

The NAAT Is Out of the Bag

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(See the article by Katz et al. on pages 814–9)

Nucleic acid amplification tests (NAATs) have greatly improved our ability to detect sexually transmitted infections, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. NAATs have revolutionized sexually transmitted disease (STD) prevention and control efforts by increasing the ease of screening populations and conducting surveillance [1]. Because of the exquisite sensitivity of these molecular-based assays, very minute amounts of target nucleic acid can be identified and amplified in clinical specimens. This analytic sensitivity allows use of urine specimens for diagnosis of cervical and urethral infections and allows female patients to self-collect urogenital specimens with vaginal swabs [2]. The transport requirements for specimens used in performance of NAATs are less demanding than those for specimens used in culture and allow for temporary storage of specimens at the point of collection. The use of NAATs has identified prevalent infections missed by traditional culture methods in anatomic sites like the oropharynx [3]. The use of NAATs has allowed for innovative public health

STD screening programs to be conducted through the US mail [4] and in large institutions, such as schools and the military [5, 6].

However, with every medical and public health technological advance, there is a cost. It is not surprising that tests that are more sensitive may be less specific. Although the specificity of NAATs is very high (>99.0%), unlike culture and isolation of the organism, the specificity is not perfect. Thus, testing in low-prevalence populations will result in some frequency of false-positive test results, as demonstrated by Katz et al. [7] in this issue of *Clinical Infectious Diseases*. For example, for any test with a specificity of 99.5%, 0.5% (1-specificity) of observed positive test results will be false positives. If the observed prevalence—the rate of test positivity in the population—is 1.0%, then one-half of the observed positives may be false, and the positive predictive value of the test will only be 50%. Specificity can be improved by additional testing with an alternative assay or by testing a second specimen and should always be a consideration in assessing test results [8]. Remember: a clinician, not a laboratory test, makes a diagnosis. Overinterpretation of test results is the first cost of molecular diagnostics.

The second cost to the molecular revolution results is overtesting. Because voided urine specimens can be used, testing becomes as easy as handing the patient

a specimen collection cup and labeling and checking off a box on a laboratory requisition slip. The ease of testing has been a significant benefit for screening programs—public health disease-control programs that target a specific population, such as sexually active women <25 years of age or recently incarcerated persons—but also enables the clinician to perform additional tests that otherwise might not be indicated or recommended. The subjects described by Katz et al. [7]—persons with clinical cases of bacterial vaginosis and asymptomatic, low-risk women aged >25 years—are part of this specific scenario and represent adverse clinical outcomes associated with overtesting. Arguably, in the cases of vaginitis, testing for gonococcal and chlamydial infection may have been indicated, but there was no indication for screening in the other cases.

The third cost to the molecular revolution is overbilling. Molecular testing techniques allow for the creation of multiplex tests by bundling analytic targets to create multiple tests within a single assay. Not only is overtesting facilitated, but because those who reimburse for STD tests pay laboratories on the basis of a specific analyte, it has been to the manufacturer's advantage to create and the testing laboratories advantage to use single test systems with multiple targets at little extra cost in production or processing. Thus, unlike immunizations, for which multiple antigens are good, multiplicity in diag-

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nostic testing, although convenient and profitable, may not be clinically indicated and may result in a substantial increase in costs and testing. Some of the newest molecular diagnostic products, like the Gen-Probe APTIMA Combo 2 Assay, are combined gonorrhea and chlamydia tests. Performing laboratories can bill third-party payers for 2 tests when the test is performed only once but with 2 targets. Compare this with a metabolic panel (“chem-7”) that has 7 analytes (Na⁺, K⁺, Cl⁻, CO₂, blood urea nitrogen, creatine, and glucose), for which 1 test is run with multiple outcomes: in an electrolyte panel, the payer is billed for the whole panel and not for individual tests.

Some third-party payers may change the reimbursement formula and only reimburse for 1 STD assay, regardless of the number of analytes (Gail Bolan, personal communication). In addition, in recognition of the problem of overtesting, product manufacturers have allowed test systems to be virtually unbundled by turning off equipment software that reads results, allowing determination of only a single analyte result.

Responsibility for the current situation of misapplied screening tests and overtesting also lies with the national organizations that publish recommendations for screening and for the use of these assays. For example, the Centers for Disease Control and Prevention (CDC) recommendation for chlamydia screening in patients >25 years of age (“screen those at high risk”) is too vague to be clinically useful, and there are no recommendations for the use of gonorrhea screening tests, despite years of availability. Because the organization relies on published data, the CDC is reluctant to issue screening recommendations without evidence of at what prevalence or in what population gonorrhea screening is clinically most effective.

However, in public health and medicine, recommendations sometimes need to be made in the absence of data to prevent the misuse of screening tests, as occurred in Hawaii [9].

But the ultimate responsibility for the application of screening tests—even those with imperfect specificity and a tendency for overuse and that were manufactured with multiple testing in mind—rests with the physician. The failure to elicit a sexual history from persons at risk for STDs and HIV infection has been called “tantamount to malpractice” and on the order of not taking a history of drug allergies in patients being prescribed medications [10]. National studies show that routine assessment of sexual behavior in primary care visits is infrequent (28%) and needs to improve [11]. All patients should be routinely asked, “Are you sexually active with men, women, or both?” The patient’s response should be documented in the chart and followed up with questions about the specific type of sexual activity and the number of sex partners in a particular period.

Given the adverse impact of improper screening documented by Katz et al. [7], it is incumbent for greater national and local leadership to educate clinicians in the proper use of STD screening tests. The response in Hawaii (i.e., to create a laboratory-based educational program) was enlightened, because clinicians can be reminded of the limitations of STD diagnostic testing with every test result. With more attention to and education in the proper use of STD screening tests and communication about sexual health, physicians can effectively harness the power of molecular diagnostics to the patient’s and public’s benefit. We must, however, use the gifts of the molecular revolution wisely, for, if misused, the costs—over-

interpretation, overuse, and overbilling—will overshadow the benefits.

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