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Rise in Lyme Cases Drives Interest in New Tests

Lyme disease is a growing problem in the United States. The disease is a tick-borne bacterial infection (Borrelia burgdorferi) that, if untreated, can have long-lasting rheumatic and neurological implications. But, early antibiotic treatment can effectively treat the infection and prevent progression of symptoms. Historically, definitive diagnosis has been complicated by reliance on antibody-based testing, which cannot determine if the infection was still active or not. But, with a surging number of cases, there is growing interest in the laboratory industry to improve diagnostic testing by turning to newer, more sensitive techniques.

The Centers for Disease Control and Prevention (CDC) reported last month that the number of geographic areas at risk for Lyme disease has substantially expanded over the past few decades, driven by climate change. Currently, the states with the highest disease concentration remain in the Northeast and upper Midwest, but cases of the disease are now spreading across the Mid-Atlantic. Lyme disease is the most commonly reported vector-borne illness in the United States and in 2013 it was the fifth most common nationally notifiable disease, with roughly 30,000 confirmed cases reported to the CDC annually. While CDC data shows the number of reported cases is steadily increasing, the agency says that the total number of people infected

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HCV Testing Strategies Falling Short in Reach

Newly available, highly effective treatment options have raised awareness of the need to screen for hepatitis C virus (HCV). However, several recent studies indicate HCV testing strategies are falling short both in reaching all positive cases and in retaining positive patients through confirmatory testing, and ultimately medical referral.

Despite national recommendations addressing birth cohort (1945 to 1965) and risk-based HCV screening, it is estimated that more than 50 percent of persons with HCV infection remain unaware of their positive status. Experts say a number of factors contribute to the lack of identification of positive cases including: patients' lack of disclosure of risk factors, non-complete implementation of birth cohort screening, and risk-based screening strategies that miss cases.

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■ Rise in Lyme Cases Drives Interest in New Tests, *Continued from top of p.1*

with Lyme disease is in excess of 350,000, or roughly 10 times higher than the yearly reported number. Poor diagnostic testing is partially to blame for this discrepancy.

A Snapshot of Current Testing

According to a September 2014 study published in *Clinical Infectious Disease* by CDC researchers, approximately 3.4 million tests are performed annually for Lyme disease at an estimated cost of $492 million. These estimates are generated from data provided by seven large commercial laboratories (ARUP, Clinical Laboratory Partners, Focus Diagnostics, LabCorp, Mayo Clinic Laboratories, Quest Diagnostics, and Specialty Laboratories), which accounted for greater than 76 percent of Lyme disease tests reported to health departments in endemic states in 2008.

Currently, clinical observations are used to diagnose patients with a history of probable exposure to infected ticks in the early weeks of symptoms (rash). According to the CDC, laboratory tests are "neither suggested nor required" to confirm diagnosis at this stage. However, for patients with musculoskeletal, neurologic, or cardiac symptoms, two-tiered serologic testing (an approved enzyme immunoassay [EIA] followed by an approved immunoblot/Western blot test, for confirmation of positive EIA tests) is recommended.

The *Clinical Infectious Disease* study found that in the large commercial laboratories, recommended two-tiered testing accounted for at least 62 percent of assays performed, standalone testing was conducted 38 percent of the time, while "alternative testing" accounted for less than 3 percent of assays.

Demand Drives New Testing Approaches

The CDC has vociferously warned against use of unapproved Lyme disease tests, but there is growing recognition of the shortcomings of current diagnostic strategies for the disease. In light of growing number of cases of suspected disease in broadening geographic areas and public awareness of the long-term impairments brought upon by untreated disease, interest is growing in tests that promise to identify active infection both earlier in the course of disease and in patients who remain symptomatic, despite negative diagnostic results or antibiotic treatment.

> *"The goal is to have a way to detect Lyme disease even before you make antibodies against it."*
>
> —Alessandra Luchini, Ph.D.

Current blood tests are referred to as indirect tests because they measure the body's immune response (antibodies) to Lyme disease infection, but not the bacteria itself. Further complicating current testing, antibodies remain detectable even after active infection is beaten. In active disease, the bacterium sheds very small pieces (antigens) that were previously beyond detection due to technological limitations.

Ceres Nanosciences (Manassas, Va.) is currently evaluating its Nanotrap Lyme Antigen Test in clinical trials. The test, developed in conjunction with George Mason University (Fairfax, Va.) utilizes nanotechnology to "trap" an antigen associated with Lyme disease from urine samples. The antigen is directly measured using Western Blot technology. The company says that the test marks an improvement in Lyme disease diagnosis, as the Lyme bacterial antigen can be detected within days of initial infection.

"The goal is to have a way to detect Lyme disease even before you make antibodies against it then you could treat the patient with antibiotics, and they wouldn't get all those terrible symptoms," says George Mason researcher Alessandra Luchini,

Ph.D., in a statement. "Or, if someone has joint problems and they're convinced they have Lyme disease—and there are thousands of people who feel that way—it gives us a way to definitively say they do or don't have Lyme disease."

In addition to providing definitive information at two critical stages of disease, Ceres says the test could help improve antibiotic stewardship by avoiding unnecessary prescriptions in patients without active disease. The company says it raised $1 million within the last year to aid with commercialization of the test.

Earlier this year, **T2 Biosystems** (Lexington, Mass.) announced development of the T2Lyme Panel, in conjunction with Canon U.S. Life Sciences (Rockville, Md.). This test is being designed to identify the bacteria directly from a patient's blood, without the need for blood culture. The assay will run on the company's U.S. Food and Drug Administration-cleared magnetic resonance-based T2Dx platform. Michael A. Pfaller, M.D., T2 Biosystem's chief medical officer, tells *DTET* that while the assay is still in the "development" stage, the platform enables "very low limits of detection."

Takeaway: There is expanding commercial and public interest in emerging tests that can potentially improve the sensitivity of Lyme disease diagnostic testing. While tests may soon be entering the marketplace, it remains to be seen if evidence is strong enough to change testing recommendations. G2

Sequencing of Sperm RNA May Improve Diagnosis of Male Infertility

Male factors can contribute to infertility in couples even when standard semen parameters are normal. Next-generation sequencing (NGS) of spermatozoal RNAs can provide a more comprehensive assessment of paternal contribution to fertility issues and may help guide choice of reproductive treatment, according to a study published July 8 in *Science Translational Medicine*. Development is underway for a prognostic assay that can predict birth outcome and the likelihood of success associated with different fertility treatments based upon the presence of certain RNA elements in sperm.

"Upon validation, this discovery may help to identify those couples who may benefit from assisted reproductive technologies [ARTs] and those couples who may be successful with minimal intervention," said senior author Stephen Krawetz Ph.D., from Wayne State University (Detroit), in a statement. "It is our goal to use this technology to reduce both the time to live birth of a healthy child and the cost when couples seek infertility treatment, so as to reduce the stress on the couple.

According to the American Society for Reproductive Medicine infertility is a common problem, affecting at least 10 percent of all couples trying to conceive. More than one factor is responsible for infertility in more than 25 percent of infertile couples, but male evaluation is generally less thorough than for females. Currently, visual assessment of semen parameters (volume, sperm concentration, sperm motility, and sperm morphology) is used to identify male infertility due to "gross deficiencies," but is ineffective for identifying male causes of infertility when sperm are morphologically normal. The large number of unique sperm transcripts revealed by RNA sequencing, experts say, suggests sperm has a role in influencing fertilization, early embryogenesis, and the offspring phenotype.

The current study assessed spermatozoal RNAs from 96 couples presenting with idiopathic infertility (infertility unexplained by standard procedures as confirmed by a reproductive endocrinologist and andrologist). Final reproductive outcome was used to evaluate sperm RNA elements (SREs) reflective of fecundity status. The 72 samples that passed all sequence quality measures were divided into three groups for analysis: group I, the positive control population, was used to determine the required SREs for live birth associated with "natural conception" (couples that achieved an LB through timed intercourse [TIC] during the first monitored cycle); group II test samples were composed of 55 couples, with the majority initially treated by intrauterine insemination [IUI] or TIC and the remainder deciding to undergo ART after semen assessment; and group III test samples included couples from an independent fertility clinic plus four couples with likely female infertility factor.

"Absence of required RNA elements in sperm correlates with infertility but can be overcome with assisted reproductive technologies [in vitro fertilization]."

—Stephen Krawetz, Ph.D.

The researchers found a total of 648 SREs required for natural conception (defined as ranking above the 99th percentile rank and present at a constant level in the control group). Nine of these 648 SREs corresponded to intergenic regions, 12 to sperm-specific intronic elements; 42 within 24 different noncoding RNAs, all of which are likely regulatory, but most (585) were within exonic regions of 262 genes. Forty percent of these exonic region SREs were ontologically classified as associated with spermatogenesis, sperm physiology, fertility, and early embryogenesis before implantation. Patients with all SREs were significantly more likely to achieve live birth by TIC or IUI, compared to those men with one or more SRE(s) absent. The absence of the required SREs reduced the probability of achieving live birth by IUI or TIC from 73 percent to 27 percent. About 30 percent of the idiopathic infertile couples presented with an incomplete set of required SREs, suggesting a male component as the cause of their infertility.

"Absence of required RNA elements in sperm correlates with infertility but can be overcome with assisted reproductive technologies [in vitro fertilization]," the authors write. "As part of the clinical assessment, the absence of an SRE may suggest the earlier use of ART that could reduce the time to achieve live birth compared to current practice."

The study was partially funded by EMD Serono (a division of Merck), which is currently in talks to license the test from Wayne State, Krawetz tells *DTET*.

Takeaway: RNA sequencing may be able to improve the non-morphological assessment of male infertility. With further validation, a comprehensive panel of SREs may be able to steer idiopathic infertile couples to the least invasive and least costly fertility treatment with the highest likelihood of success. G2

Changes in Cervical Cancer Screening Impact Chlamydia Testing

The rates of chlamydia screening have significantly declined as a result of not performing routine cervical cancer screening in young women, according to a study published in the July/August issue of the *Annals of Family Medicine*. Uncoupling screening for sexually transmitted diseases and cervical cancer screening is necessary, the authors say, to improve rates of chlamydia testing.

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Inside The Diagnostics Industry

T2 Biosystems Shifts Paradigm for Rapid Pathogen Identification Directly From Sample

John McDonough, CEO, T2 Biosystems

T2 Biosystems (Lexington, Mass.) is set to revolutionize diagnosis of sepsis infections. Within hours of sample receipt, the company's T2 Magnetic Resonance (T2MR) platform can identify the infection-causing pathogen, completely eliminating the need for blood cultures. Trimming time to results from days to hours has tremendous implications for patient care, antibiotic stewardship, and hospitals' bottom line. The company received U.S. Food and Drug Administration (FDA) clearance for the T2Dx instrument and its first panel (T2Candida) in September 2014 and earlier this year secured its initial customer contracts for the products.

The company is building a solid business case for the products with recently published studies showing not only great clinical performance in terms of the tests' significant impact on patient survival, but also that quicker definitive diagnosis of sepsis-causing infections can yield millions of dollars in savings per hospital. *DTET* recently spoke to T2 Biosystems' CEO John McDonough to learn more about the company's plans and how rapid pathogen identification will evolve.

What makes T2's T2MR platform unique?

T2MR is a novel and proprietary method of detection that uses a combination of magnetic resonance (four-inch diameter magnets) with advanced nanotechnology. We apply nanoparticles as part of our diagnostic reagents. The real power of the platform is that for the first time we have the ability to detect pathogens directly from clinical samples. The presence of a pathogen can be detected at extraordinarily low concentration levels—as little as a single cell per mL of blood, urine, or nasal swab. There are literally tens if not hundreds of applications that you can build on top of this detection method— similar to a computer's operating system on which you can develop different apps or software.

Where we have applied the technology early on is to address really large, unmet health care needs where we can quickly provide diagnostic results that cannot be delivered today. We can do this in a way that is meaningful for patients, offering, literally, the opportunity to save lives, while also taking significant costs out of the health care system. The first field for us is sepsis. We are the only FDA-approved technology in the market that can detect sepsis from a blood sample in three to five hours. The gold standard today for a suspected septic infection is a blood culture, which takes two to six days to identify the pathogen. As a result, the mortality rate for sepsis is above 30 percent. But, data shows if you put patients on the right drug within 12 hours you can cut mortality in half.

Many technologies including sequencing and mass spectroscopy are being applied to rapid pathogen identification. How will adoption of these technologies unfold?

There are use cases for most of the technologies in the marketplace. But in certain application areas where speed to results matters, I think T2 Biosystems is positioned to become the dominant diagnostic platform. Across sepsis—bacterial infections and fun-

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gal infections—a single cell puts you at serious risk of death and existing methods just can't detect down at that low level. That is why the other methods in the market require a blood culture—to grow the cells over several days until there are enough of them for the platform to detect. We are able to analyze directly from the sample, skip the blood culture, and provide the results in three to five hours. So, not only is our advantage in detecting pathogens quickly, but we detect more infected patients than blood culture. Typically, blood culture detects 50 percent to 60 percent of patients that have an infection. The sensitivity in our FDA clinical trial of over 1,800 patient samples was 91.1 percent. This is because sometimes the bug doesn't grow in the culture, like when patients are given drugs prophylactically or empirically and the drug impedes the growth in the culture even though there is an infection. But, that does not impact us.

President Obama recently unveiled a national initiative to combat antibiotic resistant bacteria, with a stated focus of improving rapid detection of infections. How will this initiative impact the diagnostic industry's efforts?

That the federal government is getting involved shows how big the problem really is. Sepsis affects more than 1.5 million Americans annually and sepsis is the single greatest cost to hospitals in the United States at over $20 billion. The President's initiative is really focused on supporting hospitals building anti-microbial stewardship programs where you get doctors, laboratorians, pharmacists, and administrators on stewardship committees to address two issues. The biggest issue is giving the right drug to the patient fast enough. But secondly, because you are waiting two to six days for blood culture results, doctors put many patients on drugs in advance of the correct diagnosis. For every one infected patient, 10 patients without infections are being treated, possibly with the wrong drug for that infection. All of that overuse has a cost, both monetarily and with increasing resistance. Many hospitals have already implemented antimicrobial stewardship programs, but the federal initiative really supports the use of those programs and puts more teeth behind the goal of reducing inappropriate use of these drugs.

T2 Biosystems By-the-Numbers

- Year Founded: 2006
- Number of employees: 150
- Patents Issued: 45 with 67 additional applications
- Time to T2Candida results: 3 to 5 hours
- T2Candida Performance: 91.1 percent sensitivity, 99.4 percent specificity
- T2MR Limit of Detection: As low as 1 CFU/mL

From T2 Biosystems' standpoint this is a very supportive initiative. Our products that are now getting adopted by hospitals are in large driven by these stewardship programs. These hospitals understand the importance of having a diagnostic that can provide rapid pathogen identification so the appropriate drug can be used first-line. This mandate raises awareness, drives changes in hospitals, and it addresses the missing piece of a real need for rapid identification and diagnosis.

Earlier this year you published a study on the economic case supporting adoption of T2 Biosystems Candida panel. Is demonstration of economic impact part of T2 Biosystems' strategic plan with all panels in the pipeline?

If you don't have a strong economic case, it is really tough to drive adoption in this health care environment. Candida fungal infections have a 40 percent mortality rate, a rate which has not changed in the last 20 years. Multiple independent publications show you can reduce that mortality

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to 11 percent if patients are treated with the right drug within 12 hours. The corollary to that is the economics. A typical patient with a candida infection is in the hospital for an average of 40 days with nine days in the intensive care unit (ICU). These are nasty, nasty infections. The average cost to treat a patient with a candida infection is $130,000. Data shows if you can treat patients with the right drug in the first 24 hours you can reduce the hospital stay by nine days and reduce the stay in the ICU by three. This translates into economic savings of between $25,000 and $30,000 to the hospital, when measuring just length of stay. There are other economic impacts like reducing treatment in patients who are negative that makes the economic picture even more compelling.

Mortality also affects economics. The patients who don't survive, end up costing 2.7 times more, on average, than patients who do survive. If you have a septic infection, you don't pass quickly. You struggle in the hospital or the ICU and in the last week you are put on all sort of drugs and interventions to gain survival and the cost is extraordinarily high. The good news is we can reduce mortality by as much as 50 to 75 percent, which translates into huge economic savings for the hospital.

"Over the next several years we will see that every symptomatic patient is given a rapid test because it would be inappropriate to not do so. The cost of the drugs avoided pays for the test."

—John McDonough, CEO, T2 Biosystems

At T2 Biosystems we have a simple mandate for everything we do. We want to develop and deliver diagnostic test results that will change therapeutic decisions in a way that is good for patients and will take significant costs out of the health care system. We must achieve both of those things before we embark on any development program. Economics studies are underway for the panels in our pipeline and we expect they will be published after the products receive FDA-clearance, much like they were with T2Candida.

How will rapid pathogen detection evolve in the next two to five years?

There will be a real paradigm shift. We are starting with sepsis as we are currently living in a world where millions of patients are aggressively treated with drugs that are not needed and it is taking too long to get patients on the right drugs. Over the next several years we will see that every symptomatic patient is given a rapid test because it would be inappropriate to not do so. The cost of the drugs avoided pays for the test. As soon as the market is aware of these diagnostics and their clinical performance, we will see the shift happen.

If we go out further in time we can take the technology to experiences you and I have had. Hopefully, you haven't had sepsis, but you have probably had a sore throat where they run a throat culture to see if it's bacterial or viral and you probably begged to be put on an antibiotic because you didn't want to wait to feel better. Ten years ago they would have given you the antibiotic—even though it will not treat a virus. Now this is done a little less often. In those cases you are not dealing with life or death, as with sepsis, but T2 Biosystems technology can address many, many applications including those that we are really familiar with, like throat infections.

HCV Testing Strategies Falling Short in Reach, *Continued from bottom of p.1*

Risk-Based Screening Misses Cases

Risk-based testing strategies miss cases of HCV-positive prisoners, according to a study published in the *Journal of Urban Health*. The authors say a more comprehensive screening model, such as opt-out universal testing, should be considered in higher prevalence populations like in correctional facilities (12 to 34 percent HCV antibody positivity rates among prisoners versus 1.6 percent in the overall U.S. population).

"Having a substantial proportion of HCV-infected patients remain untested while housed in a correctional institution presents a critical missed opportunity. Opt-out universal HCV screening of all prison entrants would adequately identify these individuals, the first step in meeting a facility's legal obligation to provide quality and equal medical care to institutionalized individuals."

—Danica Kuncio

The Federal Bureau of Prisons recommends HCV testing for all self-reported, high-risk inmates. In actual practice, correctional facility screening protocols vary from universal testing to opt-in risk-based testing. But the authors say correctional facilities provide an opportunity for case identification and secondary prevention, among an otherwise difficult-to-reach population.

To assess the size of the potential shortcomings of risk-based screening strategies, Philadelphia Department of Public Health (PDPH) researchers compared the cases identified through standard targeted testing among Philadelphia Prison System (PPS) inmates (from 2011 to 2012) to blinded HCV seroprevalence results of 1,289 prisoners (the PDPH Study Cohort). Targeted HCV testing is conducted either due to HIV-positive status (approximately one to two percent of the prison population) or because of self-reported intravenous drug use. The PDPH Public Health Laboratory tested the remaining blood from compulsory syphilis testing conducted on all prisoners in the PDPH Study Cohort.

Over the study period, PPS processed 51,562 inmates, of which 5.3 percent were identified as high-risk and underwent targeted HCV screening. Of the 2,727 tested, 57 percent were HCV antibody positive, which when extrapolated would suggest a 3 percent anti-HCV positivity rate for the entire PPS population. However, in the PDPH Study Cohort, 12 percent of tested samples were anti-HCV positive. The authors say that since only 5.3 percent of the prison population was tested due to risk, an additional 4,877 HCV-positive inmates are projected to have been missed.

Rapid HCV Antibody Testing Limited

Interestingly, the PDPH hypothesized that use of the CLIA-waived OraQuick HCV Rapid Antibody Test (which received U.S. Food and Drug Administration approval in 2012) could lead to under-reporting of HCV-infected cases. However, they found the total volume of this test was extremely small (less than 1 percent) and was unlikely to significantly impact the numbers. To assure these results are captured in the future, PDPH added HCV-positive rapid and point-of-care tests to the reportable laboratory test result list in August 2014.

"Having a substantial proportion of HCV-infected patients remain untested while housed in a correctional institution presents a critical missed opportunity," write the authors led by Danica Kuncio, from PDPH. "Opt-out universal HCV screening of all prison entrants would adequately identify these individuals, the first step in meeting a facility's legal obligation to provide quality and equal medical care to institutionalized individuals."

The authors acknowledge a correctional department's choice of a testing strategy is likely influenced by budget constraints and the expected length of stay for each inmate. However, the authors note, confirmatory testing and disease follow-up in a "controlled setting" prevents loss of patients during follow-up.

HCV Testing Strategies Contribute to Follow-Up Loss

In a separate study, PDPH researchers assessed patient loss across stages of the continuum of care (CoC; January 2010 to December 2013) using reportable data from PDPH's Hepatitis

Surveillance Program. Reporting is mandated for all positive HCV laboratory results on Philadelphia residents, including HCV antibody, RNA, and genotype results. Using National Health and Nutrition Examination Survey HCV prevalences, census data, and published homeless and incarceration rates, the expected HCV seroprevalence in Philadelphia was estimated to be 2.9 percent.

Positive HCV antibody test results were received for 47 percent of the estimated HCV-positive individuals. Only half of these patients with positive antibody results had a reported RNA result. Given the estimated 15 percent of HCV cases that spontaneously clear infection, the authors say 33 percent of antibody positive patients were not tested for RNA or their positive RNA results went unreported. The average time between the HCV antibody screening and RNA confirmatory test was 51 days before the 2012 birth cohort recommendation and 15 days post- recommendation. The authors cite reflex testing as driving the dramatic drop.

Takeaway: Given that few HCV-infected residents are successfully mobilized from screening through confirmatory testing and into care and treatment, new strategies need to be adopted to improve initial identification of HCV-positive cases and to keep these cases engaged through the CoC. G2

X Chromosome Marker Could Diagnose Serious Mental Disorders

Expression of a gene responsible for inactivation of one of the two copies of the X chromosome in women may serve as a biological marker for diagnosing serious mental health conditions, according to a study published online June 16 in *EBioMedicine*. Over-expression of XIST, the master gene for X chromosome inactivation, and the related X-linked KDM5C gene may improve diagnosis of bipolar disorder or recurrent major depression in females.

"Our results indicate that a large subpopulation of female psychiatric patients from the general population may have abnormal function of the inactive X chromosome," lead author Xianjin Zhou, Ph.D., from University of California, San Diego, said in a statement. "These results are powerful in that early diagnosis of mental illness could possibly happen with a simple blood test, leading to better interventions, therapy, and treatment options."

The researchers found that XIST is significantly over-expressed in female patients with either bipolar disorder or major depression.

Zhou and colleagues previously analyzed protein translation in lymphoblastoid cells and found significantly larger variation of activity in female psychiatric patients, compared to healthy controls. In the present study, XIST and related genes were studied in 36 lymphoblastoid cell lines from healthy females and 60 similar cell lines from female patients with bipolar disorder or recurrent major depression. Real-time polymerase chain reaction was used to quantify relative expression of all genes.

The researchers found that XIST is significantly over-expressed in female patients with either bipolar disorder or major depression. Significant upregulation was also seen in the X-linked escapee gene KDM5C in both sets of patients. Expression of the two genes was highly correlated.

"About 30 percent to 60 percent of the patients can be diagnosed by these markers using different stringency," the authors explain in the paper. They do caution, however, that most of the patients in the study have a family history of mental disorders and display severe psychiatric symptoms, which may cause an over-estimation the prevalence of abnormal XIST and KDM5C expression in the general population of female psychiatric patients without family history and/or with milder psychiatric symptoms.

Takeaway: Though needing further validation, use of gene expression markers could vastly improve diagnosis of major mental illness, where a lack of biological markers has hampered definitive diagnosis and treatment of psychiatric disorders, which rely on clinicians' subjective assessment and patients' self-reported symptoms. G2

Changes in Cervical Cancer Screening Impact Chlamydia Testing, *Continued from p.4*

The highest prevalence of chlamydia infection in the United States is among young adults aged 15 to 24 years, but cervical cancer screenings became "more restrictive" in women in 2009 following the American College of Obstetricians and Gynecologists' recommendation that cervical cancer screening should begin at age 21 years, rather than screening three years after first sexual intercourse or by age 21, whichever occurred first.

In the current study, females (aged 15 to 21 years) who made visits to five family medicine ambulatory clinics at the University of Michigan were identified. Rates of chlamydia screening were compared between eligible groups of women who made visits between January 1, 2008 and February 28, 2009 (before the guideline change; n= 1,626) and women who made visits between January 1, 2011 and February 28, 2012 (after the guideline change; n=1,846). Based on diagnostic codes, visits were excluded if Papanicolaou (Pap) and chlamydia testing were performed for diagnostic rather than screening purposes.

> *"This study suggests that we cannot rely on pelvic examinations or cervical cancer screenings as opportunities for chlamydia screening."*
>
> —Allison Ursu, M.D.

Based upon 3,472 female patients (9,852 total visits), the researchers found that both the proportion of patients having a Pap test was significantly higher before the guideline change versus after (394 versus 73 tests). Even when adjusting for age, clinician type, and clinic site, the odds of having a Pap test remained more than seven-times higher before the guideline change. Similarly, the odds of having a chlamydia screen were significantly higher (nearly 14 times higher) before versus after the guideline change. Before the guideline change, 61.9 percent of the chlamydia screens were concurrent with Pap testing versus only 10.8 percent after the guideline change.

"This unintended decrease occurred despite recommendations promoting chlamydia screening and access to noninvasive testing," write the authors led by Allison Ursu, M.D., from the University of Michigan, Ann Arbor. "This study suggests that we cannot rely on pelvic examinations or cervical cancer screenings as opportunities for chlamydia screening as has been suggested in the past.... We need to identify new opportunities for screening and put into place standard workflows that will maximize screening in this population."

Takeaway: In order to improve rates of chlamydia screening among young women, chlamydia and cervical cancer screening need to be uncoupled and new screening opportunities for sexually transmitted diseases need to be identified. G2

Military Could Use Hand-Held Spectroscopy for Pathogen Detection

It is feasible to use surface-enhanced Raman spectroscopy (SERS) for the detection of microorganisms. Further, the use of the technology to generate a "molecular fingerprint" of infection-causing pathogens is potentially clinically "valuable" to either prevent or more effectively treat high rates of wound infections in military personnel, according to a military technical report.

Current diagnostic assays used to identify the infection-causing pathogen and select appropriate treatment are limited in their sensitivity and take too long due to the need to isolate and culture bacteria. While molecular approaches have aided pathogen identification in traditional settings, they are not yet point-of-care field deployable. Researchers from the Naval Medical Research Unit-San Antonio (NAMRU-SA; Ft. Sam Houston, Texas) believe that SERS could meet a critical unmet need for rapid, sensitive diagnosis, even in field conditions.

"The data demonstrate that SERS can be used to accurately discriminate between bacterial species in a quick and efficient manner. This report sets the foundation for the utilization of a SERS platform for rapid detection of microorganisms of military relevance, which may ultimately lead to the development of a field deployable point-of-care handheld detection system."

—Rene Alvarez, Ph.D.

The NAMRU-SA scientists recently demonstrated that the SERS device could identify five bacterial species from pure culture and bacteria recovered from human serum using a proprietary lysis filtration procedure. The technique was utilized on 16 bacterial isolates. Quantitative polymerase chain reaction with melting curves was used to validate the SERS spectra. The spectra (or fingerprints) demonstrate shifts in the frequency of a fixed light as a result of structures in the bacterial cell wall. Libraries of bacterial SERS spectra can serve as a reference. A hand-held SERS biosensor system could not only generate unique "molecular fingerprints" for these organisms in under 30 seconds, but it could also discriminate between bacterial species. Additionally, mixtures of gram-negative and gram-positive bacterial species can be differentiated from either species alone.

The researchers believe the SERS biosensor will be able to aid caregivers in selecting appropriate antibiotic treatments. They say that after successful identification of an infecting microbe, drug resistance can be evaluated by observing shifts in SERS peak intensity after incubation on antibiotic coated nanoparticles. John Simecek, D.D.S., from NAMRU-SA, tells *DTET* that the group is working on additional refinements with a particular emphasis on improving the methods of isolation during sample preparation. This will increase bacterial extraction yields, reduce component equipment requirements, and cut total time from sample receipt to pathogen detection.

"The data demonstrate that SERS can be used to accurately discriminate between bacterial species in a quick and efficient manner," writes lead author Rene Alvarez, Ph.D., in the technical report. "This report sets the foundation for the utilization of a SERS platform for rapid detection of microorganisms of military relevance, which may ultimately lead to the development of a field deployable point-of-care handheld detection system."

Takeaway: Hand-held development of SERS technology could transform care for wound treatment in combat-injured military personnel and may ultimately have civilian applications at the bedside or clinic. G2

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Serum Zinc May Be Useful Marker With Alopecia

Zinc appears to be a useful marker in assessing prognosis with the hair-loss condition alopecia areata (AA). Both newly diagnosed patients and patients with treatment resistant AA have lower serum zinc levels, compared to nonaffected controls, according to a study published in the *International Journal of Dermatology*. Among patients with AA, lower levels of zinc are tied to disease duration, severity of AA, and resistance to therapies.

While the exact role zinc plays in the pathogenesis of AA is unknown, zinc is a trace element involved in important functional activities of hair follicles. AA is thought to be an autoimmune disease characterized by hair loss.

Serum zinc levels were assessed in patients with newly diagnosed AA (n=25; diagnosis within one to three months), resistant AA (n=25) and in 50 age- and sex-matched healthy controls. Participants with resistant AA had the condition for at least six months duration (actual range disease duration ranging from 6 to 30 months) and received three or more common therapies without success. AA severity was assessed using a previously validated tool. Venous blood samples (three mL fasting for six to eight hours) were taken from each participant. Serum levels of zinc were evaluated using the colorimetric method (with a spectrophotometer wavelength 560 nm) and 60 to 110 µg/dl was considered a normal value.

The researchers found significantly lower serum zinc levels in all patients with AA compared with controls, but significantly lower levels were also seen in patients with resistant AA versus patients with newly diagnosed AA. Highly significant inverse correlations were found between serum zinc level and severity of AA and disease duration in all patients as well as in patients with resistant AA. No statistically significant differences were found between mean serum zinc level and sex or between patients younger or older than 25 years of age. Similarly, no differences between zinc levels were seen by hair loss characteristics (scalp hair loss, body hair loss negative and positive, and number of patches one, two, multiple, and alopecia totalis).

"Serum zinc level may be a useful marker of disease severity and duration in AA, and zinc supplements may have beneficial therapeutic effect," write the authors led by Nermeen S. A. Abdel Fattah, M.D., from Shams University in Egypt. "Although the association between low serum zinc levels and AA does not confirm that it plays a role in the pathogenesis of AA, its significantly lower levels in patients with resistant AA could suggest that low zinc levels may have a possible role in resistance, as zinc is important in helping hair regrowth." G2

Company References

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Philadelphia Department of Public Health
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