In this issue of Clinical Chemistry, a group led by Miao He at Emory University describes a new method for the qualitative profiling of free oligosaccharides and other glycoaminocids in urine samples (1). The analytical platform is MALDI-TOF mass spectrometry, a technology that is making a rapid transition from an elite proteomics research tool to a diagnostic tool broadly adopted in laboratory medicine, particularly in clinical microbiology (2). The authors have successfully targeted 11 different lysosomal disorders that have very similar clinical presentations and are virtually indistinguishable in the first few months of life, when a diagnostic evaluation is likely to take place. Notably, the authors have provided a clear and objective road map to the interpretation of abnormal profiles. Table 1 of this report is a truly fundamental contribution that should pave the way to rapid implementation of this method as well as objective and consistent interpretation of clinical results. This outcome has been hardly the case for the last 4 decades. Indeed, the significance of this report cannot be fully appreciated by readers who have not experienced in their laboratory practice the challenging task of interpreting thin-layer chromatography (TLC)2 plates of urinary oligosaccharides (3). Even under the best circumstances, factors like intrinsic poor resolution, nuances in shades of color, rapidly fading bands, and a multitude of poorly characterized drug and nutritional artifacts represent real and constant challenges. The personal experience of the laboratory scientist performing the interpretation has been the single most important factor, and the reason why TLC of urinary oligosaccharides has been regarded more as a subjective art instead of an objective, evidence-based science as it should be in clinical practice. Equivocal profiles often trigger inconsistent behaviors spanning between 2 extremes, on one hand the overcalling of “positive” results followed by unnecessary repeat analyses and highly esoteric (and scarcely available) in vitro testing, and on the other the frequent failure to recognize actual pathological patterns. These false-negative events are likely to perpetuate a diagnostic odyssey after a number of lysosomal disorders have been incorrectly excluded from the differential diagnosis of an affected patient.

Specific features of this work that should be highlighted are the reported ability to biochemically distinguish galactosialidosis [Online Mendelian Inheritance in Man (OMIM) #256540] from sialidosis (OMIM #256550) and to more reliably detect mucolipidosis II/III (OMIM #252500/252600/252605) and especially asparylglucosaminuria (OMIM #208400), previously a very difficult diagnosis to make in early childhood. There is, of course, room for future improvements. It remains to be seen if this method can consistently differentiate GM1 gangliosidosis (OMIM #230500) from mucopolysaccharidosis type IVB (Morquio disease, OMIM #253010) and Sandhoff disease (OMIM #268800) from Tay-Sachs disease due to AB and B1 variants (OMIM #272750 and #272800), as well as different subtypes of Gaucher disease (OMIM #230800, #230900, #230100, and others). The possibility of detecting Schindler disease (OMIM #609241) and β-mannosidosis (OMIM #248510), a condition known to remain undetected by TLC analysis (3), has not been explored yet.

This method could also benefit from additional postanalytical data processing. Instead of using a basic qualitative measure of relative abundance, raw peak intensity data could be used to calculate ratios between different oligosaccharides, both pathological and physiologically present species. This approach has been applied to the analysis, for example, of transferrin isoform species performed with on-line immunooaffinity electrospray ionization mass spectrometry (4) for the biochemical diagnosis of another very challenging group of metabolic disorders, the congenital disorder...
of glycosylation (5). This approach could offer a more effective strategy to pursue the goal stated by the authors of correlating urinary patterns to clinical severity. Adding a prognostic dimension could make this assay even more attractive, and of course could provide the foundation for biochemical monitoring of new experimental therapies. Finally, it would be very appealing to foster collaboration and data sharing between multiple laboratories to create condition-specific disease ranges and eventually allow stratification of affected cases on the basis of clinical severity. A model that could be followed is what has been accomplished recently for expanded newborn screening by tandem mass spectrometry (6). Such an initiative could eventually lead to the implementation of postanalytical tools (7) with the potential to perform automated pattern recognition and interpretation of profiles that retain a high degree of complexity. The availability of these tools to support routine clinical practice could become a determining factor toward a favorable decision to make the sizeable investment necessary to acquire a MALDI-TOF instrument used primarily, if not exclusively, for clinical applications.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.
Patents: P. Rinaldo, patent number 07039-1191P01/2012-165.

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