An Occult Specimen Provenance Errors in Routine Clinical Practice

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Key Words: Switching errors; Specimen provenance; Specimen identification errors; Microsatellite analysis; Short tandem repeat analysis; Prostate biopsy; Patient safety

Abstract

Occult specimen provenance complications (SPCs), which occur when there is an absence of any direct or indirect indication that a specimen switch or contamination may have occurred, constitute a significant patient safety and medical-legal problem because they can lead to misdiagnosis. However, the rate at which occult SPCs occur is unknown because, by definition, this category of errors is not identified by standard laboratory practices. In this study, we evaluated a data set comprising almost 13,000 prostate biopsies that were prospectively tested for specimen provenance errors as part of routine clinical practice. The frequency of occult type 1 errors (a complete transposition between patients) and type 2 errors (contamination of the patient’s tissue with 1 or more unrelated patients) was 0.26% and 0.67%, respectively; every urology practice setting and surgical pathology laboratory type with a representative sample size experienced at least 1 type 1 and 1 type 2 error during the study period. Overall, the mean frequency of SPCs across practice settings was 0.22% for type 1 errors and 1.69% for type 2 errors. The type 1 rate showed no correlation with a surgical pathology laboratory setting or urologic practice group setting; the type 2 rate correlated solely with a surgical pathology laboratory setting. The occult SPC rate in this limited data set provides an estimate of the scope of the problem of potential misdiagnosis as a result of occult specimen provenance errors in routine clinical practice.

Specimen identification issues are an ongoing problem in clinical laboratories. In the context of surgical pathology, specimen labeling problems occur in about 6% of accessioned cases, and extraneous tissue contaminants can be identified in up to 2.9% of slides1,2; it is noteworthy that, of the tissue contaminants encountered prospectively, approximately 30% are abnormal or neoplastic, and about 10% present some degree of diagnostic uncertainty.1 Particularly troublesome is the fact that specimen identification errors (also known as specimen provenance complications [SPCs]) can arise at any phase of the surgical pathology test cycle, including the preanalytic phase of specimen collection, which is completely outside the control of the pathology laboratory.3-9 Although recent reports have demonstrated that the application of new technologies can decrease preanalytic SPCs,10-12 misdiagnosis due to specimen mix-ups remains a significant patient safety concern in all surgical pathology laboratories.13-15 Despite more than a century of process improvements and technical innovation, the potential for specimen mix-ups, cross-contamination, floaters, or carryover artifacts has not been eliminated completely.

Over the past decade, short tandem repeat (STR) analysis has emerged as a DNA-based method with clinical applicability for specimen identity testing. The panel of STRs (also known as microsatellites) used in the testing is based on the Combined DNA Index System (CODIS) loci originally selected by the Federal Bureau of Investigation of the United States.16 The CODIS loci feature high-level polyallelism and broad distribution of the different alleles across various population groups, characteristics that provide STR-based testing with a very high power of discrimination for assigning specimen provenance in clinical settings. The utility of STR...
analysis using the CODIS loci is enhanced by the ease of testing (commercial kits are available), the availability of technical resources to support test interpretation, and demonstrated clinical utility for the resolution of a wide variety of specimen labeling and identification issues.9,14,17

STR analysis has been shown to be particularly useful in identifying occult specimen identity errors, the class of complications for which there is an absence of any direct indication that a specimen switch or contamination may have occurred.9 Occult SPCs constitute a significant patient safety and medical-legal problem because they can have a profound impact on diagnosis and treatment.9,14,17-19 but the rate at which occult SPCs occur is unknown because, by definition, this category of errors is not identified by standard laboratory practices. Data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial suggests that undetected SPCs occur at a rate of up to 0.5%.20 but because the REDUCE trial was a multicenter international trial, it is uncertain whether the documented error rate is representative of specimens processed exclusively in the United States.

To obtain some measure of the rate of occult specimen identity errors in the United States, we contacted a private laboratory (Strand Analytical Laboratories, Indianapolis, IN) that markets a system designed to detect occult SPCs in routine clinical practice (the know error system; knowerror.com). The laboratory agreed to provide us with unfettered access to their data set from testing for occult SPCs in the setting of transrectal prostate biopsy performed to rule out adenocarcinoma of the prostate (a data set comprising almost 13,000 biopsy specimens, which were prospectively tested for specimen provenance using STR analysis, in real time, as part of routine clinical practice). The results of our analysis of this data set not only provide an estimate of the rate of occult SPCs in the United States but also demonstrate that errors occur across the range of practice settings and diagnostic laboratories.

**Materials and Methods**

**Data Set**

DNA specimen provenance analysis is a relatively new test, and there is no standardized clinical testing paradigm. However, some clinical groups and surgical pathology laboratories have elected to incorporate prospective provenance testing into their clinical practice for patient safety and medical-legal reasons, and the subset of those practices that use the know error system formed the study group in this analysis.

Strand Analytical Laboratories (Clinical Laboratory Improvement Amendments [CLIA] licensed to perform high-complexity DNA testing) received orders from physicians (on a fee-for-service basis) to perform DNA specimen provenance testing as part of routine care using the know error system on a total of 13,294 patients from May 1, 2009, through July 31, 2011. Within this period, 40 orders were placed because of a suspected SPC; because the objective of this study was to measure the incidence of occult SPCs, these 40 cases were excluded from the data set. In addition, 307 orders were placed for DNA specimen provenance testing of tissue types other than prostate biopsies; these 307 cases were also excluded from the data set. The remaining 12,947 cases therefore represent all orders during the study period for DNA specimen provenance testing of prostate biopsies for which there was no suspicion of an SPC.

For each case ordered during the period, the data set provided for analysis included the unique barcode identifier associated with the case, the test result, the dates of service and sample receipt by Strand, the name of the practice collecting the biopsy and of the pathology lab performing the pathology, ordering physician identification, diagnosis codes, duration of the urology practice’s usage of the know error system, size of the physician practice (when known), and a classification of the laboratory setting.

**Clinical Testing Paradigm**

All specimens tested were collected using standardized know error biopsy kits, which incorporate forensic chain of custody principles and patient-specific barcoding of all specimen containers. All components within each know error kit receive a matching barcode in an International Organization for Standardization–certified manufacturing facility, and each kit is sealed with a tamper-evident security seal prior to delivery to the physician practice to ensure the integrity of the barcoding schema assigned to a given kit. Personnel at collection sites were trained in the proper use of the know error system, and clear instructions for proper specimen collection and handling were printed inside each kit, including the importance of opening only one kit at a time and only in the procedure room in front of the intended patient.

Buccal swabs were collected prior to performance of the biopsy procedure, sealed with tamper-evident security seals, self-identified by the patient and/or a witness, and sent directly to Strand for archival storage. The tissue cores from the transrectal biopsy procedure were placed in the fixative jars in the know error kit (which had barcodes matching that kit’s corresponding buccal swab), resealed using fresh security seals, and sent for standard processing and histopathologic diagnosis by an anatomic pathology laboratory according to the urologist’s routine referral pattern. DNA specimen provenance testing was ordered on a reflex basis only for patients with a diagnosis of adenocarcinoma (in most pathology labs, additional tissue scrolls from the block were cut after the diagnosis of adenocarcinoma, placed by the pathology laboratory...
into the barcoded Eppendorf tubes contained within the know error kit, and delivered to Strand; in a minority of labs, tissue scrolls were sent to Strand in advance of the final diagnosis).

The reference and biopsy specimens were processed by Strand based on the barcode identifier, and the STR profiles were classified according to the scheme in **Table 1**, as illustrated in **Figure 1** and **Figure 2**. Among the various quality control (QC) steps performed on all kits as part of Strand’s normal testing process was a computerized DNA profile search in which the profiles observed in each test kit were compared against the profiles obtained from other samples in the immediate test batch, as well as against a database that contains the profiles of Strand employees, employees of the know error kit manufacturers, employees from referring pathology laboratories (when submitted), and all other DNA provenance testing previously performed at Strand—a profile search designed to identify incidents of transposition, duplication, or contamination occurring within the test process itself. Additional QC testing was performed for those cases in which the DNA profiles obtained from the reference and tissue sample(s) indicated a nonmatch; specifically, a second reference swab (if available) was tested to ensure that the reference profile was correct, DNA from the various intermediate steps performed at Strand was retested, and the nonmatch data and any conclusions regarding the nature and origin of the nonmatch were verified by 2 independent technical reviewers. In those cases in which a provenance complication was detected that was determined to have occurred outside Strand, the urologist was immediately notified of the result, and recommendations to resolve the SPC were discussed. In this current study, the only cases included as a nonmatch were those for which the origin of the nonmatch was determined to have occurred outside Strand.

**Table 1**
Classification of Specimen Provenance Complications

<table>
<thead>
<tr>
<th>Specimen Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Transposition: Reference and tumor tissue each show an allelic pattern consistent with an origin from a single individual, but the reference and tumor specimen do not originate from the same individual.</td>
</tr>
<tr>
<td>Type 2</td>
<td>Contamination: Additional allelic peaks are present within the tumor specimen indicative of a mixed short tandem repeat profile derived from the reference profile and 1 (or more) other individuals.(^a)</td>
</tr>
<tr>
<td>Type 3</td>
<td>Quantity not sufficient</td>
</tr>
<tr>
<td>Type 4</td>
<td>Match</td>
</tr>
</tbody>
</table>

\(^a\) Approximately 0.53% of cases contained 1 or more specimens that exhibited an allelic profile that was not a match to the reference profile but could not be delineated as a mixture of DNA from 2 or more individuals; these cases (which may represent microsatellite instability within the tumor) were excluded from specimen provenance complications identified as type 1 or type 2 complications.

**Figure 1** Example of a type 1 specimen provenance complication. The reference (A) and tumor tissue (B) each show an allelic pattern consistent with an origin from a single individual, but the profiles do not originate from the same individual.
In the majority of practices submitting orders during the period covered by the data set, DNA specimen prov-\nenance testing was performed on every tissue core that demonstrated adenocarcinoma; in a minority of practice settings, only a subset of positive cores was tested (typically the cores that showed adenocarcinoma with the highest Gleason score). No attempt was made to correlate nonmatch rates between the 2 testing paradigms because it was not always evident from test orders what percentage of positive cores from each patient were sent for testing (and institutional review board [IRB] limitations precluded any attempt to contact the ordering urologist to obtain this information).

**STR Typing**

DNA was extracted from the target samples according to established protocols, and STR typing was performed via multiplex fluorescent polymerase chain reaction amplification using AmpFlSTR Identifiler, Identifiler Plus, or Mini-\nFiler amplification kits (Applied Biosystems, Foster City, CA). Amplicons were separated by capillary electrophoresis on a 3130xl or 3730 Genetic Analyzer (Applied Biosystems), and the STR marker profile was evaluated using the fragment analysis program GeneMapper ID v3.2.1 (Applied Biosystems).

**Statistical Analysis**

To group practices with similar specimen-handling processes and characteristics, we classified each pathology laboratory into 1 of 5 laboratory settings based on workflow model, location, and management structure. Classifications included physician-owned laboratories located in a facility owned and operated by the physician group performing the biopsies, independent reference laboratories with no common ownership or facilities shared with the ordering physician practice, hospital laboratories, laboratories physically located in a facility shared with the physician practice but operated under the management or control of an independent third party, and laboratories wherein the technical histopathology component and professional pathology read are performed in different physical locations, necessitating transport of prepared slides between those locations.

Descriptive statistics were calculated for the primary outcome in the study sample—namely, the occult error rate. Correlations with laboratory characteristics (including uro-\nlogic practice type, surgical pathology laboratory setting, and number of doctors in the urology practice) and the primary outcome were analyzed using a negative-binomial model. All tests were 2-sided, and the significance level was set at .05. SAS version 9.3 (SAS Institute, Cary, NC) was used to perform all statistical analyses.

**Regulatory Approval**

For occult specimen complication rate analysis, the data were stripped of all patient identifiers and evaluated retrospec-\ntively in aggregate only, in accordance with IRB guidelines governing Strand Analytical Laboratories and Washington University School of Medicine.
Results

The frequency of type 1 and type 2 errors of the urology practices using the know error system and of the surgical pathology laboratories performing the histopathologic diagnosis of the prostate biopsies is presented in Table 2. Specifically, the frequency of occult type 1 and type 2 SPCs among 54 laboratories was 0.26% and 0.67%, respectively. However, it is important to note that for each complication event, (at least) 2 individuals are implicated—specifically, the target patient and the foreign patient (or patients) whose tissue was misidentified as originating from the target patient. In some of the captured events, the source of the occult provenance error was readily determined by virtue of the fact that the foreign patient’s STR profile was already in the laboratory database; in other events, the source of the occult provenance error was unidentified, either because the foreign DNA profile was not sufficient to determine a match within the database or because the foreign DNA was from a patient not in the database. In either event, the complication was reported as a single observation in the data set, and thus the results underestimate the percentage of patients affected by the provenance errors by at least a factor of 2.

Table 3 presents the descriptive statistics for the type 1 and type 2 complication rates. Overall, the mean percentage in all practice settings was 0.22% for type 1 provenance errors and 1.69% for type 2 provenance errors. It is noteworthy that every urology practice setting and pathology laboratory type with a representative sample size (at least 1,000 specimens included in the data set) experienced at least 1 type 1 and 1 type 2 error. Use of a negative-binomial model to investigate the relationship between the occult error rates and lab characteristics shows that surgical pathology laboratory setting and urologic practice group setting are not correlated with type 1 complications, but surgical pathology laboratory setting is correlated with type 2 complications Table 4.

Table 2
Frequency of Occult Type 1 and Type 2 Complications

<table>
<thead>
<tr>
<th>No. of Laboratories</th>
<th>No. of Cases</th>
<th>No. of Occult Type 1 Complications</th>
<th>No. of Occult Type 2 Complications</th>
<th>Type 1 Rate, %</th>
<th>Type 2 Rate, %</th>
<th>Total Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical pathology lab setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third party managed</td>
<td>1</td>
<td>1,457</td>
<td>3</td>
<td>4</td>
<td>0.21</td>
<td>0.27</td>
</tr>
<tr>
<td>Hospital</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Physician-owned lab</td>
<td>25</td>
<td>5,929</td>
<td>16</td>
<td>41</td>
<td>0.27</td>
<td>0.69</td>
</tr>
<tr>
<td>Reference lab</td>
<td>23</td>
<td>3,748</td>
<td>14</td>
<td>35</td>
<td>0.37</td>
<td>0.93</td>
</tr>
<tr>
<td>Technical component/ professional component split</td>
<td>1</td>
<td>1,731</td>
<td>1</td>
<td>7</td>
<td>0.06</td>
<td>0.40</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total or average</td>
<td>54</td>
<td>12,947</td>
<td>34</td>
<td>87</td>
<td>0.26</td>
<td>0.67</td>
</tr>
<tr>
<td>Urology practice group setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multispecialty</td>
<td>30</td>
<td>5,512</td>
<td>15</td>
<td>37</td>
<td>0.27</td>
<td>0.67</td>
</tr>
<tr>
<td>Single specialty</td>
<td>23</td>
<td>7,356</td>
<td>19</td>
<td>50</td>
<td>0.26</td>
<td>0.68</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total or average</td>
<td>54</td>
<td>12,947</td>
<td>34</td>
<td>87</td>
<td>0.26</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 3
Descriptive Statistics for the Primary Outcome (Occult Error Rate) in the Study Sample

<table>
<thead>
<tr>
<th>No. of Laboratories</th>
<th>Type 1 Rate, Mean ± SD</th>
<th>Type 2 Rate, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical pathology lab setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third party managed</td>
<td>1</td>
<td>0.21 ± NA</td>
</tr>
<tr>
<td>Hospital</td>
<td>3</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Physician-owned lab</td>
<td>25</td>
<td>0.13 ± 0.38</td>
</tr>
<tr>
<td>Reference lab</td>
<td>23</td>
<td>0.37 ± 1.39</td>
</tr>
<tr>
<td>TC/PC split</td>
<td>1</td>
<td>0.06 ± NA</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Total or average</td>
<td>54</td>
<td>0.22 ± 0.94</td>
</tr>
</tbody>
</table>

Table 4
Univariate Analysis of the Frequency of Type 1 and Type 2 Complications Using a Negative-Binomial Model

<table>
<thead>
<tr>
<th>Type 1 Rate, P Value</th>
<th>Type 2 Rate, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical pathology laboratory setting</td>
<td>.4802</td>
</tr>
<tr>
<td>Urology practice group setting</td>
<td>.8163</td>
</tr>
</tbody>
</table>

Discussion

The fundamental observation of this study is that, when prospectively evaluated in routine clinical practice, the frequency of occult type 1 provenance errors (complete transposition between patients) and type 2 provenance errors (contamination of the target patient’s tissue with that of 1 or more unrelated patients) among a number of urology practices and surgical pathology laboratories was 0.26% and 0.67%,
respectively. Furthermore, every urology practice setting and pathology laboratory type (for which at least 1,000 specimens were included in the data set) had a nonzero error rate and experienced at least 1 type 1 error and 1 type 2 error.

It must be emphasized that the data set employed in this analysis has some significant limitations. First, the precise details of the clinical testing paradigm were not standardized across practice settings, and the clinical impact of the detected occult provenance errors was unknown (because of IRB limitations). Second, the prospective STR analysis was ordered as part of routine patient care by individual urologists and urology practice groups that voluntarily chose to implement the know error system into their practice, and it is uncertain whether this self-selection introduced any bias into the data. Third, it is unclear whether pairings between specific urologic pathology practices and specific pathology laboratories created workflows that introduced bias to the data set; the correlation between type 2 complications and surgical pathology setting may be due to some intrinsic practice pattern that is not evident in this data set. Fourth, we cannot exclude that the know error system itself, or associated awareness by the urology practices/pathology labs that their processes were under scrutiny, may have decreased the intrinsic rate of occult SPCs due to what is colloquially referred to as the Hawthorne effect,

likewise, we cannot exclude the possibility that the workflow associated with the know error system introduced SPCs in some cases. Fifth, it is unknown whether the knowledge that an occult SPC had occurred resulted in specific process improvements in the involved urology practice or pathology lab and how those improvements may have affected the data set. Sixth, the know error system incorporates a number of best-practice strategies for error reduction, including forensic chain of custody protocols, barcoding, and the physical and temporal isolation of specimen containers by the patient (to prevent batching and prelabeling); because many practices employ only a subset (if any) of these strategies, the occult error rate in practices that do not use the know error system cannot be extrapolated from this data set. Despite these limitations, the data set nonetheless provides an estimate of the scope of the problem of occult specimen identity errors in routine clinical practice. Namely, for every urology practice setting and pathology laboratory type, the rate of type 1 occult errors is nonzero (specifically, between 0.06% and 0.37%) and that of type 2 errors is also nonzero (specifically, between 0.27% and 0.93%).

There is an extensive literature on the origin of SPCs. SPCs associated with deficiencies in specimen labeling, mismatches between the patient name on the container and the requisition slip, accessioning errors, and the like occur in about 6% of accessioned cases, according to the College of American Pathologists Q-Probes study. Specimen identification issues due to presumably extraneous tissue contamination in surgical or cytology specimens occur in about 0.6% of slides evaluated prospectively and 2.9% of slides evaluated retrospectively with specific intent to identify contaminants.

Although all SPCs raise patient safety issues, those that occur at the time of specimen collection are especially problematic because they engender identification errors that persist throughout the surgical pathology test cycle but are, by definition, unknown to the pathology laboratory and thus beyond established laboratory QC and quality assurance (QA) activities. Conversely, misidentification of specimens upon initial receipt in the pathology laboratory may be likewise undiscoverable by established laboratory QC activities and invisible to the practice collecting the specimen.

The demonstrated utility of STR-based testing to detect SPCs in the absence of any direct indication that a specimen switch may have occurred highlights the utility of the methodology to detect specimen switches not captured by current laboratory protocols. Nonetheless, most studies addressing SPCs have not been designed to detect occult SPCs. To date, only 1 reported study, the REDUCE trial, has attempted to measure the rate of occult SPCs prospectively. Although prospective specimen provenance testing was not an initial component of the trial’s design, the discovery of 3 instances of occult biopsy misidentification in the first 2 years of the trial led to a study change in which all protocol-mandated biopsy samples underwent STR analysis. In the first 2 years of the trial, a 0.4% occult prostate biopsy misidentification error rate was discovered; multiple changes in specimen handling and process improvements were instituted for the final 2 years of the trial, which resulted in a reduction of the occult prostate biopsy error rate to 0.02%. However, a 0.5% occult error rate persisted in the identification of blood samples that served as patient reference samples, which is noteworthy because it suggests that process improvements focused on decreasing misidentification errors in the prostate biopsies did not generalize into improvements in the misidentification rate of the reference samples.

Because the REDUCE trial was a multicenter multinational study and the root cause of the SPCs in the trial was not reported, it is difficult to make direct comparisons between its measured specimen misidentification rates and the rates in the data set we here report. All laboratories in the current data set are in the United States and are CLIA-licensed labs. Although attention to detail and the introduction of process improvements and technical procedures designed to eliminate specimen switches (including, for example, differential inking, use of barcoding, and even implementation of radiofrequency identification tags) may be able to reduce the frequency of identification errors,

no level of attention to laboratory processes and procedures will address SPCs that occur in the biopsy suite outside of the surgical pathology lab’s control. It is unknown from our data set at which point in the test cycle
(preanalytic, analytic, or postanalytic) the identification errors occurred that were captured by the know error system or, in most cases, whether mismatches were caused by misidentification errors relating to the reference specimen or the tissue biopsy specimen itself. However, the multiple QA and QC steps performed at Strand (as detailed in the Materials and Methods section) make it difficult to argue that the STR test process itself was responsible for the errors.

As noted earlier, IRB approval for this study required the data set to be stripped of all patient identifiers and evaluated retrospectively in aggregate only; clinical follow-up could therefore not be collected on cases with demonstrated provenance errors. Consequently, it is beyond the scope of this study to determine the clinical impact of the occult provenance complication events that were detected and whether any of the errors would have resulted in adverse patient outcomes had they not been detected by STR testing. Nonetheless, it is possible that in a subset of cases, the adenocarcinoma from the foreign patient that was the source of the extraneous tissue exhibited sufficiently similar characteristics to those of the target patient such that either patient’s diagnosis would have resulted in the same course of therapy. Regardless of the portion of cases in which patients may have, by chance, received the correct treatment despite the specimen identity error, the fact remains that in 0.26% of cases (and perhaps as many as 0.93%), a diagnosis was assigned to the wrong patient with no knowledge or even suspicion of the error that had occurred.

A recent study performed a full economic analysis of prospective DNA specimen provenance testing to prevent occult specimen provenance errors. Based on the modeled occult error rates in that analysis, the actual occult error rates documented in this study support the conclusion that prospective DNA testing to confirm the identity of prostate biopsies that show adenocarcinoma is likely a cost-effective method for preventing treatment errors stemming from misidentification and is also likely to reduce total costs to the health care system associated with otherwise undetected SPCs. Nonetheless, it remains uncertain whether the cost of DNA-based testing (as with most health care–related expenditures) is best borne by insurers, providers, or patients.

The concept of a “DNA timeout” implies that patient safety can be improved by providing the opportunity to rule out a diagnostic error due to an occult SPC in those settings where a specific diagnosis will lead to aggressive surgical or medical therapy. The occult SPC rate we report, derived from a routine patient care paradigm, provides an initial estimate of the scope of the problem in a rather narrow clinical setting. However, this data set can serve as a basis for analyzing the role of prospective specimen provenance testing for individual patients, specific diseases, and the health care industry. Different testing approaches will be associated with different cost structures, and it remains to be determined which approaches will be optimal from both patient safety and medical economic perspectives.

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