Laboratory Evaluation of New Reusable Blood Glucose Sensor

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An enzyme-electrode sensor designed specifically for pocket-portable self-monitoring of blood glucose is described. The sensing device in this instrument is unique because it is reusable for at least 30 days, at which time it is easily replaced by placing a new enzyme-membrane cartridge over the electrode. As little as 7 μl of undiluted whole blood, plasma, or serum is applied directly to the sensor, and glucose is automatically determined in 30 s. No manual timing or wiping step is required after sample application. On eight production instruments, plasma glucose concentration was determined (n = 20) at 57, 125, 246, and 347 mg/dl. The average coefficient of variation for the 80 determinations for each instrument ranged from 2 to 5%, averaging 3.7%. The instrument is inherently linear, independent of hematocrit, and without oxygen limitation when dissolved oxygen concentration is >35 mmHg. No interferences were found from plasma constituents, heparin, or acetaminophen. *Diabetes Care* 11:801–807, 1988

The technology of reagent-strip reflectance photometry has improved sufficiently to make self-monitoring of blood glucose clinically useful. However, there are inherent difficulties with this technology. It is technique sensitive (1–5), and calibration at the factory may drift in the field (2). Each determination consumes another strip; therefore, users avoid recalibration or testing control solutions because of the expense. Plasma proteins and the formed cellular elements in the blood cause interference (5–8). For example, Glucometer II results were recently reported 19–30% falsely high at hematocrit 20% and 37–43% falsely low at high hematocrit (5).

A comprehensive study of reagent-strip technology on five instruments reported 35–70% of blood glucose estimates were ≤85% of the clinical laboratory reference value until a 1.12 correction factor was used to bring whole-blood estimates up to the serum values obtained in the clinical laboratory (8). A more recent study reported similar worrisome deviation from the reference method in five of seven reagent-strip methods studied (7). The problem is caused by the lower glucose concentration found inside the erythrocyte (9) and/or interference caused by the presence of erythrocytes when using a reflectance photometer.

Our goal has been to develop an analytical system that improves on the performance of, and eliminates the difficulties typically found with, reagent-strip methods. To eliminate technique-sensitive steps such as wiping or blotting, we developed an automated analytical system that determines glucose directly from the applied sample. To facilitate comparison with glucose determined in the clinical laboratory, our device was designed to directly measure glucose in the plasma of the sample without interference from erythrocytes. Thus, our method responds in the same way to glucose whether the sample is whole blood, serum, or plasma and estimates the value obtained from the clinical laboratory without the necessity of using a hematocrit-dependent correction factor.

Finally, we wanted calibration to be quick and simple and without additional cost to the patient. This was achieved by making the sensor reusable for at least 30 days. The sensor is electrochemically based with an optimized version of the well-known glucose oxidase enzyme electrode (10–12).

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MATERIALS AND METHODS

Instrumentation. The enzyme-electrode sensor with controlling electronics was designed and developed in our laboratory and mass-produced by Markwell Medical (Racine, WI). The proprietary membrane system is multilayered and fine-tuned to provide maximum rejection of interferences while maintaining linearity of glucose signal to 500 mg/dl. Signal development is partly based on the amperometric detection of hydrogen peroxide by a rate method (11).

Each instrument kit includes a solution to initially wet the electrode surface, an enzyme-active membrane that snaps easily over the electrode, a 200-mg/dl glucose-calibration solution, and a solution used both to clean the sensor's membrane surface and to maintain hydration of the sensor membrane between glucose determinations. A tightly fitting, hinged cover prevents evaporation or spillage of the solution between glucose determinations, thereby making the instrument pocket portable.

A drop of blood obtained by lancing a fingertip is applied to the sample well as shown in Fig. 1. The sample well of the electrode sensor was designed to accept an undiluted 7- to 50-μl sample of plasma, serum, or whole blood.

The instrument is operated by pressing the button on the front panel. The user follows instructions given on the liquid crystal display (LCD). The LCD first instructs the user to dry the well by blotting with tissue and then indicates readiness to accept either a blood sample or the instrument-calibration solution. Application of either is automatically detected, and signal analysis is triggered. Within 30 s, the LCD reads out the blood glucose value or the status of the calibration acceptance. No user timing or wiping steps are required during analysis. The LCD then prompts the user to dry the well containing the blood sample and fill it with cleaning (storage) solution. The button is then pressed one final time to turn off the display (shutdown will automatically occur within 3 min if the user forgets).

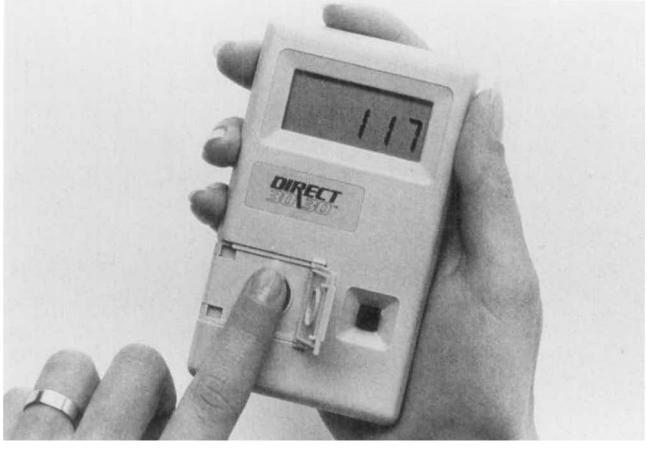

FIG. 1. Pocket-portable blood glucose analyzer.

The user can check the performance of the instrument anytime by placing a drop of the calibration solution in the sample well instead of the blood sample requested by the LCD. Unless the instrument correctly reads out a value for the calibration solution within ±15% (170–230 mg/dl), the user should recalibrate. In addition, at least once every 22 h the instrument forces the user, through a prompt on the LCD, to recalibrate the system by requesting calibration solution instead of a blood sample. The instrument sensor is reusable for at least 30 days at which time the LCD requests that a fresh enzyme-active membrane-lid assembly be snap-fitted into place. The old assembly is then discarded.

Plasma glucose standards. Zero plasma glucose was prepared from heparinized (14,000 U/L) normal human blood obtained by venipuncture with sterile technique. The whole blood was gently shaken and kept at room temperature for enough time to allow the glucose concentration to decay by glycolysis to zero. The plasma was obtained by centrifugation and shown to contain <2 mg/dl glucose by the Du Pont ACA hexokinase standard clinical laboratory method (13). The plasma was stored frozen until used. To obtain plasma glucose standards over the range from 40 to 400 mg/dl, known amounts of anhydrous D-glucose were added to known volumes of this plasma, and the targeted glucose values were confirmed by duplicate testing on the Du Pont ACA. This standard glucose method has a coefficient of variation (C.V.) of 0.7% (13).

Whole-blood glucose standards. Heparinized whole-blood samples were similarly adjusted to give values in the clinically relevant range. All whole-blood samples were assayed within 30 min, and the initial and final glucose values were checked by ACA analysis of plasma samples obtained by centrifugation.

Cleaning and storage solution. Tenth molar NaCl was phosphate-buffered (0.033 M) and adjusted to a pH of 7.05. Both thimerosal and EDTA were added as preservatives at a final concentration of 0.01%.

Calibration solution. Glucose was added to the isotonic phosphate-buffered cleaning and storage solution described above to make its final glucose concentration 200 mg/dl.

Evaluation of interferences. Uric acid (10 mg/dl), ascorbic acid (5 mg/dl), creatinine (15 mg/dl), heparin (40 U/dl), and acetaminophen (3 mg/dl) were individually added to plasma samples to produce high clinically relevant levels. High lipid (1350 mg/dl triglycerides; 540 mg/dl cholesterol) and bilirubin (direct 14.7 mg/dl; total 24.6 mg/dl) samples were obtained directly from hospital laboratory samples. In all cases, plasma glucose was adjusted to ~200 mg/dl (actual values determined by ACA) and then run in triplicate on the enzyme-electrode instrument.

To test for interference from any of the numerous low and high molecular weight components of plasma, a glucose standard (200 mg/dl) was prepared by addition

TABLE 1
Percent coefficient of variation for eight glucose instruments at various glucose concentrations

Instrument number	Glucose concentration (mg/dl)				Average C.V. for each instrument (%)
	57	125	246	347	
1	6.7	2.5	6.0	4.8	5.0
2	6.8	3.0	5.6	2.3	4.4
3	10.5	4.6	2.0	1.9	4.7
4	7.2	3.9	3.2	4.2	4.6
5	2.7	2.8	1.6	2.4	2.4
6	7.0	5.3	1.8	2.5	4.2
7	5.8	1.8	1.6	2.3	2.9
8	3.0	1.5	1.7	1.9	2.0
Average C.V. for each glucose concentration (%)	6.2	3.2	2.9	2.8	3.7

Values are percent coefficients of variation (C.V.s) for $n = 20$ at each glucose concentration for each instrument.

of a gravimetrically determined amount of glucose to pH 7.05 phosphate-buffered isotonic saline solution and compared to a similar glucose standard made from glucose-depleted pooled human plasma.

Determination of accuracy, precision, and sensor lifetime. Eight representative instruments were selected at random from 300 instruments that passed initial product qualification testing. The instruments were used for replicate plasma tests at four glucose levels during an 8-h period. Each glucose concentration was determined 20 times on each instrument. The cleaning solution was applied for ≥150 s between each sample application. This time interval ensured that ≥95% of the previous sample signal had decayed before the next sample application. The worst case of changing glucose concentrations from high (400 mg/dl) to low (50 mg/dl) can result in a maximum negative error of 5–10 mg/dl. Sample size was between 7 and 50 μl.

The test of accuracy and precision was performed at sensor lifetimes of 2 and 6 wk. In addition, sensors tested through 6 wk by our diabetic users group had undergone ~300 sample applications. Representative units were further tested through 500 samples to ascertain no degradation in accuracy or precision. The sensor was stressed to twice the predicted maximum usage of a typical diabetic patient over a 30-day period.

Effect of hematocrit. Heparinized whole blood was gently centrifuged to allow separation of most of the plasma from erythrocytes, then mixed in the appropriate ratios to provide hematocrits of 0, 15, 30, 45, and 65%. Glucose was adjusted to give values of 72, 146, and 298 mg/dl as measured with the ACA hexokinase method (13). Triplicate glucose determinations of each of the 15 samples were made on each of four representative enzyme-electrode instruments.

Effect of sample size. Micropipetted sample volumes of 5, 7, 10, 25, and 50 μl (Gilson model Pipetman) of glucose standards were analyzed in quadruplicate at glucose concentrations of 65, 125, 200, 250, and 350 mg/dl.

Effect of low oxygen tension. To severely test whether oxygen might be limiting (14), we compared the measured glucose value obtained in heparinized whole-blood samples exhibiting elevated glucose levels (250 and 360 mg/dl, ACA reference method) at oxygen tensions of 35–90 mmHg. The lower oxygen tension was obtained by tonometry by use of a gas mixture with P_{O_2} 25 mmHg and P_{CO_2} 40 mmHg with the balance nitrogen. Oxygen tension was verified with a Radiometer BMS3 Mk2 blood gas analyzer (Copenhagen).

RESULTS

Precision. Table 1 presents the data on instrument precision expressed as percent C.V. ($n = 20$) for each of the four blood glucose levels tested for each of the eight instruments. The average C.V. for each glucose concentration and for each instrument is shown. Average C.V. for each instrument ranged from 2 to 5% with a mean of 3.7%.

Accuracy. Figures 2 and 3 are plots generated from the 640 plasma glucose determinations made with the eight glucose sensors. The instruments had membranes that had been in service for 2 wk. Figure 2 shows the distribution of differences from the reference method expressed both as percent difference and absolute difference in milligrams per deciliter. Each of the eight instruments was studied at four different reference glucose values, with 20 determinations performed at each value. Each box and associated data points in Fig. 2 represent these 20 determinations as detailed in the figure legend. Sixty-six (10.3%) of 640 values fell outside ±10% of the reference values. Six (0.9%) of 640 glucose values fell outside ±20% (Fig. 2, *open symbols*). Results of a similar study of these instruments after 6 wk of membrane service were comparable with the average instrument C.V. ranging from 2.7 to 4.5%. At the end of the 500-sample stress test, the worst-case C.V.s were still <8%.

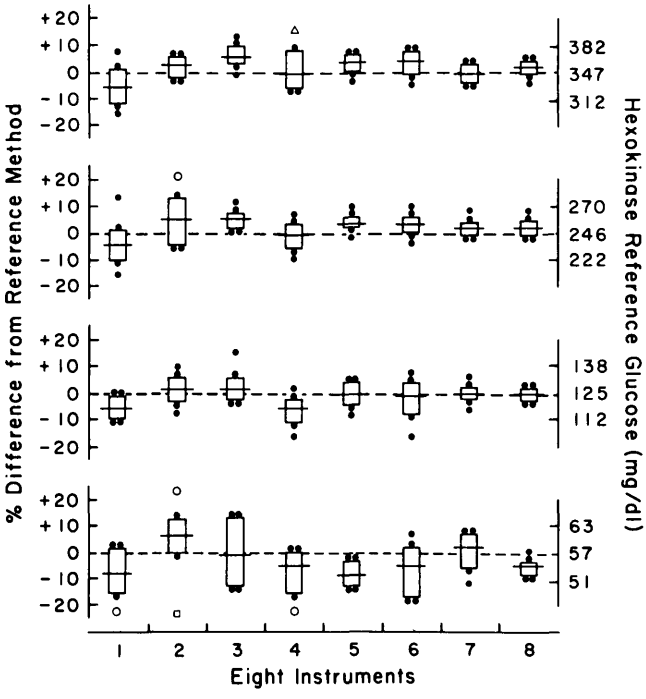

FIG. 2. Distribution of differences from the reference method expressed as percent difference and absolute difference. Each *box* represents 10th–90th percentile or 16 of 20 determinations. Mean for all 20 determinations is shown as *line* across each *box*. ●, Remaining 4 determinations, which lie outside 10th–90th percentile. Six of 640 determinations were outside ±20% (*open symbols*). One determination read low (<40 mg/dl; □), and another determination read high (>400 mg/dl; △).

Figure 3 is a linear least-squares plot of enzyme-electrode glucose values versus reference glucose values for all eight instruments. The slope is 1.029 with an intercept of −4.0 mg/dl glucose and a correlation coefficient of 0.995.

Hematocrit. The relationship between measured blood glucose and hematocrit is shown in Fig. 4. Note that at all three glucose levels, the effect of hematocrit is negligible over the entire hematocrit range of 0–65%.

Interferences. None of the potentially interfering substances tested had an effect of more than ±5 mg/dl on the plasma glucose value obtained by the enzyme-electrode instrument. A 200-mg/dl glucose standard in isotonic phosphate-buffered saline measured 198.4 mg/dl (σ = ±3.2, n = 32). A similar standard at 200 mg/dl dissolved in glucose-depleted plasma measured 200.6 mg/dl (σ = ±3.3, n = 32), giving a difference of only 2.2 mg/dl (1%).

Sample size. At sample sizes of ≥7 μl, the observed signal was constant at all tested glucose concentrations. When sample size dropped to 5 μl and no attempt was made to manually spread the sample, there was a 1 in 5 chance that the observed signal would be up to 25% low. This finding was probably due to the incomplete wetting of the sensor-membrane surface area.

Effect of low Po_2. At the site of immobilized glucose oxidase within the membrane, oxygen needs to be in non-rate-limiting excess. All glucose oxidase–dependent analytical systems require oxygen and can potentially become oxygen limited (14), especially when glucose in the sample is at the upper range of glucose values.

We determined a maximum error of −10% when whole-blood glucose was 360 mg/dl and Po_2 was 35 mmHg. At blood Po_2 >70 mmHg, there was no detectable error due to oxygen limitation for this glucose level. When the glucose level was reduced to 250 mg/dl, there was no observable oxygen error even at the lowest oxygen level tested (Po_2 35 mmHg).

DISCUSSION

The improvements in sensing blood glucose described herein should be attributed to the use of an electrode sensor. In contrast to the reagent-strip photometric sensor, the electrode sensor is not interfered with by the presence or absence of erythrocytes in the sample.

The photometric reagent-strip method senses hydrogen peroxide chromogenically by coupling the reaction to the production of a dye. The user stops the reaction at the appropriate time by wiping or blotting the strip and then places the strip into a reflectance photometer to measure the color change (6,15). The photometer responds not only to the dye but also to the presence or absence of erythrocytes. Thus, there is an hematocrit effect. For example, with the Ames Glucometer II, keeping glucose concentration constant but lowering the hematocrit from 60 to 20% more than doubles the readout of the blood glucose concentration (5). In addition to an optical effect, erythrocytes can also present chemical interferences. For example, erythrocytes have high catalase activity, which can affect the H_2O_2 produced by immobilized glucose oxidase unless there is an outer membrane that excludes such effects. Furthermore, physical surface effects may also play a role by enhanc-

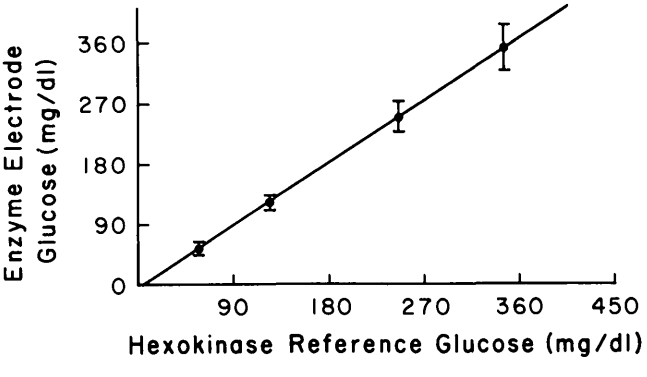

FIG. 3. Linear least-squares plot of 640 plasma glucose determinations made on 8 instruments (slope = 1.029, intercept = −4.0 mg/dl glucose, r = .995). *Bars* show ±2SD.

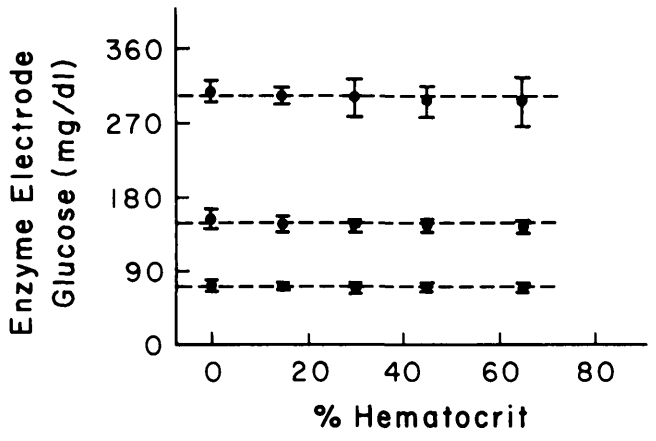

FIG. 4. Electrode-sensor response to 3 levels of glucose concentration at 5 different percent hematocrits. *Bars* show ±2SD. *Dashed lines* show theoretical response if hematocrit has no effect.

ing or preventing hemolysis and the concomitant release of erythrocyte catalase into the sample. In summary, the analysis of the hematocrit effect associated with reagent-strip methods is complex. In this regard, we emphasize that the electrode sensor, as shown by the data presented in Fig. 4, shows no such optical, chemical, or physical effect of hematocrit. Note that these studies were conducted throughout the entire hematocrit range of 0–65%.

Reagent strips are calibrated at the factory and typically used without recalibration by the patient, even though wet recalibration may be recommended by the manufacturer. The more recently introduced reflectance photometers have a built-in ability to adjust to the batch-to-batch variation of strips that occurs during manufacture (16). A bar code containing calibration data is added to each strip at the factory and uncoded by the instrument before use. However, during the interval between factory calibration and patient use, error may be caused by decay in enzyme activity or humidity-mediated hydration of the strips.

Furthermore, the use of a wiping or blotting technique or timing interval different from that used during calibration at the factory may cause error. These differences in techniques also explain some of the variance in accuracy and precision obtained when different laboratory testers use strips with the same lot number (1–3,5).

Once calibrated for whole blood, none of the reagent-strip methods are able to directly determine glucose in plasma or serum. This limitation creates a problem if a pocket-portable blood glucose method is to be periodically compared to glucose determination in the clinical laboratory, where plasma or serum is invariably used instead of whole blood. The enzyme-electrode sensor that we have developed does not have this limitation.

Interferences. Plasma protein can also interfere with reagent-strip methods. When protein is present, less chromogen is generated. This means that the glucose concentration of the aqueous control solution must be lower than the stated calibration level to compensate for the absence of protein. For example, the 130-mg/dl GLUCOSCAN control reagent (Lifescan, Mountain View, CA), as stated in the package insert, actually contains only 65 mg/dl glucose. Unlike plasma or whole blood, this control reagent contains no protein, and thus, about twice as much chromogen is generated. Our sensor does not have this problem. Protein, when present, never enters the membrane covering the electrode, and thus, the presence or absence of protein in the sample or control reagent has no effect on glucose determination.

Similarly, potential small-molecular-weight interferences are eliminated by preventing them from reaching the electrode. This is accomplished by use of a multilayer proprietary polymer/membrane chemistry that protects against such interferences.

In summary, this sensor responds the same to glucose whether formed elements and/or plasma constituents are present or absent. No correction for hematocrit or protein concentration is ever needed. Although a whole-blood sample is applied, the glucose value obtained should be the same as that determined in the clinical laboratory.

Other fundamental differences. Reflectance photometry is inherently nonlinear (15) and requires addition of linear correction terms or an expedient nonlinear function that has constant, linear, and hyperbolic components (6). In contrast, the electrode sensor in our system is inherently linear both in theory and in practice, which simplifies signal processing and calibration (12).

Our instrument is powered by the relatively small Eveready 175 mercury cell. Electrode sensors typically require much less current than the light-emitting, diode-based photometric sensors and this is one of the reasons that our instrument weighs less (3.8 oz) and is smaller (4.5 × 2.7 × 0.6 inches) than any of the 18 different reflectance photometers described by McCall and Mullin (17).

Earlier studies. Before we evaluated the eight production instruments as described herein, we evaluated a similar precursor prototype enzyme-electrode instrument. Performance of this prototype instrument was compared directly with three reagent-strip methods. Glucose was determined in heparinized whole-blood samples obtained from 65 diabetic patients, and the results were referenced against the hexokinase glucose method. The enzyme-electrode method compared favorably with the percent C.V. for both electrode and strip methods measuring 3–7% (18). This prototype instrument was also evaluated by an independent reference laboratory (Folas, Indianapolis, IN) and compared directly with three strip methods (19). Percent C.V.s measured 2–6% with whole-blood samples adjusted to target values of 50, 100, 150, 250, and 350 mg/dl. The performance of the electrode sensor was as good or better than that of the strip methods.

Brooks et al. (1) have recently published a comprehensive study of the performance of reagent-strip technology. Three different reagent-strip methods were eval-

uated. If the data on accuracy and precision generated by our system are compared with data obtained by Brooks, improved performance over the strip methods can be inferred.

Note that Fig. 2 shows 6 of 640 determinations were outside ±20%. These occasional aberrant determinations appear to be due to electromagnetic interference from static discharge near the instrument. This aberrant behavior can actually be simulated by deliberately discharging ionizing static electricity near the instrument at the time of sample application with a Zerostat static generator (Discwasher, Columbia, MO). Fortunately, shielding the instrument in a Faraday cage by applying a conductive coating on the inside surface of the outer case protects the instrument from static discharge. This shielding technique needs to be incorporated into future production runs of the instrument.

Elimination of manual timing (20) and wiping or blotting steps should lead to improved analytical performance. Our instrument detects sample application automatically, which starts a timer within the instrument and initiates a rate-determination process that is performed automatically by the instrument's microprocessor. Once the sample is applied, the entire assay is performed automatically. The glucose concentration is reported in 30 s.

The electrode-based, glucose-sensing system described here is unique in that it is reusable for at least 30 days, during which at least 500 tests can be performed. The instrument was designed to allow ease of calibration and recalibration, which can be performed without additional cost to the patient. This system accepts a smaller sample (7 μl) than is required by most of the reagent-strip technology (1).

In summary, we describe the first enzyme-electrode sensor designed specifically for pocket-portable self-monitoring of blood glucose. Advantages are apparent. No manually performed wiping or timing steps are required. The sensor is reusable for at least 30 days. More evaluation is needed to directly compare this instrument with the reagent-strip reflectance photometric devices. The instrument needs to be evaluated in other laboratories and by more patients.

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Rights to this instrument have been assigned to Markwell Medical, Inc., of Racine, Wisconsin, the industry partner supporting this project. S.J.U. is a consultant to Markwell Medical, and M.C.S. works half-time for Markwell Medical.

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