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Development of a Decision-Analytic Model for the Application of STR-Based Provenance Testing of Transrectal Prostate Biopsy Specimens

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A B S T R A C T

Background: The diagnostic algorithm for most cancers includes the assessment of a tissue specimen by a surgical pathologist, but if specimen provenance is uncertain, the diagnostic and therapeutic process carries significant risk to the patient. Over the last decade, short tandem repeat (STR) analysis has emerged as a DNA-based method with clinical applicability for specimen identity testing (also known as specimen provenance testing). Although the clinical utility of identity testing using STR-based analysis has been demonstrated in many studies, its economic value has not been established. **Methods:** We developed a decision-analytic model of the application of STR-based provenance testing of transrectal prostate biopsy specimens obtained as part of routine clinical care to rule out the presence of adenocarcinoma of the prostate, as compared with no STR-based testing. Using parameter values drawn from the published literature, the cost-effectiveness of STR-based testing was quantified by calculating the incremental cost-effectiveness ratio per quality-adjusted life-year gained. **Results:** In comparison to the current standard practice of no identity testing, identity testing by STR-based analysis has an incremental cost-effectiveness ratio of $65,570 per quality-adjusted life-year gained at a testing cost of $618 per person. At a cost of $515 per person, identity testing would meet the conservative standard of $50,000 per quality-adjusted life-year. At a test cost of $290 per person, identity testing would be cost saving. **Conclusion:** Given the rapidly declining pricing of STR-based identity testing, it is likely that testing to confirm the identity of positive prostate biopsy samples will be a cost-effective method for preventing treatment errors stemming from misidentification. Studies to formally establish the frequency of specimen provenance errors in routine clinical practice would therefore seem justified.

Keywords: incremental cost-effectiveness ratio (ICER), prostate biopsy, short tandem repeat analysis, specimen identity testing, quality-adjusted life-year (QALY).

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Introduction

The diagnostic algorithm for most cancers includes the assessment of a tissue specimen by a surgical pathologist. The sample is taken from a patient with a known or suspected disease as part of a procedure in the office or surgical suite, labeled, and transported to the pathology lab for evaluation. The pathologist prepares the report, which then becomes the basis for treatment decisions. Underlying this series of events is the assumption that there is perfect continuity in the labeling and transport of the patient specimen that ensures that the specimen evaluated by the pathologist corresponds to the specimen obtained from the patient. If specimen provenance is uncertain, the diagnostic and therapeutic process carries significant risk to the patient [1,2].

There is an extensive literature on specimen identification errors (also known as specimen provenance errors, or SPEs), which can arise in the preanalytic (collection and processing), analytic, or postanalytic (reporting) stages of the specimen test cycle [3–8]. Although recent reports have demonstrated that the application of new technologies in the clinical laboratory can decrease analytic SPEs [9–11], specimen mix-ups (which are a major class of identification errors) remain a significant high-risk concern in all surgical pathology laboratories [12,13]. Despite more than a century of process improvement and technical innovation, the potential for specimen mix-ups, cross-contamination, floaters, or carry-over artifacts has not been eliminated completely [3,5,14–16].

Over the last decade, short tandem repeat (STR) analysis has emerged as a DNA-based method with clinical applicability for specimen identity testing (also known as specimen provenance testing). The panel of STRs (also known as microsatellites) utilized in the testing is based on the Combined DNA Index System loci originally selected by the Federal Bureau of Investigation of the United States [17]. The Combined DNA Index System loci feature extreme polyallelism and widespread distribution of the different alleles across different population groups, characteristics that provide STR-based testing with a very high power of discrimination for assigning specimen provenance in clinical settings. The clinical utility of STR-based testing using the Combined DNA Index System loci is enhanced by the ease of testing (commercial kits for analysis are available), the availability of technical resources to support test interpretation, and an extensive literature that has demonstrated clinical utility for the resolution of a wide variety of specimen labeling and identification issues [14,16,18].

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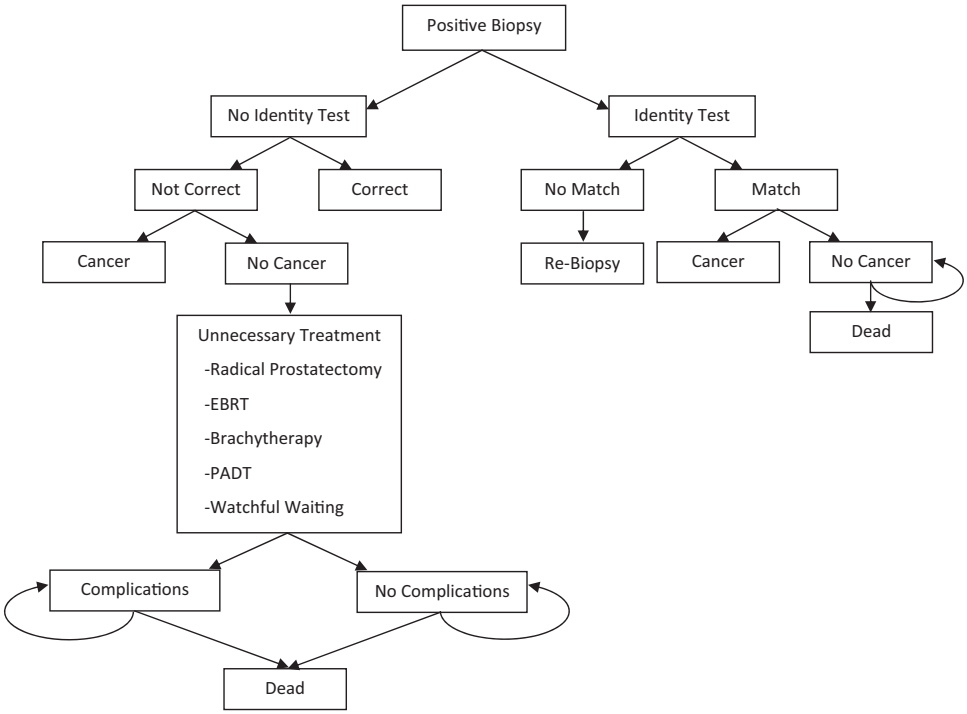

Fig. 1 – Markov model to evaluate the potential adverse outcomes of cancer treatment. EBRT, electron beam radiation therapy; PADT, primary androgen disruption therapy.

Although the clinical utility of STR-based analysis has been demonstrated in many studies, its economic value has not been established. Nearly 40% of men with an abnormal digital rectal exam result or an elevated prostate-specific antigen who undergo transrectal prostate biopsies to rule out adenocarcinoma have a positive biopsy result [19]. Given this high percentage of men with latent disease, the occurrence of a specimen switch could frequently result in a correct, albeit accidental, finding. In most cases, however, the result of an SPE for the patient would be unnecessary morbidity and mortality associated with treatment, including the potential for incontinence or impotence. Avoiding this iatrogenic harm is the benefit of STR-based analysis, but a rigorous economic evaluation to determine whether the benefit outweighs the cost of this test has not been performed.

We conducted an economic evaluation of the application of STR-based provenance testing, versus no testing, of transrectal prostate biopsy specimens obtained as part of routine clinical care to rule out the presence of adenocarcinoma of the prostate. The parameter values in our model were drawn from the published literature, and we conducted extensive sensitivity analyses to identify those factors most associated with the cost-effectiveness of STR-based provenance testing.

Methods

We constructed a decision analytic model to compare the cost-effectiveness of identity testing to prevent SPEs for prostate cancer biopsies positive for cancer, versus the current practice of no identity testing. Parameters in this model included estimates of the SPE rate in surgical pathology, the percentage of men biopsied who are diagnosed with prostate cancer, the usage of prostate cancer treatments by age, and the prevalence of side effects from treatment. We also included estimates for the quality-of-life effects of different combinations of side effects from treatment. Estimates for costs of DNA testing, prostate cancer treatment, and treatment of side effects were applied to the model on the basis of expert opinion and Medicare allowable. Uncertainty in the model stemming from variability in the values of the parameters was tested by using one-way and two-way sensitivity analyses. Analysis was conducted from a payer perspective, while assuming that quality-adjusted life-year (QALY) has meaning to a third-party payer. Costs were estimated by using the Medicare allowable.

Modeling the costs and effectiveness of identity testing for prostate cancer biopsies

In Figure 1 we provide an illustration of the Markov model to evaluate the potential adverse outcomes of cancer treatment. The treatment for prostate cancer differs by age, and so the model was stratified by age, with individuals aging throughout the modeling process (and mortality risk adjusted accordingly). Individuals whose specimen is correctly labeled face the same risk and benefit in both arms of our model; therefore, their outcomes do not affect the incremental result and are not illustrated here. Similarly, individuals with a mislabeled specimen who have prostate cancer in spite of the mislabeled sample (i.e., a surreptitious "true positive") also face the same risk and benefit in both arms of the model; therefore, their outcomes are not illustrated and were not modeled.

We assume that genetic testing is 100% accurate; therefore, no one in the "Identity Test" branch faces iatrogenic harm due to misdiagnosis; however, these patients do face the cost of a second biopsy to correct the initial erroneous diagnosis. We make the assumption that this second biopsy is 100% accurate with no identification error. In the "No Test" arm, misclassified patients undergo treatment for their incorrectly diagnosed cancer, facing the potential for adverse outcomes of treatment.

A Markov model was constructed to estimate the cost and benefit of long-term outcomes of treatment. The Markov model is a mathematical method of representing an iterative process, in this context, the medical/surgical process faced by a patient following a positive finding by the biopsy. The Markov process consists of a

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