biologically active molecules in future publications, a point lost in many recent reports observed in the literature, will be important. Furthermore, several organizations that provide newborn screening programs may be unaware of this problem and may miscalculate the true concentrations of certain acylcarnitines in blood. In addition, questions concerning the reasons that octanoylcarnitine is hydrolyzed in blood preparations may be more properly answered. On the basis of our study, the conclusion of Turner and Dalton *(5)*, that blood or serum should be calibrated against aqueous calibrators rather than blood, appears false. Furthermore, their conclusion that an enzyme in plasma of both healthy subjects and patients with medium chain acylCoA dehydrogenase deficiency hydrolyzes octanoylcarnitine is also false because the physiologically active form of octanoylcarnitine is L-octanoylcarnitine. Furthermore, because L-octanoylcarnitine is not hydrolyzed in the blood, we must conclude that the conversion of L-octanoylcarnitine to free carnitine is unlikely. However, nonspecific hydrolytic enzymes in the blood appear to remove D-octanoylcarnitine from the blood. This fact is certainly an interesting observation and may stimulate further interest in its mechanism and its role in blood.

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Semiautomation of Nucleic Acid-based Assays for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, *Shirley J. Johnson,[1*] Diane H. Green,[2] David A. Reed,[1] and Linda S. Wood[1]* ([1] Gen-Probe Incorporated, 10210 Genetic Center Drive, San Diego, CA 92121-4362; [2] Philadelphia Department of Public Health, 500 S. Broad St., Philadelphia, PA 19146; * author for correspondence: fax 858-410-8870, e-mail shirleyj@gen-probe.com)

The US prevalence rates of sexually transmitted diseases associated with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) are as high as 27% *(1)* and 56% *(2)*, respectively. Routine screening for both conditions is recommended for several risk groups, and infections with CT and GC frequently coexist *(3)*. Because both infections are often asymptomatic, screening is important in efforts to slow the spread of infection.

Recent studies compared amplified with nonamplified testing *(4–10)* and swab with urine specimens *(4, 8, 11–20)*. Because recommendations vary *(21–25)*, each laboratory must decide which test(s) to use by considering the prevalence of infection, assay sensitivity and specificity, cost-effectiveness, laboratory work flow, and types of specimens received. Several tests may be required to best serve customers with different needs. We developed a menu of semiautomated tests, including amplified CT, nonamplified CT, and nonamplified GC assays. We describe two novel menu choices here: (*a*) a combination of the nonamplified PACE® 2 GC assay (Gen-Probe, Inc.) with the AMPLIFIED™ Chlamydia Trachomatis Assay (AMP CT; Gen-Probe, Inc.) for swab specimens; and (*b*) AMP CT for urine specimens.

We used the TECAN GENESIS RSP instrument (1.426 m × 0.780 m × 1.200 m; TECAN US, Inc.). It has an eight-tip arm and uses 1-mL, extended length, disposable, filter pipette tips with level-sensing capability. We designed and machined custom deck plates to support the necessary specimen racks, assay racks, and reagent reservoirs.

With approval from the Institutional Review Board, four clinical sites collected urogenital swab specimens using the standard PACE 2 specimen collection method, and two clinical sites collected urine specimens. Each site collected additional specimen(s) for their usual laboratory testing for CT and GC, and those test results were provided along with the specimens for studies at Gen-Probe. In addition, 48 healthy volunteers donated urine specimens. The Philadelphia Department of Public Health independently obtained Institutional Review Board approval to collect specimens and conduct studies. Approximately 70% of the specimens used in all studies were from females. Studies at Gen-Probe were blinded, and studies at the Philadelphia Department of Public Health were done with previously untested clinical specimens.

We divided our investigation into four parts as described below. The objective of parts 1 through 3 was to measure the agreement between two different processing methods. In the event that initial test results at Gen-Probe did not agree between the two processing methods, the test result from the specimen collection site was assumed correct. To confirm the collection-site result, we retested specimens in disagreement in the appropriate manual assay (either AMP CT or PACE 2 GC). Because specimens tested at the Philadelphia Department of Public Health were all unknowns, we used the PACE 2 Probe Competition Assay to resolve disagreement in the PACE 2 GC assay. There were no disagreements in AMP CT testing at the Philadelphia Department of Public Health.

Swab expression vs nonexpression for PACE 2 GC (part 1). According to the current package insert for PACE 2 GC, all liquid must be expressed from the swab, and the swab

must be discarded. We compared results with and without swab expression for PACE 2 GC on 334 swab specimens at Gen-Probe and 412 at the Philadelphia Department of Public Health. The specimens were vortex-mixed and centrifuged at 300*g* for 5 min; 40 μL of Specimen Preparation Reagent (SPR) was then added with mixing. The specimens were incubated at 60 °C for 10 min, after which a 100-μL specimen was pipetted into an empty assay tube for the "swab-not-expressed" sample. The specimens were vortex-mixed, the swab was expressed and discarded, and the specimens were vortex-mixed once more. A 100-μL specimen was then pipetted into an empty assay tube for the corresponding "swab-expressed" sample. The swab-not-expressed and swab-expressed assay tubes were randomized and processed together through the remainder of the assay, following package insert instructions. Six operators were involved in running the manual assay, including swab expression.

Initial assay test results for swab expression and nonexpression agreed for 741 of 746 specimens. Of the five specimens that disagreed, four were from patients who tested negative at the clinical collection site and one was an unknown from the Philadelphia Department of Public Health. The retest results were all negative, leading to 100% agreement for 191 positive and 555 negative specimens. The assay agreement based on all 191 positive specimens corresponded to a 99% confidence interval with a half-width <3%.

The sex of the patient was recorded for 369 specimens. Swab expression and nonexpression were not significantly different among GC-negative specimens from females (n = 162; $P = 0.70$, paired *t*-test), GC-negative specimens from males (n = 51; $P = 0.14$), and GC-positive specimens from females (n = 87; $P = 0.09$). Relative light units (RLUs) differed between swab expression and nonexpression for GC-positive specimens from males (n = 69; $P = 0.01$). The data for positive specimens are graphed in Fig. 1, showing that several specimens from males gave substantially higher RLU readings with the swab expressed. The viscous exudate from males infected with GC can be difficult to pipette, and we suspect that swab expression and subsequent vortex-mixing helped homogenize particularly viscous specimens, leading to a more consistent sample transfer and correspondingly higher RLU readings. In any case, the percentage of agreement between swab expression and nonexpression was not affected because all RLU signals were much higher than the assay cutoff value. Our demonstration that swab expression was not required for PACE 2 GC enabled semiautomation of PACE 2 GC + AMP CT from a single swab specimen because the swab remains in the tube for AMP CT.

Semiautomated vs manual assay performance for PACE 2 GC + AMP CT swab specimens (part 2). Gen-Probe performed a side-by-side comparison of PACE 2 GC + AMP CT semiautomated vs manual processing using 111 swab specimens, running both assays simultaneously from the same swab specimen. The Philadelphia Department of Public Health independently evaluated PACE 2 GC and AMP CT semiautomated vs manual protocols by running each assay separately, using 100 specimens for AMP CT and 358 specimens for PACE 2 GC. For the semiautomated protocol, the TECAN GENESIS RSP instrument automated sample preparation steps, including pipetting the SPR, Specimen Dilution Buffer, Amplification Reagent, Oil Reagent, and specimen, as well as mixing of the specimen in Specimen Dilution Buffer and transferring the diluted specimen. We processed the assays according to package insert instructions, with the exception that we added SPR and did not express the swab for PACE 2 GC.

The initial test results for PACE 2 GC + AMP CT agreed with those obtained for the manual processing method in 107 of 111 swab specimens. The four specimens that did not agree were from patients who tested negative for both CT and GC at the clinical collection site. All four specimens retested negative in accordance with the collection site results, leading to 100% agreement between the semiautomated and manual assays. For PACE 2 GC and AMP CT assays run separately to compare the

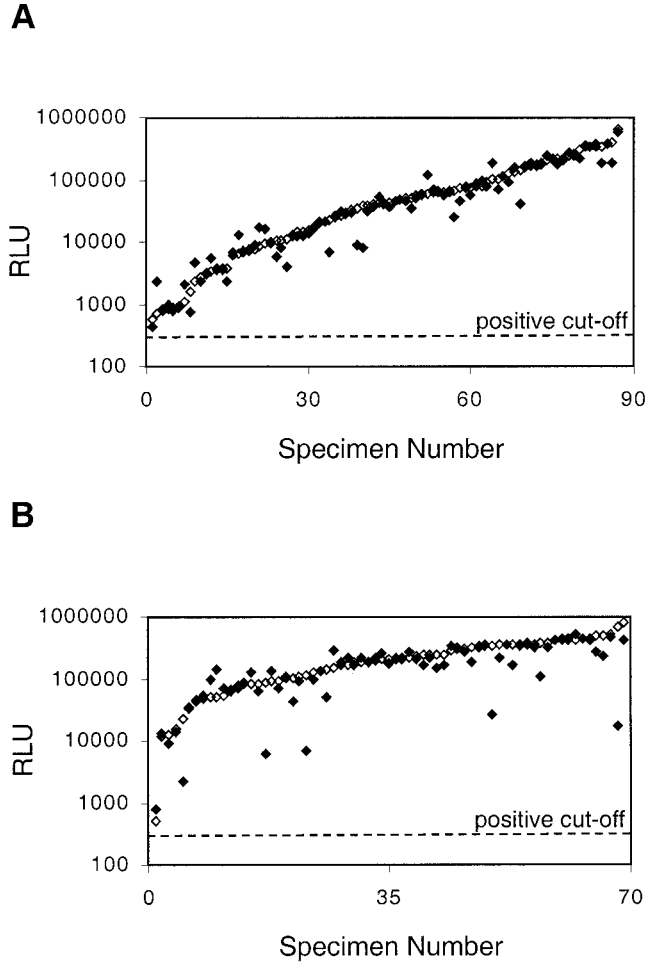

Fig. 1. RLU signals for swab expression vs nonexpression for GC-positive specimens in the PACE 2 GC assay.

The data are sorted in ascending RLU order for swab expression (◇) with the corresponding result for swab nonexpression (◆) plotted at the same specimen number. The *dashed line* shows the positive cutoff for PACE 2 GC. (*A*), specimens from females. (*B*), specimens from males.

semiautomated with manual protocols, 458 of 458 initial test results agreed, for 100% agreement.

Semiautomated vs manual assay performance for AMP CT urine specimens (part 3). Gen-Probe conducted part 3 in-house with 187 urine specimens and on-site at the Philadelphia Department of Public Health with 24 urine specimens. To increase the number of positive specimens, we added 2 CT inclusion-forming units per assay to 81 specimens. For the semiautomated protocol, the TECAN GENESIS RSP instrument automated sample preparation steps as in part 2. The package insert instructions were followed for both manual and semiautomated assays with the only noteworthy change being that instead of vortex-mixing to resuspend the urine pellet, the TECAN GENESIS RSP instrument resuspended the urine pellet by repeated aspiration and dispensing.

Initial test results for semiautomated and manual processing for AMP CT urine specimens showed agreement for 207 of 211 specimens. Four specimens tested negative in the manual assay, but were positive in the semiautomated assay. We expected the results to be positive because three of the specimens were from patients who tested positive at the clinical collection site and one was a specimen with added CT. Three specimens retested positive, but one true positive still gave a negative result by manual AMP CT. To resolve the disagreement, we retested this specimen in the APTIMA Combo 2 assay *(26, 27)*, and the result was positive. Therefore, we concluded that the manual AMP CT assay yielded one false-negative result, giving 99.5% agreement between semiautomated and manual processing.

Contamination study (part 4). Gen-Probe evaluated contamination in the semiautomated protocol using one batch of 144 tubes containing transport medium and a swab. We added purified RNA to 72 tubes at 1000- and 15-fold the positive control concentrations for AMP CT and PACE 2 GC, respectively. An amplified assay is a more sensitive test for contamination; therefore, we added a higher CT target to stress the system. We randomized the tubes and ran PACE 2 GC + AMP CT assays using the TECAN GENESIS RSP instrument, following the semiautomated protocol as in part 2. There were no false results for either CT or GC; hence there was no evidence that the TECAN GENESIS RSP instrument produces cross-contamination.

Our study shows, for the first time, equivalent assay performance with and without swab expression for PACE 2 GC. The PACE 2 GC transport medium is formulated to lyse the cells, releasing the RNA target into solution, thus reducing the impact of swab expression. In addition, PACE 2 GC performance without swab expression is presumably enhanced by the addition of SPR. SPR breaks down mucous, making the RNA target more accessible, which probably leads to acceptable assay performance without swab expression. We did not test swab expression vs nonexpression without the addition of SPR. SPR is required for AMP CT; therefore, it was used with PACE 2 GC when the same swab specimen was tested simultaneously in both assays.

The combination of an amplified CT assay with a nonamplified GC assay for urogenital swab specimens is a judicious choice. Reports in the literature indicate sensitivities for the amplified CT assays 0–26% higher than the sensitivity for the nonamplified PACE 2 CT assay *(4, 6, 8, 20, 28)*. In contrast, the reported sensitivities are comparable for amplified GC assays *(4, 9, 29)* and the nonamplified PACE 2 GC assay *(2, 23, 30)*. The slightly lower sensitivity of nonamplified CT tests combined with the comparable sensitivity of amplified and nonamplified GC tests supports the selection of PACE 2 GC + AMP CT as a useful test option. Furthermore, the combination of PACE 2 GC + AMP CT takes advantage of the sensitivity of the CT amplification assay while avoiding some of the more serious limitations of GC amplification tests, such as poor specificity and contamination *(31)*. The nonamplified PACE 2 GC assay is highly specific *(23)*, allows verification of positive results *(32)*, and is cost-efficient for the laboratory. Additionally, the semiautomated protocol for PACE 2 GC + AMP CT described here, together with elimination of swab expression for PACE 2 GC, represents a substantial time savings and reduction in manual labor.

For AMP CT urine specimens, the TECAN GENESIS RSP instrument shows equivalent or better performance than the manual assay. The ability of the instrument to resuspend the urine pellet by repeated aspiration and dispensing is potentially superior to vortex-mixing. We optimized pipetter settings for high shearing flow in the vicinity of the urine pellet, thus yielding good resuspension of the pellet in Specimen Dilution Buffer. We speculate that complete resuspension of the urine pellet by the instrument caused the semiautomated assay to identify one positive specimen that the manual assay missed.

Of all 891 tests comparing semiautomated with manual processing, there were 8 results that did not agree after initial testing. Seven of the false results arose from the manual protocol, and the eighth was from the semiautomated protocol. We believe that the eighth false result almost certainly occurred from cross-contamination during manual handling subsequent to automated pipetting. Although manual processing is reasonable for low-volume testing, the tedium of high-volume testing can cause operator fatigue or lapses in attention, leading to incorrect test results, as we observed in our study. This emphasizes the benefits of automation in high-volume testing to help reduce the possibility of operator error and cross-contamination during manual handling.

In conclusion, semiautomation of AMP CT and the PACE 2 System offers the reproducibility of automation, the flexibility to accommodate both swab and urine specimens, and the ability to choose the most cost-effective option for the laboratory. Assay validation showed equivalent performance for semiautomated and manual processing. The throughput in 8 h is 432 GC and 432 CT results for semiautomated PACE 2 GC + AMP CT swab specimens and 432 CT results for semiautomated AMP CT urine specimens.

We acknowledge the staff of the clinical microbiology laboratory at the Philadelphia Department of Public Health, and the laboratory assistance of Teena Dean,

Sandy Hite, Carlos De La Barra, Lisa Tran, Denise Riggan, Scott Neynaber, Chris Eng, and Ron Williams at Gen-Probe.

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Sensitive Method for Detection and Semiquantification of Bence Jones Protein by Cellulose Acetate Membrane Electrophoresis Using Colloidal Silver Staining, *Kazuyuki Matsuda,[1] Nobuo Hiratsuka,[1] Takatoshi Koyama,[1] Yuriko Kurihara,[1] Osamu Hotta,[2] Yoshihisa Itoh,[3] and Kiyoko Shiba[1*]* ([1] Graduate School of Allied Health Sciences, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, Tokyo 113-8519, Japan; [2] Department of Nephrology, Sendai Shakaihoken Hospital, Tsutsumimachi, 3-16-1, Aoba-ku, Sendai 981-8501, Japan; [3] Department of Laboratory Medicine, Asahikawa Medical College, Midorigaoka-higashi 2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan; * Author for correspondence: fax 81-3-5803-0166, e-mail k.shiba.mtec@tmd.ac.jp)

The monoclonal free light chain of immunoglobulin, Bence Jones protein (BJP), is associated with malignant monoclonal gammopathies, in particular with multiple