DNA-based Testing for Diagnostic Specimen Confirmation

The Problem

Specimen labeling errors and sample cross-contamination are well recognized sources of errors in all laboratories, including clinical and anatomical pathology facilities (1-10). Instances when there is no direct or indirect indication of specimen mislabeling, switch, or cross-contamination, so called occult errors, pose a particular risk to patient safety as they can easily lead to a misdiagnosis. The literature categorizes these errors as Type 1; i.e., a complete switch of a patients’ sample(s). Type 2 errors refer to contamination of a patient’s sample with tissue(s) from one or more unrelated patients (colloquially called ‘floaters’); unfortunately these errors can also lead to misdiagnosis. Type 1 errors will always involve two patients while Type 2 errors can involve one, or two patients, depending on the circumstances. The misdiagnosis due to Type 1 or Type 2 errors can be serious as an undetected error can lead to a healthy patient being diagnosed with cancer, or lead to a missed diagnosis of a life-threatening condition. The current litigious medico-legal environment does not favor either outcome; however a simple solution for both Type 1 and Type 2 error is available.

There is now a considerable scientific literature describing numerous studies and reports which evaluate the level, type and rate of cross-contamination and mis-labeling errors (sometimes referred to as sample provenance errors). Importantly many of these studies also offer suggestions on how to reduce, or possibly eliminate, laboratory mis-labeling errors (1-10). A recent study reviewed 13,000 prostate biopsies from 54 laboratories which included 25 physician-owned and 23 reference laboratories (1). The error rate data shows that any facility that processed at least 1,000 specimens incurred at least one Type 1 error and at least one Type 2 error – apparently no laboratory was immune to this problem. This study found an overall average error rate of 0.26% for Type 1 errors (i.e., on average, at least 2 instances of undetected patient sample switches per 1,000 pathology samples) and an overall rate of 0.67%
for Type 2 errors (i.e., on average, at least 6 instances of cross-contamination between patients’ samples per 1,000 tests). Unfortunately the authors declined to extrapolate these rates to the overall, and larger, population of patients who receive a diagnosis from the examination of pathology samples.

The Solution

A well understood solution to identifying, and rectifying, both Type 1 and Type 2 errors is the use of DNA-based identify testing. This approach can identify both Type 1 and Type 2 errors by matching the tested specimen to a standard obtained from the patient. This solution is easy to implement and relatively inexpensive.

The logistics of DNA-based identity testing are straightforward. The patient’s sample (the reference) is a non-invasive Buccal (cheek) swab collected at a physician office, or at the hospital. The Buccal swab is stable at room temperature and can be mailed to the DNA identity testing laboratory. The pathology/clinical sample (the questioned sample) is also sent to the DNA identity testing laboratory; both samples are processed to determine their respective DNA profiles and the results compared. The statistics of DNA profiling are well understood and matching the patient to the pathology sample can be made to an extremely high degree of certainty. DNA profiles that do not match indicate (essentially without discussion) that a mismatch needs to be explored further.

The science behind DNA “fingerprinting” (technically a forensic DNA profile) is well established both scientifically and legally. The genetics of identity testing is based on a panel of Short Tandem Repeat (STR) markers and is an accurate, fast and inexpensive identification method which has undergone extensive validation. DNA-STR analysis is now the ‘gold’ standard for individualized human identification (11). The data for the DNA profile are obtained by using state-of-the-art, validated and QA/QC tested commercially available PCR (polymerase chain reaction) amplification kits, capillary electrophoresis instrumentation and proven software. Currently a panel of 15 autosomal STR loci and the Amelogenin gender-determining marker are amplified in a single multiplex PCR reaction (12, 13). This PCR reaction is analyzed using highly
reproducible capillary electrophoresis instrumentation followed by a computer assisted analysis of the electropherogram to produce the unique DNA profile of the sample. Data comparison of the patient’s reference sample and the pathology sample is automated: the combined power of discrimination exceeds $1 \times 10^{15}$ for unrelated individuals (12, 13). In other words if the specimen in question and patient’s known sample are derived from unrelated individuals, there is a greater than 99.9999% probability that the resulting DNA STR profiles will be different at one or more markers. Put yet another way; both Type 1 and Type 2 errors are easily detected using DNA-based identity testing. In rare cases when samples derived from tumors that demonstrate high-microsatellite instability and extensive loss of heterozygosity (i.e., the sample produces less data from fewer markers due to DNA loss or damage) additional STR markers can be used for the testing.

DNA testing laboratories are extensively inspected and audited; there are numerous quality control requirements including both administrative and technical review of all case files and reports issued by the laboratory. Additionally, all cases with a ‘mis-match’ are repeated thereby taking into account (and eliminating) the possibility that the DNA laboratory itself may have a Type 1 error.

The cost of DNA profiling for sample provenance assurance is now quite reasonable – in the $200-250 range for patients, and less for institutions and is recognized as a cost-effective approach to improve patient safety (14). Reimbursement is still in flux and it may take a little longer before the healthcare and medical insurance industries sort out who should pay for this test. But, patients and doctors should not wait. It may be especially important for newly diagnosed patients facing aggressive surgical or medical therapy to verify that the pathology sample their diagnosis is based upon is proven to be theirs through an independent DNA test.

References:

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10) Patient Identification Error Among Prostate Needle Core Biopsy Specimens—Are We Ready for a DNA Time-Out?  

11) Forensic DNA Typing: Biology, Technology, and Genetics of STR Markers.  

12) AmpFISTR® Identifiler® PCR Amplification Kit User Manual

13) PowerPlex™ 16 System User Manual

14) Development of a decision-analytic model for the application of STR-based provenance testing of transrectal prostate biopsy specimens.  