Performance and Diagnostic Accuracy of a Urine-Based Human Papillomavirus Assay in a Referral Population

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Abstract

Background: Human papillomavirus (HPV) testing from clinician-collected cervical and self-collected cervico-vaginal samples is more sensitive for detecting CIN2⁺/CIN3⁺ than cytology-based screening, stimulating interest in HPV testing from urine. The objective was to determine the performance of the Trovagene HPV test for the detection of CIN2⁺ from urine and PreservCyt cervical samples.

Methods: Women referred for colposcopy at St Mary’s Hospital (London, United Kingdom), following abnormal cytology, were recruited to this diagnostic accuracy study by convenience sampling (September 2011 to April 2013). A total of 501 paired urine and cervical samples were collected. Primary outcomes were sensitivity for CIN2⁺/CIN3⁺ and specificity for <CIN2; secondary outcomes were comparisons with other HPV tests and agreement/kappa values between urine and cervical samples.

Results: Trovagene HPV test sensitivity and specificity from PreservCyt were similar to well-established tests [sensitivity for CIN3⁺ (n = 145) 96.3% (95% confidence interval (CI), 89.6–99.2); CIN2⁺ (n = 81) 94.5% (95% CI, 89.4–97.6); specificity for <CIN2 25.3% (95% CI, 20.8–30.1)] Sensitivity from urine was slightly, but not significantly, lower [CIN3⁺ 91.4% (95% CI, 83.0–96.5), P = 0.3; CIN2⁺ 88.3% (95% CI, 81.9–93.0), P = 0.06]. Specificity for <CIN2 was similar: 24.7% (95% CI, 20.3–29.5), P = 0.9. A total of 403 Trovagene cervical and 396 urine HPV tests were positive. Overall agreement between paired samples was 82.6% (95% CI, 79.3–86.0).

Conclusions: Trovagene HPV test’s performance on PreservCyt cervical samples was comparable with established HPV tests. Sensitivity in urine, although slightly lower, may nevertheless be adequate for self-sampling. This referral population’s higher HPV positivity rate affects specificity, warranting further studies in a screening population.

Impact: This may prove useful for women not attending for cervical screening. Cancer Epidemiol Biomarkers Prev; 26(7): 1653–9. ©2017 AACR.
correlation with disease outcome was provided. Bernal and colleagues (2014) found good agreement between urine and clinician-collected cervical samples (cervical brush placed in PCR medium; \( k = 0.76; 95\% \text{CI}, 0.46–0.86; \text{concordance}, 87.5\% \text{(95\% CI, 77.6–94.1)}) and a 92.3\% (95\% CI, 74.9–99.1) sensitivity for CIN2 \(^+\) for the prototype Trovagene HPV test from urine samples. This sensitivity was higher than for Linear Array in urine (80.8\% 95\% CI, 60.6–93.4), and similar to that for Linear Array performed on cervical samples (96.2\%; 95\% CI, 80.4–99.9). Thus, the performance of HPV testing in urine appears to be dependent on the methods used for collection and assay.

The objective of this study was to determine the performance and diagnostic accuracy of the Trovagene HPV test (Trovagene) from urine samples for the detection of high-grade CIN in a large referral population, and to compare the results with those using the same test from paired cervical samples collected at the same visit in PreservCyt Solution (Hologic). The Trovagene HPV test performance was also compared with five other HPV DNA or RNA tests based on separate aliquots of the same PreservCyt cervical sample. Fuller details of the other tests have been reported elsewhere, where the main comparison was the performance of a range of HPV tests taken in either PreservCyt Solution or SurePath Preservative Fluid (Becton Dickinson) in two separate samples from each woman (14).

**Materials and Methods**

**Population**

This work was a substudy of the PreservCyt versus SurePath: PREDICTORS 4 prospective study among women with abnormal cytology newly referred to the St Mary’s Hospital colposcopy clinic (London, United Kingdom) between September 14, 2011, and April 26, 2013. All women were sent a patient information sheet with their appointment letter giving full details of the study and assuring them that their care would not be affected if they chose not to participate. Women were eligible if referred as a result of one or more abnormal cervical cytology screening results with the most recent being within 3 months of their colposcopy visit, were not pregnant, had not been treated previously for CIN, nor had a hysterectomy. Participants were recruited by convenience sampling with no selection but based on staff availability and not interfering with the patient waiting times. All women provided written informed consent.

**Sample collection methods**

Prior to colposcopy and biopsy, women were asked whether they would provide a urine sample for HPV testing. The participant was asked not to wipe the labia before urinating and to provide 40 to 100 mL of urine. A proprietary preservative solution was added to the urine sample within 10 minutes by clinic staff. Women were also asked to consent to their clinician collecting two cervical cytology samples with Cervex brushes (Rovers Medical Devices B.V.) for research purposes at the start of their colposcopy examination. One brush sample was placed in a ThinPrep vial containing 20 mL PreservCyt Solution and the other went into a vial containing 10 mL of SurePath Preservative Fluid (BD Diagnostics). The order of cervical sampling was randomized to eliminate potential bias associated with sampling order. Only the urine sample and a 1-mL aliquot of the PreservCyt cervical sample were used for Trovagene HPV testing for this substudy.

**Data collection and binding**

All samples were pseudoanonymized and identifiable only by participant number. Study results were used for research purposes only. Participants were made aware prior to consent that they would not be informed of their test results. Pseudoanonymized aliquots, blind to all other information, were shipped at ambient temperature to the Trovagene laboratory in San Diego, CA, where the HPV testing was performed. Results were then sent to the Centre for Cancer Prevention in London, United Kingdom, where data entry and all analyses were performed according to a predefined statistical analysis plan. All pathology results were centrally reviewed by an external, independent expert pathologist (M.H. Stoler), who was blinded to all data and whose histologic diagnosis was used for analyses. Worst histology was defined as the highest grade of histology, whether diagnostic punch biopsy or excision biopsy collected at baseline or within 9 months.

**HPV assay details**

For the Trovagene HPV test, DNA was extracted from 0.5 mL of the urine sample using the QiAamp MinElute Virus Vacuum Kit (Qiagen) according to the manufacturer’s instructions. Cells from a 1-mL aliquot of the PreservCyt cervical sample were pelleted, washed with PBS, and then DNA was extracted with the QiAamp DNA Mini Kit (Qiagen) according to the manufacturer’s instructions. Isolated DNA from both urine and PreservCyt samples (5 L) was tested with the Trovagene HPV test (Trovagene Inc.), a PCR test that amplifies a region in the E1 gene of 13 HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and provides a consensus positivity result. The assay also detects the RNaseP gene as a control.

The PCR product was subjected to capillary electrophoresis for fragment size analysis on the ABI 3130 instrument (Thermo Fisher Scientific), and results were reported as HR-HPV positive or negative based on the presence of a 92-96 bp fragment above a predefined threshold (500 RFU). The 95\% detection limit for most of the 13 HR-HPV types is \( \leq 100 \) copies, with some types (HPV 39 and HPV 51) higher (1,000 or more copies). Cross-reactivity was observed with HPV types 30, 53, 67, and 70, but not with HPV 6, 11, 26, 34, 69, and 82 (data on file).

**Disease assessment**

Histopathology, reviewed by a single well-recognized external expert (M.H. Stoler), was used as the reference standard to determine disease status. Histopathologically diagnosed high-grade CIN (CIN2\(^+\)) is a well-recognized surrogate marker for cervical...
cancer. The pathologist was blinded to all HPV results and clinical information. The three laboratory personnel conducting the Trovagene HPV testing were based in the manufacturer’s laboratory, had extensive experience with the assay, and were also blinded to the disease status of the women and all other HPV results.

Statistical analysis
Sensitivity and specificity (with 95% CIs) were used to describe the test performance, and comparisons between samples were made using a simple binomial agreement test and McNemar test for discordant pairs, both overall and within the CIN3+, CIN2+, and <CIN2 groups.

A sample size of 500 women was chosen to give a 95% CI of (0.84–0.94) for sensitivity for CIN2+, assuming that its true value was 90% and prevalence was 30%, based on previous PREDICTORS studies.

Ethical approval
This study received ethical approval on August 2, 2011, from NHS Health Research Ethics Service, NRES Committee London – Hampstead (reference 11/LO/1147).

Results
A flow diagram for the study is shown in Fig. 1. A total of 652 women agreed to have two cervical cytology specimens taken, one PreservCyt and one SurePath, and of these, 564 also consented to provide a urine sample. Of these, 20 were excluded after enrolment for the following reasons: not meeting the referral criteria (9), incomplete consent forms (3), having no biopsy taken despite an abnormal colposcopy (5), or due to deviation from study procedures (3). In addition, 26 urine samples were excluded before transportation to Trovagene because of insufficient volume

Figure 1.
Flow diagram.
(<10 mL). omission of preservative, or inadequate labeling. A total of 518 urine samples were tested and all produced valid results. Of these, 17 subject-matched PreservCyt cervical samples were deemed unevaluable by control RNaseP results. Samples that failed RNaseP also lacked the 93-96 bp HR-HPV E1 peak. This left 501 women with valid paired urine and cervical results. This was the primary analysis population. The median age of these women was 30 years (IQR = 27–34) with a range of 18 to 69 years. Referral cytology and the worst histology results are shown in Table 1. The mean time from baseline colposcopy visit to date of worst history was 13 days. Of these 501 women, 32% had borderline cytology, 58% had mild dyskaryosis, and 10% had moderate or severe dyskaryosis. Histologic evaluation of the biopsies indicated 29% (145/501) had CIN2−, of which 81 were CIN3−.

The HPV positivity rate with the Trovagene HPV test was 80% (403/501) for the cervical samples and 79% (396/501) for the urine samples, which was the same when using all urine samples, including those not matched to cervical samples (408/518). There was no difference in HPV positivity when the PreservCyt was the first or second cervical sample [80% when PreservCyt was the first sample (199/250) vs. 81% when it was the second sample (204/251)]. There were 47 HPV-positive cervical samples that were urine negative and 40 HPV-positive urine samples that were negative for the cervical sample (Table 2; Fig. 1), yielding an agreement between the samples of 82.6% (95% CI, 79.3–86.0), a kappa of 0.46 (95% CI, 0.37–0.56), and a McNemar OR for discordant pairs of 0.85 (95% CI, 0.54–1.33; P = 0.52). Using the PapType full typing test (Genera Biosystems), multiple HPV types were found in 108 samples. Positivity was four times more common in the cervical samples than urine (86 vs. 22). In no case was discordance by HPV type significantly different in the two sample types, although numbers were small. There was no statistically significant difference in positivity by age (data not shown).

As shown in Table 2, for the cervical samples, the Trovagene HPV test sensitivity was 96.3% (95% CI, 89.6–99.2) for CIN3+ and 94.5% (95% CI, 89.4–97.6) for CIN2+, with a specificity (1 minus positivity rate) of 25.3% (95% CI, 20.8–30.1) for <CIN2. For the urine samples, the sensitivity for CIN3+ was 91.4% (95% CI, 83.0–96.5) and 88.3% (95% CI, 81.9–93.0) for CIN2+. The specificity for <CIN2 was 24.7% (95% CI, 20.3–29.5). Of the 81 CIN3+ cases, there were 10 discordant pairs giving an agreement of 87.7% (95% CI, 80.5–94.8). Of the discordant pairs, seven were cervix positive, urine negative, and the remaining three were cervix negative, urine positive (McNemar OR = 0.43; 95% CI, 0.07–1.88; P = 0.34). No CIN3+ cases were negative for both sample types with the Trovagene HPV test. Of the 356 subjects with <CIN2, there were 33 cervix positive, urine negative versus 35 cervix negative, urine-positive discordant pairs (McNemar OR = 1.06; 95% CI, 0.64–1.76, P = 0.90). For the PreservCyt cervical samples, the Trovagene HPV test performed similarly to other well-established HPV assays (Table 3; Fig. 2). Pairwise agreement was ≥84% for all five tests, with the highest agreement observed for HC2 (89.7%). Trovagene positivity for cervical samples was higher than all tests except HC2, but only significantly so for the Abbott RealTime and Hologic Aptima tests.

### Discussion

These results indicate that the Trovagene HPV test performs similarly to other sensitive HPV tests for PreservCyt cervical samples and is only slightly, but not significantly, less sensitive and equally specific for urine samples. The very high sensitivity in cervical samples suggests that the lower sensitivity in urine is due to specimen type differences and not the assay itself. Similar findings, that is, lower sensitivity with urine compared with cervical samples, for an HPV genotyping test have been reported elsewhere. In that study (15), Linear Array HPV Genotyping Test (LA-HPV; Roche Molecular Systems) was used for evaluating both urine and cervical samples, with a greater difference in sensitivity (LA-HPV; Roche Molecular Systems) was used for evaluating both urine and cervical samples, with a greater difference in sensitivity for CIN2+ between the sample types (urine 80.8% vs. cervical 96.2%). A prototype of the Trovagene HPV test yielded 92.3% sensitivity for CIN2/3 in urine samples (15). The current study is the first to evaluate Trovagene HPV test using paired urine and

### Table 1. Referral cytology vs. worst histology in the next 9 months

<table>
<thead>
<tr>
<th>Referral cytology (N)</th>
<th>No biopsy</th>
<th>Inadequate</th>
<th>Normal</th>
<th>CIN1/HPV only</th>
<th>CIN2</th>
<th>CIN3 or CGIN*</th>
<th>Invasive carcinoma</th>
<th>Total (% N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline dyskaryosis (no HPV triage)</td>
<td>17</td>
<td>1</td>
<td>56</td>
<td>14</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>107 (21.4)</td>
</tr>
<tr>
<td>Borderline dyskaryosis (HPV +ve)</td>
<td>3</td>
<td>0</td>
<td>23</td>
<td>16</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>53 (10.6)</td>
</tr>
<tr>
<td>Mild dyskaryosis (no HPV triage)</td>
<td>43</td>
<td>3</td>
<td>97</td>
<td>54</td>
<td>35</td>
<td>28</td>
<td>0</td>
<td>260 (51.9)</td>
</tr>
<tr>
<td>Mild dyskaryosis (HPV +ve)</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>12</td>
<td>5</td>
<td>0</td>
<td>32 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Moderate dyskaryosis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>21</td>
<td>0</td>
<td>30 (5.99)</td>
</tr>
<tr>
<td>Severe dyskaryosis/glandular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>68 (13.6)</td>
<td>4 (0.8)</td>
<td>185 (36.9)</td>
<td>99 (19.8)</td>
<td>64 (12.8)</td>
<td>79 (15.8)</td>
<td>2 (0.4)</td>
<td>501 (100.0)</td>
</tr>
</tbody>
</table>

*Percentage of total in (HPV test positivity in PreservCyt cervical and urine samples overall and according to histology result with number of discordant pairs, percent agreement, and McNemar test.

### Table 2. HPV test positivity in PreservCyt cervical and urine samples overall and according to histology result with number of discordant pairs, percent agreement, and McNemar OR for discordant pairs

<table>
<thead>
<tr>
<th>Population</th>
<th>Total</th>
<th>Positive cervix % (95% CI)</th>
<th>Positive urine % (95% CI)</th>
<th>Agreement% (95% CI)</th>
<th>OR (95% CI)</th>
<th>P (McNemar test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>501</td>
<td>403 (80.4 (76.7–83.8)</td>
<td>396 (79.0 (75.2–82.5)</td>
<td>82.6 (79.3–86.0)</td>
<td>0.85 (0.54–1.33)</td>
<td>0.5</td>
</tr>
<tr>
<td>CIN3+</td>
<td>81</td>
<td>78 (96.3 (89.5–99.2)</td>
<td>74 (91.4 (83.0–96.4)</td>
<td>87.7 (80.5–94.8)</td>
<td>0.43 (0.07–1.88)</td>
<td>0.3</td>
</tr>
<tr>
<td>CIN2+</td>
<td>145</td>
<td>137 (94.5 (89.4–97.6)</td>
<td>128 (88.3 (81.9–93.0)</td>
<td>86.9 (81.4–92.4)</td>
<td>0.36 (0.10–1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td>&lt;CIN2</td>
<td>256</td>
<td>106 (41.4 (34.9–48.1)</td>
<td>128 (49.8 (43.2–56.3)</td>
<td>65.7 (59.1–72.9)</td>
<td>1.51 (0.91–2.48)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*NOTE: Column with +/− denotes cases positive for cervix and negative for urine and vice versa for −/+. *Percentage of total in (+/− or −/−) groups.
Table 3. Agreement between the Trovagene HPV test and other HPV tests using the PreservCyt cervical sample

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Positive (%)</th>
<th>+/+</th>
<th>+/-</th>
<th>-/+</th>
<th>-/-</th>
<th>Agreement (%)</th>
<th>McNemar OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hC2</td>
<td>281</td>
<td>239 (85.1)</td>
<td>222</td>
<td>17</td>
<td>12</td>
<td>30</td>
<td>89.7 (86.1–93.2)</td>
<td>0.71 (0.31–1.57)</td>
</tr>
<tr>
<td>RealTime</td>
<td>501</td>
<td>381 (76.0)</td>
<td>352</td>
<td>29</td>
<td>51</td>
<td>69</td>
<td>84.0 (80.8–87.2)</td>
<td>1.76 (1.09–2.88)</td>
</tr>
<tr>
<td>Onclarity</td>
<td>501</td>
<td>389 (77.6)</td>
<td>364</td>
<td>25</td>
<td>39</td>
<td>73</td>
<td>87.2 (84.5–90.3)</td>
<td>1.56 (0.92–2.69)</td>
</tr>
<tr>
<td>PapType</td>
<td>488</td>
<td>392 (80.3)</td>
<td>348</td>
<td>28</td>
<td>44</td>
<td>68</td>
<td>85.2 (82.3–88.4)</td>
<td>1.57 (0.96–2.62)</td>
</tr>
<tr>
<td>Aptima</td>
<td>495</td>
<td>380 (76.8)</td>
<td>354</td>
<td>26</td>
<td>12</td>
<td>30</td>
<td>89.7 (86.1–93.2)</td>
<td>1.76 (1.09–2.88)</td>
</tr>
</tbody>
</table>

NOTE: Positivity for the other assays and concordant and discordant pairs are given along with agreement and McNemar OR for discordant pairs. Column with +/+ denotes cases positive for the other assay and negative for Trovagene and vice versa for -/-.

*Percentage of all samples that give concordant results (+/+ or -/-).
*bRatio of number of cases that are +/+ to those that are -/+ (with 95% CIs).

cervical samples from the same woman. We found the sensitivity observed for urine in this study to be comparable with cytology in our previous referral population study conducted in the same clinic, where a sensitivity of cytology for CIN2+ of 88.9% (95% CI, 85.1–91.9) was observed (2). The low specificity is also representative of results found for other tests in a referral population (2).

Testing urine for sexually transmitted infections is widely performed and accepted by both men and women. Such testing requires first catch (initial stream of 20–50 mL) from a void at any time of day (16). It has been suggested that the accuracy of HPV testing from urine samples might be improved if the initial stream specimen was used to increase HPV DNA concentration, or a DNA conservation buffer. In our study, we sent an average of 55 mL (minimum 20 mL) of urine for testing, but did not specifically collect first catch (initial stream) or clean catch (midstream) urine that is collected for the detection of sexually transmitted infections and urinary tract infections, respectively. This was based on a small pilot urine sampling study using a morning void urine sample, and initial stream and midstream samples from urine samples collected at the clinic. Urine samples were tested using the Trovagene HPV test, and all samples showed the same sensitivity for CIN2+ (0.88; 95% CI, 0.56–0.99) and specificity appeared comparable, suggesting that the results may be less dependent on the timing and urine stream of the sample collection (17). Within our reported study, samples were collected at the clinic, at any time of the day, with a preservative manually added immediately after collection to maintain the integrity of the sample; however, tubes precoated with a preservative would be better suited for self-collection. Additional research is needed to identify optimal urine sample collection parameters and to improve the preservative delivery process.

In our study, women were not surveyed to assess the acceptability and preference for physician-collected cervical samples versus self-collected urine samples. However, in the pilot urine sampling study, when surveyed, women preferred self-sampling over physician-sampling and specifically urine sampling over self-collected cervico-vaginal samples (17). The sample size of that study was small, and thus, more work also should be done to understand whether women prefer to provide a self-collected vaginal sample or a urine sample and to understand whether there are cultural differences in different populations.

Lack of compliance remains the limiting feature in cervical screening. In the long term, vaccination against HPV infection in early adolescence will help to address the problem of lack of screening, but this does not help women who are now over the age of 25 years, where screening remains the primary preventive measure (18–21). Self-sampling is an important addition to cervical screening, enabling samples for HPV testing to be

Figure 2.

Sensitivity and specificity of the Trovagene HPV test in matched urine and PreservCyt cervical samples compared with other sensitive HPV tests (Cuzick, et al. 2015) for CIN3+ (A) and CIN2+ (B). Parts of Fig. 2 are reprinted from J Clin Virol 2016;82:145–51, Cuzick J, Ahmad AS, Austin J, Cadman L, Ho L, Terry G, and colleagues. A comparison of different human papillomavirus tests in PreservCyt versus SurePath in a referral population-PREDICTORS 4, with permission from Elsevier.

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obtained from unscreened or underscreened women. Most studies have been conducted on self-collected cervico-vaginal samples, but urine may prove to be a more acceptable sample for many women.

Previous studies have shown that a referral population is usually an efficient and accurate measure of sensitivity in a screening context, but its higher HPV positivity rate may make it is less reliable for assessing the specificity (2, 22). This was not however seen by Combita and colleagues, who found overall HPV prevalence in paired urine and cervical samples from unvaccinated 18 to 25 year olds attending for screening was 64.7% and 60.0%, respectively (23). This does not support the common view that HPV prevalence is lower in urine. Further studies are needed to validate the performance of the Trovagene HPV test with urine sampling, especially for specificity in a screening population. This should potentially include self-samples, although a previous study in a UK screening population, using self-sampling for the Trovagene test, did not show statistically significant differences in sensitivity in self-samples (19% difference; 95% CI, 0.2–40) and only a marginally significant difference in specificity (2% difference; 95% CI, 0.3–4; ref. 24).

Disclosure of Potential Conflicts of Interest

M.H. Stoler has received speakers bureau honoraria from BD Life Sciences and Roche and is a consultant/advisory board member for BD Life Sciences, Cepheid, Hologic/GenericProbe, Invitrogen Pharmaceuticals, Merck, and Roche/Ventana. David Robbins is the vice president (product development) at and has ownership interest (including patents) in Trovagene. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: J. Cuzick, L. Cadman, D. Robbins


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Cadman, L. Ho, G. Terry, M. Kleeman, D. Lyons, J. Austin, M.H. Stoler, D. Robbins

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Cuzick, L. Cadman, A.S. Ahmad, C.R.T. Vibat, M.G. Erlander

Writing, review, and/or revision of the manuscript: J. Cuzick, L. Cadman, L. Ho, G. Terry, D. Lyons, M.H. Stoler, J. Dockter, P.R. Billings, M.G. Erlander

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Cadman, L. Ho, G. Terry, M. Kleeman, J. Austin, C.R.T. Vibat

Study supervision: L. Cadman, L. Ho, G. Terry, C.R.T. Vibat, P.R. Billings

Other (lead colposcopist, recruited patients for study, reviewed manuscript or created, encouraged all in the department to undertake study and recruit patients, answered queries): D. Lyons

Other (funding): P.R. Billings

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References


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