The study analyzed the significance of an atypical cytology and whether indexing to NMP22 could improve its clinical utility. One hundred ninety-seven patients with risk factors for bladder cancer (hematuria, lower urinary tract symptoms, and known history of bladder cancer) were identified to have atypical urine cytology. Cystoscopy and TURBT (if necessary) was performed. All cases are histologically confirmed. One hundred twenty-six with atypical cytology were incident (screening) cases and 71 were prevalent (known) cases of bladder cancer. The atypical cytologies were retrospectively indexed to NMP22 values. In the screening group, the 126 atypical cytologies detected 17 cancers, for a positive predictive value (PPV) of 13% and when stratified by NMP22 (>10U/mL) the PPV increased to 67% (12/18). In the monitoring group, the 71 atypical cytologies detected 43 cancers for a PPV of 61%, but when stratified by NMP22 (>6U/mL) the PPV increased to 92% (35/38). The clinical utility of atypical cytology is significantly enhanced in both screening and monitoring patients for bladder cancer when indexed to NMP22.