was submitted to both the fluorometric assay with 6-hexadecanoylamino-4-methylumbelliferylphosphorylcholine (HMU-PC) (3) and to the MS/MS assay with C6-sphingomyelin (2). As shown in Fig. 1 (left panel), the fluorescence response was approximately 3-fold higher in culture medium from cells expressing wild-type acid sphingomyelinasin than in medium from nontransfected cells (treated with transfection reagent but no plasmid DNA added). With medium from cells expressing the Q292K mutant, the fluorescence response was approximately 5-fold higher than the response with nontransfected cells. This higher activity of the Q292K mutant is consistent with the earlier study using fibroblast lysates from patients harboring the Q292K mutation (4). The results show that the Q292K shows high activity on HMU-PC.

Fig. 1 (right panel) shows the assay results using C6-sphingomyelin and the MS/MS assay. Because these were transfected cells, we did not convert the observed MS/MS response to the standard activity (i.e., μmol product per hour per mg cell protein). Rather, we show the ratio of acid sphingomyelinase product MS/MS ion counts to internal standard MS/MS ion counts. Assays contained a known amount of internal standard, a close analog of the product, but with a shorter fatty acyl chain (C4-sphingomyelin). The product/internal standard ratio was approximately 4.5-fold higher when culture medium from cells transfected with wild-type acid sphingomyelinasin was used compared to culture medium from nontransfected cells. In contrast, the Q292K mutant displayed essentially no activity in the MS/MS assay. Thus, the MS/MS assay with C6-sphingomyelin gave an activity with the Q292K mutant similar to that reported using the radiometric assay with natural sphingomyelin (approximately 2% of normal activity) (4).

In conclusion, the MS/MS assay for acid sphingomyelinase should provide more reliable newborn screening and diagnosis for Niemann-Pick-A/B than that provided by the fluorometric assay. The use of the fluorometric assay may lead to a substantial number of missed cases (false negatives) due to the Q292K mutation. The MS/MS assay will be useful in laboratories not able to use radiometric assays. At the very least, if the fluorometric assay is used, 2 independent assays for each sample need to be carried out in the presence and absence of the natural substrate sphingomyelin as noted previously (3).

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References


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Performance of 10 Systems for Self-Monitoring of Blood Glucose by Trained Healthcare Professionals and in the Hands of the Users

To the Editor:

Accurate and reproducible blood glucose results are important for adequate therapeutic decision for people with diabetes. Few studies assessing the accuracy of systems for self-monitoring of blood glucose (SMBG)1 systems against the requirements from the International

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1 Nonstandard abbreviations: SMBG, self-monitoring of blood glucose; ISO, International Organization for Stan-
dardization; FDA, US Food and Drug Administration; BLS, biomedical laboratory scientist; SKUP, Scandina-
vian evaluation of laboratory equipment for primary health care.
Letters to the Editor

Organization for Standardization (ISO) standard 15197:2013 (1) have been published, and none of them has addressed analytical quality in the hands of the users. To our knowledge, no studies have evaluated SMBG systems against the requirements for accuracy in the new US Food and Drug Administration (FDA) draft guidance for SMBG systems for over-the-counter use (2). The aim of this study was to assess the accuracy of 10 SMBG systems under optimal conditions achieved by biomedical laboratory scientists (BLSs) and by people with diabetes against the minimum accuracy requirements specified in ISO 15197:2013, ISO 15197:2003, and FDA draft guidance.

We used data from 10 SMBG system evaluations performed from 2005 to 2013 by the Scandinavian evaluation of laboratory equipment for primary healthcare (SKUP). The evaluations were carried out in line with common guidelines and standardized protocols according to international recommendations. All measurements on each SMBG system were compared with a glucose hexokinase method. Standard reference material from the National Institute of Standards and Technology was used to secure traceability of the comparison method. Detailed reports from each evaluation including recruitment of individuals with diabetes, design of the evaluations, lot numbers, information about reagents and dates of expiration, and traceability of the comparison method can be found at SKUP’s web page (www.SKUP.nu). General approval for the evaluations was obtained from the Norwegian Regional Committee for medical research. We calculated the percentage of results within the limits for minimum requirements for accuracy from ISO 15197:2013 (1) and FDA (2). A description of calculation of imprecision and bias can be found at www.SKUP.nu. Statistical significance was set to 5%.

All the SMBG systems except GlucoMen LX fulfilled the minimum requirements for accuracy from ISO 15197:2013 (1) and the FDA draft guidance (2) when the measurements were performed by a BLS (Table 1). When people with diabetes performed the measurements, 6 of the 10 SMBG systems fulfilled the minimum requirements from ISO 15197:2013 and FDA (Table 1). All SMBG systems fulfilled the minimum requirements for accuracy from ISO 15197:2003 when the measurements were performed by both BLSs and people with diabetes (Table 1).

The repeatability (CV) of all the SMBG systems obtained by BLS under optimal conditions was below a recommended limit of 5%. When people with diabetes performed the measurements, all SMBG systems except Dana DiabeCare II SG and GlucoMen LX had a CV < 5%. Significant bias from the comparison method varied between −5.9% and +7.7% depending on the SMBG system and glucose level. There was no overall correlation between the year of evaluation and mean precision or bias.

Our accuracy results are in accordance with a study published in 2014 evaluating 12 SMBG systems against the accuracy requirements in ISO 15197:2013 (3). However, that evaluation was performed in a laboratory by trained clinical personnel under controlled conditions and not by intended users.

In the present study, all 10 SMBG systems met the minimum accuracy requirements from ISO 15197:2003, which are less strict than the minimum requirements in ISO 15197:2013 (Table 1). In a study performed in 1998, none of the 5 SMBG systems tested fulfilled the minimum requirements in ISO 15197:2003 in the hands of the user, and only 2 of the 5 SMBG systems met the requirements when the measurements were performed by a BLS (4). Three of 9 SMBG systems did not fulfill the requirements in ISO 15197:2003 in a study performed between 2004 and 2006, whereas all met the minimum requirements when BLSs did the measurements (5). Thus, it seems that SMBG systems have become more user-friendly: the difference between trained personnel and end users is less in the present study compared with previous studies (4, 5).

In conclusion, we show that 9 of the 10 SMBG systems fulfilled the minimum requirements for accuracy specified in ISO 15197:2013 and in the FDA draft guidance when BLSs performed the measurements. Furthermore, 6 of the 10 SMBG systems fulfilled the requirements when people with diabetes performed the measurements. Comparison of the data reviewed here with earlier published data suggests that the analytical quality and user-friendliness of the SMBG systems have improved over the last 10–16 years.

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.

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References


### Table 1. Assessment of accuracy for SMBG systems according to ISO 15197:2003, ISO 15197:2013, and FDA draft guidance as performed by BLSs and people with diabetes.

<table>
<thead>
<tr>
<th>SMBG system</th>
<th>Manufacturer</th>
<th>Year/SKUP evaluation no.</th>
<th>Measurement performed by:</th>
<th>Results within ISO 15197 limits (%)</th>
<th>Results within FDA limits (%)</th>
<th>95% &lt;15%</th>
<th>99% &lt;20%</th>
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<tr>
<td>Accu-Chek Aviva</td>
<td>Roche Diagnostics</td>
<td>2005/44</td>
<td>BLS</td>
<td>n</td>
<td>Yes (99)</td>
<td>Yes (96)</td>
<td>Yes (96)</td>
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<td></td>
<td></td>
<td>2005/44</td>
<td>People with diabetes</td>
<td>75</td>
<td>Yes (99)</td>
<td>No (93)</td>
<td>No (93)</td>
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<tr>
<td></td>
<td></td>
<td>2013/98</td>
<td>BLS</td>
<td>90</td>
<td>Yes (99)</td>
<td>Yes (98)</td>
<td>Yes (98)</td>
</tr>
<tr>
<td>Accu-Chek Mobile</td>
<td>Roche Diagnostics</td>
<td>2009/74</td>
<td>BLS</td>
<td>86</td>
<td>Yes (100)</td>
<td>Yes (98)</td>
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<td></td>
<td></td>
<td>2009/74</td>
<td>People with diabetes</td>
<td>86</td>
<td>Yes (99)</td>
<td>Yes (97)</td>
<td>Yes (95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2013/99</td>
<td>BLS</td>
<td>90</td>
<td>Yes (98)</td>
<td>Yes (96)</td>
<td>Yes (96)</td>
</tr>
<tr>
<td>Ascensia BREEZE</td>
<td>Bayer Healthcare</td>
<td>2007/59</td>
<td>BLS</td>
<td>77</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
<td>Yes (99)</td>
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<td></td>
<td>2007/59</td>
<td>People with diabetes</td>
<td>75</td>
<td>Yes (100)</td>
<td>Yes (97)</td>
<td>Yes (97)</td>
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<td>Contour XT</td>
<td>Bayer Healthcare</td>
<td>2012/94</td>
<td>BLS</td>
<td>82</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
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<tr>
<td></td>
<td></td>
<td>2012/94</td>
<td>People with diabetes</td>
<td>82</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
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<tr>
<td>DANA DiabeCare IISG</td>
<td>SOOI Development Co.</td>
<td>2008/66</td>
<td>BLS</td>
<td>83</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
<td>Yes (98)</td>
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<tr>
<td></td>
<td></td>
<td>2008/66</td>
<td>People with diabetes</td>
<td>83</td>
<td>Yes (98)</td>
<td>No (94)</td>
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<tr>
<td>FreeStyle Lite</td>
<td>Abbott Diabetes Care</td>
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<td></td>
<td>2007/64</td>
<td>People with diabetes</td>
<td>76</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
<td>Yes (99)</td>
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<tr>
<td>GlucoMen LX</td>
<td>Menarini Diagnostics</td>
<td>2009/71</td>
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<td>84</td>
<td>Yes (99)</td>
<td>No (92)</td>
<td>No (91)</td>
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<tr>
<td></td>
<td></td>
<td>2009/71</td>
<td>People with diabetes</td>
<td>84</td>
<td>Yes (96)</td>
<td>No (94)</td>
<td>No (94)</td>
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<td>Mendor Discreet</td>
<td>Mendor Oy</td>
<td>2012/95</td>
<td>BLS</td>
<td>79</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
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<tr>
<td></td>
<td></td>
<td>2012/95</td>
<td>People with diabetes</td>
<td>79</td>
<td>Yes (99)</td>
<td>Yes (96)</td>
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<td>mylife Uno</td>
<td>Ypsomed Bionime</td>
<td>2013/100</td>
<td>BLS</td>
<td>81</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
<td>Yes (100)</td>
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<tr>
<td></td>
<td></td>
<td>2013/100</td>
<td>People with diabetes</td>
<td>81</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
<td>Yes (98)</td>
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<tr>
<td>OneTouch Verio</td>
<td>LifeScan, Johnson &amp; Johnson</td>
<td>2011/86</td>
<td>BLS</td>
<td>87</td>
<td>Yes (100)</td>
<td>Yes (99)</td>
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<td></td>
<td>2011/86</td>
<td>People with diabetes</td>
<td>87</td>
<td>Yes (99)</td>
<td>No (91)</td>
<td>No (91)</td>
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</tbody>
</table>

* Minimum requirement: 95% of the results must be within 15 mg/dL (0.83 mmol/L) at glucose concentrations <76 mg/dL (<4.2 mmol/L) and within 20% at glucose concentrations ≥76 mg/dL (≥4.2 mmol/L) vs a comparison method.

* Minimum requirement: 95% of the results must be within 15 mg/dL (0.83 mmol/L) at glucose concentrations <100 mg/dL (<5.55 mmol/L) and within 15% at glucose concentrations ≥100 mg/dL (≥5.55 mmol/L) vs a comparison method.

* 95% of all SMBG results must be within 15% of the reference measurement and 99% of all SMBG results must be within 20% of the reference measurement.

* Reexamined in a second evaluation by BLS after a modification of the test strip chemistry.