Analytical and Clinical Evaluation of the NOWDiagnostics ADEXUSDx Human Chorionic Gonadotropin Test Using Whole Blood

Robert D. Nerenz,1,2* Jennifer R. Bell,1 Nancy Montes de Oca,1 Joann Short,3 Theresa Mims,3 Patrick A. Cleeton,4 J. Daniel Moore,3 and Roger L. Humphries3

Background: Point-of-care (POC) urine qualitative human chorionic gonadotropin (hCG) devices are used to rapidly assess pregnancy status, but many of these devices are susceptible to false-negative results caused by increased concentrations of hCG β core fragment (hCGβcf) that does not contain hCGβcf.

Methods: Purified hCG was added to hCG-negative heparinized whole blood to generate samples with known hCG concentrations, and the resulting samples were used to evaluate device sensitivity, low-end reproducibility, high-dose hook effect, intermediate range performance, acceptable sample volume, acceptable hematocrit range, and lot-to-lot variation. Device performance was also prospectively evaluated in 40 pregnant and 40 nonpregnant women aged 18–44 years in a hospital-based clinic or an academic hospital emergency department.

Results: All device observations were positive using a whole blood sample containing a plasma hCG concentration of $2.2 \times 10^6$ IU/L, and all device observations were positive from 18 IU/L to $1.2 \times 10^3$ IU/L and from $2.5 \times 10^4$ IU/L to $2.2 \times 10^6$ IU/L. Three invalid results were observed in the intermediate range because of decreased control line intensity. The minimum sample volume was 30 μL, and maximum hematocrit was 46%. In 40 pregnant and 40 nonpregnant women aged 18–44 years, the device generated 100% concordance with urine qualitative and plasma quantitative test results.

Conclusions: The ADEXUSDx™ hCG test demonstrates acceptable performance for the determination of pregnancy status using capillary fingerstick samples.

IMPACT STATEMENT

Patients undergoing pregnancy testing performed at the point-of-care will benefit from the information presented here. Evidence presented on the performance of the ADEXUSDx™ hCG test will allow better characterization and selection of point-of-care pregnancy test devices. Knowledge in the field of point-of-care pregnancy testing will be advanced by the information presented.

1Department of Pathology and Laboratory Medicine, University of Kentucky Medical Center, Lexington, KY; 2Current affiliation: Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH; 3Department of Emergency Medicine, University of Kentucky Medical Center, Lexington, KY; 4Department of Obstetrics and Gynecology, University of Kentucky Medical Center, Lexington, KY

*Address correspondence to this author at: Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756. Fax 603-650-4845, e-mail robert.d.nerenz@hitchcock.org.

DOI: 10.1373/jalm.2016.020297

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Nonstandard abbreviations: hCG, human chorionic gonadotropin; POC, point-of-care.
Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced by placental trophoblast cells after uterine implantation of a fertilized egg. As a sensitive and specific biomarker of pregnancy, hCG is frequently measured in many healthcare environments to assess pregnancy status before initiating treatment or imaging studies that could harm a developing fetus.

Most often, hCG measurement is performed on urine samples using qualitative point-of-care (POC) devices. These devices are CLIA-waived, facilitate test performance close to the patient, and generate rapid results. Unfortunately, urine qualitative hCG devices are subject to false-negative results in early pregnancy when urinary hCG concentrations fall below the devices' limit of detection and after week 6 of pregnancy due to the “hook effect” caused by high concentrations of hCG variants. Furthermore, collection of urine often delays testing in trauma patients, dehydrated women, or individuals who choose not to provide a urine sample. As an alternative approach, quantitative hCG measurement in plasma or serum can detect pregnancy earlier than urine-based methods and eliminates the risk of false-negative results caused by hCG variants found only in urine. Despite its superior analytical performance, quantitative plasma/serum hCG testing has not been widely adopted for the rapid determination of pregnancy status because it requires transporting the sample to a central laboratory, processing, and analysis, all of which contribute to an unacceptably long turnaround time.

A device that could be used at the POC using a whole blood sample would harness the benefits of plasma/serum-based testing while providing reduced turnaround time relative to central laboratory testing. Some have suggested testing whole blood samples with qualitative hCG devices approved for urine or serum, but using any in vitro diagnostic test in a manner inconsistent with its approved use without performing the necessary validation studies is inappropriate and likely to generate misleading results. Small, handheld instruments are approved for the quantitative measurement of hCG in whole blood, but these instruments are expensive and require refrigeration of reagent cartridges.

The NOWDiagnostics ADEXUSDx™ hCG test is a qualitative immunoassay device approved for the detection of hCG in anticoagulant-free whole blood, heparinized whole blood, or heparinized plasma. In this study, we evaluate the analytical and clinical performance of this device using heparinized whole blood containing purified hCG and anticoagulant-free capillary fingerstick samples obtained from pregnant and nonpregnant women.

**METHODS**

**Device description**

The ADEXUSDx hCG test is a 2-site lateral flow immunoassay that uses a solid-phase anti-hCGα capture antibody and an anti-hCGβ detector antibody. The device is cleared by the US Food and Drug Administration for use with nonanticoagulated whole blood, heparinized whole blood, and heparinized plasma and includes a filter that retains blood cells but allows plasma to flow through to the test area. The manufacturer’s claimed analytical sensitivity is 10 IU/L (as determined by the Abbott Architect assay calibrated to the WHO 3rd International Standard 75/537). After introduction of the patient sample, device results must be interpreted between 10 and 30 min, according to the following criteria: detectable test line and control line = positive result, detectable control line only = negative result, and no detectable control line = invalid result. Lot 1012 (expiration October 31, 2016) was used for all assessments of device performance. Lots 1011 (expiration September 9, 2016) and 1013 (expiration November 30, 2016) were also used in the assessment of lot-to-lot variability.
Reagents

hCG-negative whole blood was collected from nonpregnant volunteers in lithium heparin tubes and stored at 4–8 °C for a maximum of 5 days before use. Purified hCG (≥99% pure; Scripps Laboratories, catalog C0714, expiration October 19, 2017) was stored at −20 °C before resuspension in hCG dilution buffer containing 100 mmol/L Tris and 1 g/L bovine serum albumin, pH 8.0 (Scripps Laboratories, catalog B1011, expiration March 10, 2016). After resuspension at a concentration of 1.3 × 10^7 IU/L, the hCG stock solution was stored at −80 °C and thawed on ice immediately before use. Stock solution concentration was calculated from the manufacturer’s certificate of conformance (Siemens Centaur CP standardized against the WHO 3rd International Standard 75/537).

Validation of analytical sensitivity

Device sensitivity was established using 7 whole blood samples. The stock hCG solution was diluted in hCG dilution buffer to a concentration of 300 IU/L, which was further diluted in human whole blood to give solutions with intended plasma concentrations of 30, 20, 15, 10, 5, 3, and 0 IU/L. Immediately after preparation, each whole blood solution was tested by adding 35 μL to each of 2 ADEXUSDX hCG test devices, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and plasma hCG concentrations were determined to be 27, 17, 13, 8, 4, 2, and 0 IU/L using the Roche e602 hCG+β assay.

Validation of low-end reproducibility

Low-end reproducibility was assessed using 2 whole blood samples. The stock hCG solution was diluted in hCG dilution buffer to a concentration of 300 IU/L, which was further diluted in human whole blood to give solutions with intended plasma concentrations of 30 and 20 IU/L. Immediately after preparation, each whole blood solution was tested by adding 35 μL to each of 10 ADEXUSDX hCG test devices, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and plasma hCG concentrations were determined to be 28 and 18 IU/L using the Roche e602 hCG+β assay.

Validation of high-dose hook effect

Susceptibility to the high-dose hook effect was evaluated using 6 whole blood samples. The stock hCG solution was diluted in human whole blood to give solutions with intended plasma concentrations of 2.0 × 10^6, 1.0 × 10^6, 5.0 × 10^5, 2.5 × 10^5, 1.5 × 10^5, and 1.0 × 10^5 IU/L. Immediately after preparation, each whole blood solution was tested by adding 35 μL to each of 2 ADEXUSDX hCG test devices, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and plasma hCG concentrations were determined to be 2.2 × 10^6, 1.2 × 10^6, 6.0 × 10^5, 3.0 × 10^5, 1.8 × 10^5, and 1.1 × 10^5 IU/L using the Roche e602 hCG+β assay.

Validation of intermediate range performance

Device performance in the intermediate hCG concentration range was assessed using 5 whole blood samples. The stock hCG solution was diluted in hCG dilution buffer to a concentration of 2 × 10^6 IU/L, which was further diluted in human whole blood to give solutions with intended plasma concentrations of 5.0 × 10^4, 2.0 × 10^4, 1.0 × 10^4, 5.0 × 10^3, and 1.0 × 10^3 IU/L. Immediately after preparation, each whole blood solution was tested by adding 35 μL to each of 2 ADEXUSDX hCG test devices, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and plasma hCG concentrations were determined to be 6.5 × 10^4, 2.5 × 10^4, 1.2 × 10^4, 5.7 × 10^3, and 1.2 × 10^3 IU/L using the Roche e602 hCG+β assay.

Assessment of sample volume

The acceptable sample volume was determined using 1 whole blood sample. The stock hCG solu-
tion was diluted in hCG dilution buffer to a concentration of $2.0 \times 10^5$ IU/L, which was further diluted in human whole blood to give a solution with an intended plasma concentration of $1.0 \times 10^4$ IU/L. Immediately after preparation, the whole blood solution was tested by adding 40, 35, 30, 25, 20, or 15 μL to each of 2 ADEXUSDx hCG test devices, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and the plasma hCG concentration was determined to be $1.1 \times 10^4$ IU/L using the Roche e602 hCG+β assay.

**Assessment of acceptable hematocrit range**

The acceptable hematocrit range was determined using 1 whole blood sample. The stock hCG solution was diluted in hCG dilution buffer to a concentration of $2.0 \times 10^5$ IU/L, which was further diluted in human whole blood to give a solution with an intended plasma concentration of $1.0 \times 10^4$ IU/L. An aliquot of the whole blood sample was centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube, and the plasma hCG concentration was determined to be $1.1 \times 10^4$ IU/L using the Roche e602 hCG+β assay. The whole blood and plasma fractions from the same initial sample were combined to generate solutions containing hematocrit values of 59%, 50%, 46%, 42%, 35%, 32%, 24%, and 19%. Because separated erythrocytes and plasma from the same whole blood sample were recombined to generate samples with increasing hematocrit values, the ratio of erythrocytes to plasma changed, but the plasma hCG concentration remained constant in all samples. Hematocrit was calculated from hemoglobin concentrations determined using an ABL90 analyzer (Radiometer Medical). Immediately after preparation, the whole blood solutions were tested by adding 35 μL to each of 3 ADEXUSDx hCG test devices from each lot, centrifuged for 7 min at 10,000g; plasma supernatant was transferred to a clean tube; and plasma hCG concentrations were determined to be $4.8 \times 10^5$ and $28$ IU/L using the Roche e602 hCG+β assay.

**Device interpretation**

Devices were interpreted by 10 laboratory technologists with different levels of experience in the interpretation of qualitative hCG test results. Whenever possible, direct device interpretation was performed between 10 and 30 min after addition of a sample. High-definition images of each device were also obtained and verified to accurately represent each device. When direct device interpretation could not be performed within 30 min, device images were interpreted instead. Each device was interpreted as either positive, negative, or invalid, and test results are displayed as the number of results relative to the total number of interpretations (e.g., 2 device replicates interpreted by 10 technologists = 20 total interpretations).

**Prospective patient recruitment**

Informed consent was obtained from pregnant and nonpregnant women seeking care at the University of Kentucky clinics or the University of Kentucky Emergency Department from October 2015 to March 2016. Prisoners, women with impaired consent capability, and women <18 years of age or >44 years of age were excluded from the study. Three independent hCG measurements were performed during the same episode of care: qualitative fingerstick whole blood testing using the ADEXUSDx hCG test (lot 1012, expiration October
31, 2016), qualitative urine testing using the Beckman Coulter ICON® 20 device (lot 035F21, expiration February 28, 2017), and quantitative plasma testing using the Roche e602 hCG+β assay. Pregnancy status was determined postenrollment using the quantitative plasma hCG result as the gold standard reference method. Once 40 pregnant and 40 nonpregnant patients were enrolled in the study, enrollment was terminated.

This study was approved by the University of Kentucky Institutional Review Board.

**Qualitative whole blood hCG measurement**

Capillary fingerstick samples were applied to the ADEXUSDx hCG test device according to the manufacturer's instructions. Results were documented by study nurses between 10 and 30 min after application of the sample. For all patients, capillary fingerstick testing was performed and results documented before qualitative urine and quantitative plasma testing to avoid bias in the interpretation of the capillary fingerstick result.

**Qualitative urine hCG measurement**

Urine samples were collected and applied to the Beckman Coulter ICON 20 hCG device according to the manufacturer’s instructions. Results were documented between 3 and 5 min after application of the sample by study nurses who had not seen the patient’s previously generated capillary fingerstick result.

**Quantitative plasma hCG measurement**

Single hCG measurements were performed on all plasma samples using the Roche e602 hCG+β assay. Using this assay, results ≥5 IU/L are considered positive. Results for samples with an hCG concentration ≤10,000 IU/L were reported directly; results for samples with an hCG concentration >10,000 IU/L were reported after an automatic onboard 100-fold dilution performed using Roche Universal Diluent. Specimens with an hCG concentration >1 × 10^6 IU/L were manually diluted 10-fold in Roche Universal Diluent before being placed on the instrument, and results were reported after an additional automatic onboard 100-fold dilution.

**RESULTS**

**Sensitivity**

Sensitivity results for whole blood are shown in Fig. 1. Twenty of 20 device interpretations were positive at a plasma hCG concentration of 27 IU/L, and 18/20 were positive at 17 IU/L. Positive interpretations were also documented at lower concentrations, but significant disagreement between device interpreters was observed (16/20 positive at 13 IU/L, 9/20 at 8 IU/L, and 4/20 at 4 IU/L).

**Low-end reproducibility**

Low-end reproducibility was assessed using whole blood solutions with plasma hCG concentrations of 28 and 18 IU/L. One hundred of 100 device interpretations were positive at a plasma hCG concentration of 28 IU/L, and 100/100 were positive at 18 IU/L.

**High-dose hook effect**

Device susceptibility to the high-dose hook effect using whole blood samples is shown in Fig. 2. Twenty of 20 device interpretations were positive at all hCG concentrations tested, including the maximum concentration of 2.2 × 10^6 IU/L. The device showed susceptibility to the high-dose hook effect, as decreasing test line intensity was observed at concentrations ≥6.0 × 10^5 IU/L, but all devices were interpreted as positive.

**Intermediate range performance**

Intermediate range performance results for whole blood are shown in Fig. 3. Twenty of 20 device interpretations were positive at plasma concent
centrations of $1.2 \times 10^3$ IU/L, $2.5 \times 10^4$ IU/L, and $6.5 \times 10^4$ IU/L, but 3 invalid results were observed in the intermediate range (2/20 invalid at $5.7 \times 10^3$ IU/L and 1/20 invalid at $1.2 \times 10^4$ IU/L) because of decreased control line intensity.

**Acceptable sample volume**

The acceptable sample volume for whole blood was determined to be $\geq 30\ \mu$L using a whole blood sample containing a plasma hCG concentration of $1.1 \times 10^4$ IU/L (Fig. 4). Sixty of 60 device interpretations were pos-
itive when ≥30 μL of the sample were added to the test device, but only 1/60 device interpretations was positive when ≤25 μL of the sample were used.

**Acceptable hematocrit range**

The acceptable hematocrit range was determined to be ≤46% using a whole blood sample containing a plasma hCG concentration of 1.1 × 10^4 IU/L. Sixty of 60 device interpretations were positive when hematocrit ranged from 19% to 46%; 16/20 device interpretations were positive at a hematocrit of 50%. The remaining 4/20 interpretations at 50% and 20/20 at 59% were invalid because of the absence of a control line.

**Lot-to-lot variability**

Equivalent performance of 3 device lots was observed when used to test whole blood samples

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### Fig. 3. Assessment of intermediate range performance using whole blood samples.
Each whole blood solution was tested in duplicate and interpreted by 10 observers for a total of 20 observations. After testing, each solution was centrifuged and plasma hCG concentrations were determined. T, test line; C, control line.

<table>
<thead>
<tr>
<th>Solution number</th>
<th>Plasma hCG concentration, IU/L</th>
<th>Number of positive observations</th>
<th>Number of negative observations</th>
<th>Number of invalid observations</th>
<th>Representative device images T</th>
<th>C</th>
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<td>6.5 × 10^4</td>
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<tr>
<td>4</td>
<td>5.7 × 10^3</td>
<td>18/20</td>
<td>0/20</td>
<td>2/20</td>
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<tr>
<td>5</td>
<td>1.2 × 10^3</td>
<td>20/20</td>
<td>0/20</td>
<td>0/20</td>
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### Fig. 4. Assessment of acceptable sample volume using a whole blood sample.
The indicated volumes of a single whole blood solution containing a plasma concentration of 1.1 × 10^4 IU/L were tested in duplicate and interpreted by 10 observers for a total of 20 observations. After testing, the solution was centrifuged and plasma hCG concentration was determined. T, test line; C, control line.

<table>
<thead>
<tr>
<th>Solution number</th>
<th>Volume of whole blood, μL</th>
<th>Number of positive observations</th>
<th>Number of negative observations</th>
<th>Number of invalid observations</th>
<th>Representative device images T</th>
<th>C</th>
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<td>30</td>
<td>20/20</td>
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<td>1/20</td>
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with plasma concentrations of $4.8 \times 10^5$ IU/L and 28 IU/L. Thirty of 30 device observations were positive for all 3 lots using both whole blood samples.

**Prospective evaluation using capillary fingerstick samples**

Summary characteristics of the prospectively recruited pregnant and nonpregnant women are listed in Table 1. Concordance between the capillary fingerstick, qualitative urine, and quantitative plasma hCG results generated during the same visit from these women is shown in Table 2. The capillary fingerstick results were 100% concordant with urine qualitative results and plasma quantitative results. No invalid results were observed for any of the pregnant patients despite the fact that hCG concentrations for 9 of the 40 patients fell within the intermediate range of $5.7 \times 10^3$ to $1.2 \times 10^4$ IU/L, associated with diminished control band intensity.

### DISCUSSION

Medical personnel frequently perform hCG testing to rule out pregnancy before performing procedures that could harm a developing fetus. This testing is typically performed using urine qualitative hCG test devices that are susceptible to false-negative results, resulting in undesirable outcomes if pregnant women are subjected to inappropriate imaging studies or other interventions. Furthermore, urine collection often presents a challenge in dehydrated women, trauma patients, and individuals who choose not to provide a urine sample. Blood-based testing provides advantages over urine-based testing because blood samples can be obtained in most patients without substantial delay, and hCG variants known to cause false-negative results in urine-based testing are not present in plasma. Despite these qualities, physicians are often reluctant to pursue plasma/serum hCG testing because it must be performed in a central laboratory environment, which delays the availability of test results. A device designed for blood-based assessment of pregnancy status at the POC using capillary fingerstick samples would eliminate false-negative concerns associated with urine-based testing, avoid delays caused by difficulties collecting urine, and shorten turnaround time relative to central laboratory testing. Other blood-based hCG POC devices have been developed, but these require substantial financial investment and refrigeration of test cartridges.

The ADEXUSDx hCG test is cleared by the Food and Drug Administration for use with whole blood, which facilitates the rapid assessment of pregnancy status at the POC with a capillary fingerstick sample. In our study, the device demonstrated an analytical sensitivity of 18–20 IU/L (plasma concentration), which is slightly higher than the manufacturer’s claim of 10 IU/L but sufficient for clinical use as a replacement for qualitative urine-based testing. Given that currently available POC devices indicate an analytical sensitivity in urine of 20–25 IU/L and that hCG concentrations are almost always higher in plasma than in concurrently collected urine samples (13), the analytical sensitivity of 18–20 IU/L in the plasma fraction of whole blood should provide a clinical sensitivity at least equivalent to currently available urine qualitative hCG devices. However, until demonstrated other-

<table>
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<th>Table 1. Study patient characteristics.</th>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Median age, years (range)</td>
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<tr>
<td>Median plasma hCG concentration, IU/L (range)</td>
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<td>Median gestational age, weeks (range)</td>
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</table>
wise, the ADEXUSDx hCG test device should not be considered equivalent or superior to plasma quantitative hCG testing.

Because lateral flow immunoassays are subject to false-negative results caused by the high-dose hook effect, we evaluated the hCG concentration above which the ADEXUSDx hCG test would generate misleading false-negative results. Although the device showed susceptibility to the high-dose hook effect with decreasing positive signal above $6.0 \times 10^5$ IU/L, clear positive results were still observed at $2.2 \times 10^6$ IU/L. This outcome is expected to be sufficient for clinical use because the highest plasma hCG concentration observed in pregnant women enrolled in this study was $1.4 \times 10^5$ IU/L, our medical center typically encounters only 2 patients per year with plasma hCG values $\geq 5.0 \times 10^5$ IU/L, and the highest concentration observed at our medical center is $1.0 \times 10^6$ IU/L.

Although approved for use with heparinized plasma samples, it is expected that the ADEXUSDx hCG test will most frequently be used with whole blood fingerstick samples. Specimens with increased hematocrit may result in false-negative or invalid results if insufficient plasma is present to flow through the device. In our study, all samples with a hematocrit value $\leq 46\%$ generated positive results. Given that the hematocrit reference interval is 35%–45% in nonpregnant adult females and 30%–40% in pregnant females, the device will likely demonstrate acceptable performance in the majority of women encountered in routine clinical practice. In women with invalid test results due to increased hematocrit, pregnancy assessment must be performed using an alternate test method.

As a final assessment, we compared results generated by the ADEXUSDx hCG test using capillary fingerstick samples to concurrently performed urine qualitative and plasma quantitative hCG testing in 80 prospectively recruited women. A total of 100% concordance was observed between all 3 test results for 40 nonpregnant women and 40 pregnant women with plasma hCG concentrations ranging from $2.4 \times 10^3$ IU/L to $1.4 \times 10^5$ IU/L, confirming the acceptability of the ADEXUSDx hCG test for clinical use.

According to the manufacturer’s instructions, approximately 40 $\mu$L whole blood is required to ensure a valid test result, and the results of our study demonstrate that valid results are reliably generated with as little as 30 $\mu$L. Study personnel performing the collection of fingerstick samples indicated that after a brief initial training, a sufficient sample volume was easily collected from all study participants on the first attempt.

One device limitation observed in our study was diminished control line intensity between $5.7 \times 10^3$ and $2.5 \times 10^4$ IU/L, resulting in a small number of invalid test results during the laboratory assessment of device performance in the intermediate range. In all cases, a clearly visible test line was detected, which would prevent inappropriate imaging studies or other intervention, but the initial invalid result may delay care for a substantial number of patients by requiring assessment of pregnancy status by alternate means. However, 9 participants in our study had plasma hCG concen-
trations in this range, and a detectable control line on the ADEXUSDx hCG test was observed for all 9 patients.

In summary, the ADEXUSDx hCG test generated positive results in a controlled laboratory environment over a clinically appropriate range of hCG concentrations. When the manufacturer’s instructions were followed, no false-positive or false-negative results were observed, although some invalid results were observed with samples containing intermediate hCG concentrations or physiologically unlikely hematocrit values. Evaluation of device performance in prospectively recruited women revealed identical performance to that of currently available pregnancy devices. Further work is required to determine the impact of capillary fingerstick hCG testing on length of stay and patient throughput.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 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; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

**Authors’ Disclosures or Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

**Role of Sponsor:** No sponsor was declared.

**REFERENCES**