed a two-tier LC-MS/MS newborn screening method for NPC disease using the most sensitive marker. The method was fully validated in accordance with FDA guidelines with respect to selectivity, sensitivity, precision, accuracy, and stability. We analyzed dried blood spots from 1013 control, 130 carrier and 25 NPC1 subjects to establish a cutoff, which provides a sensitivity of 96% and specificity of 100% in identifying NPC1 patients, and was able to distinguish carriers from NPC1 patients with high specificity. The cutoff has been validated by analysis of a second set of DBS samples including 4992 normal newborns, 130 NPC1 carriers, and 65 NPC1 patients. The screening showed exceptional performance - 100% positive and 99.98% negative predictive for discrimination of NPC1 subjects from controls and NPC1 carriers. The data indicate excellent potential for the use of this marker in NPC1 newborn screening, which may enable routine early intervention before onset of clinical disease. In addition, the assay showed potential for screening of NPB disease.