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Letter to the Editor

Misinformation regarding tandem mass spectrometric vs fluorometric assays to screen newborns for LSDs

Sir – Newborn screening (NBS) programs are actively considering investment in one of two available platforms for multiple lysosomal storage disease (LSD) enzyme testing – tandem mass spectrometry (MS/MS) or digital microfluidic fluorometry (DMF) system. Both use reagent kits supplied by commercial vendors (Perkin-Elmer Life Sciences and Baebies, Inc., respectively) that are inexpensive and readily available. However, the enormous cost differential for infrastructure, capital investment, personnel and ongoing maintenance between MS/MS and DMF is difficult to justify unless there is substantial evidence of superior performance by the more expensive platform (MS/MS) [1]. We are alarmed that proponents of MS/MS repeatedly make claims to that effect without relevant supporting evidence [1–4]. The clinical decision point (high risk for an LSD) is made near the LSD assay's low limit of quantification, where pre-analytical factors, including leukocyte count, pseudodeficiency alleles and sample quality cause low enzyme activity that overlaps the high-risk range [5]. In this context, the "analytical/dynamic range" of a method [3,4] is irrelevant; the appropriate metric for assay performance is the ability to discriminate normal from confirmed positive cases when screening prospectively. Rich data sets (Table 1) are available from two programs screening for LSDs prospectively: Missouri (DMF) [6] and Illinois (UPLC-MS/MS) [7]. These and more recently presented data [8,9] do not support claims of superior performance by MS/MS. Particularly noteworthy is that the confirmatory rate reported for Fabry disease in Illinois using MS/MS was lower than in an earlier pilot in Illinois using DMF [10]; the latter rate being similar to that reported in neighboring Missouri. We conclude that DMF is at least as effective as MS/MS for high throughput screening of multiple LSDs and recommend that NBS programs consult the Missouri and Illinois programs as part of their due diligence before making a decision that will affect their costs for many years to come.

Table 1
Summary of published results for Fabry disease, Pompe disease, Gaucher disease and Hurler syndrome (MPS I) from programs prospectively screening for multiple LSDs. Generally, DMF has lower false-positive rates and significantly higher PPVs compared with MS/MS. Confirmed positive cases include infantile onset, late onset and undetermined phenotypes (e.g. genotype of unknown significance, unknown onset). Positive predictive value (PPV) is calculated as: the number of confirmed positive/ number of (normal + carrier + pseudodeficient).

	GAA (Pompe)		IDUA (MPS I)		GLA (Fabry)		GBA (Gaucher)	
	MO (DMF)	IL (MS/MS)	MO (DMF)	IL (MS/MS)	MO (DMF)	IL (MS/MS)	MO (DMF)	IL (MS/MS)
Total infants	175,000	63,007	175,000	63,007	175,000	63,007	175,000	63,007
Screen Positives	**84**	**54**	**51**	**48**	**110**	**40**	**20**	**38**
Pending	5	11	1	17	11	19	0	4
Normal	32	26	15	22	43	15	13	27
Carrier	15	8	4	1	0	0	2	0
Pseudodeficient	14	4	29	5	0	0	0	0
Confirmed Positive	**17**	**6**	**1**	**1**	**51**	**4**	**4**	**1**
Refused/Lost to follow-up/Died	1	3	1	2	5	2	1	6
PPV	22%	14%	2%	3%	54%	21%	21%	4%
False positive rate	0.03%	0.06%	0.03%	0.04%	0.02%	0.02%	0.01%	0.04%
Estimate false positive per 100,000	35	60	27	44	25	24	9	43

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