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Editorial

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Time to Critique the Paradigm: "If no Specimen is Collected, it is not a Laboratory Test"

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Abstract

The current paradigm for laboratory tests holds that if a specimen is not collected, the diagnostic test is not a laboratory test. College of American Pathologists does not include such diagnostic testing in its accreditation program. However, there are increasing number of diagnostic tests that are being conducted on exhaled breath, and by transcutaneous measurements. Miniaturization of mass-spectrometry equipment has the potential to broaden the range of breath analysis to monitor the course of disease, without collecting specimens. Multiphoton imaging of skin and accessible mucus membranes can provide histologic grade resolution of lesions without collecting a specimen. Improvements in magnetic resonance imaging has the potential to increase the resolution to light microscopy level detail. It would be prudent for the pathology national organizations to address this issue and plan for the upcoming advancements in diagnostic testing without collecting specimens.

Keywords: *Laboratory tests; Breath testing; Mass spectrometry; Chronic disorders*

Introduction

Conventional laboratory diagnostic testing is dependent on examination of physical specimens, including tissues from biopsy or resections, needle aspirates of tissues, exfoliated cells, hair, blood, urine, cerebrospinal fluid, amniotic fluid, semen, aspirates from bone marrow, viscera and body cavities, saliva, sputum, sweat, stool, drainage from natural openings, cavities, and wounds, smears from skin and mucus membrane lesions etc. The testing techniques include histologic and cytologic morphology examination, special stains, molecular testing, culture and chemical examination of tissues, cells, and various fluids. Additional testing methods include blood group typing and compatibility testing for blood, blood components, tissues, and organs through immunologic and molecular testing. Mass spectrometry provides and additional means of testing for various chemicals, molecules, drugs, and substances of abuse.

The current state of the art holds that if a specimen is not collected for testing, it does not fall under the purview of pathology and laboratory medicine [1,2]. The College of American Pathologists does not include tests like breathalyzer for alcohol, breath tests for small intestinal bacterial overgrowth or *H pylori* infection, pulse ox monitors, transcutaneous measurements of bilirubin and hemoglobin in the standards for laboratory accreditation [3]. These tests are based on chemical or physicochemical analyses but are not included in clinical pathology. The analyzers are medical devices and require approval by the Food and Drug Association (FDA) for medical use before companies can market the devices [4].

Common examples of diagnostic testing not requiring collection of a physical specimen are addressed below:

Breath testing

Breathalyzer for alcohol use is a familiar form of "diagnostic" testing not dependent on collection of a physical specimen [5]. The use of breath analysis could include a much larger range of medical issues, and chemicals. Testing for entities detectable in breath could include ammonia, products from microbes, tumor breakdown products, and chemicals in metabolic disorders and more. FDA has approved a breath test for COVID-19 testing and testing for other infectious organisms is feasible [6]. A point-of-care breath test for active pulmonary tuberculosis has been described [7]. Even if breath testing only differentiates bacterial infection from other causes of fever, it would be a major advancement.

Breath analysis for detecting lung and head and neck cancers have been described [8,9]. Evaluation of colonic lesions suggests that cancer screening may not be limited to advanced cancers but that pre-malignant lesions may also be detectable [10].

Monitoring ammonia and ketones in breath may obviate repeated blood collections in assessing the improvement or deterioration

of the clinical status [11]. Similarly, measurement of ketones in breath would obviate blood testing for management of ketoacidosis [12]. Ingested or inhaled volatile substances, e.g., alcohols, could be detected and monitored by testing breath [13,14].

Non-invasive testing for blood components

Mention has been made of pulse oximeters, and transcutaneous measurement of bilirubin. Spectroscopic examination of nail beds has been used for hemoglobin measurement [15]. Hemoglobin concentration in fetal blood can be estimated by measuring the rate of blood flow in middle cerebral artery by ultrasonography [16]. A similar approach could be taken in resuscitation efforts requiring massive blood transfusion and intraoperative monitoring by measuring radial artery blood flow. Rheological properties of arterial blood may be useful in monitoring states associated with increased viscosity, e.g., polycythemia and hypergammaglobulinemia [17].

Transcutaneous measurements are subject to variations based on skin pigmentation, however, these forms of testing could still be used to monitor changes in a given patient, e.g., patient with beta thalassemia could monitor hemoglobin at home by nail spectrometry, using a cell phone and only report to a healthcare facility, if and when blood transfusion may be needed. In some instances, even if the transcutaneous measurement is not entirely accurate, it could still serve as a screening test to rule out low risk patients, especially neonates, from the need for further testing by blood collection, e.g., bilirubin [18].

Skin-based testing

Skin based monitors are being used for blood glucose monitoring and in theory could be used for measuring other chemicals, e.g., substances of abuse, and therapeutic drugs [19]. Continuous monitoring for use of banned substances could be implemented by use of skin-based sensors that would record the data and could be placed securely like an ankle bracelet. Probes penetrating the upper skin layers could provide increased capability without the need to collect samples and expand the repertoire of chemicals that could be measured and monitored in chronic disorders [20].

Additional issues

A. Trans-mucous membrane spectrometry: Accuracy of transcutaneous measurements could be improved by conducting the measurement across a thin mucus membrane, e.g., frenulum of the tongue. This modality may be less subject to pigmentary interference and allow for measurements of additional chemicals.

B. Mass-spectrometry: Advancement in technology and miniaturization could make it feasible to install such devices in emergency rooms and intensive care units to perform breath analyses for multiple analytes, without the need for anemia causing repeated blood sampling [21].

C. 30 Tesla magnets in Magnetic Resonance Imaging (MRI): Currently the MRIs use magnets with a maximum strength of about 3 Tesla. In research settings imaging with 7 tesla magnets provides cellular detail in central nervous system tissues [22,23]. With advancements in magnet strength generated by research in nuclear fusion and room temperature superconductivity, it may be possible to increase the magnet strength 10-fold. At 30 Tesla the images generated could have light microscopic resolution of lesions and obviate the need for biopsies to differentiate benign from malignant lesions. Malignancy could be further corroborated by selective venous sampling and analyzing tumor DNA, ala, liquid biopsy. Similarly, the status of draining lymph nodes for metastatic tumors could be resolved for staging of tumors. This advancement in technology could result in an overlap of radiology and pathology. Of the various issues suitable for a section/unit of diagnostic medicine, the combination of imaging and histopathology would be an appropriate one. Dell Medical School may be the only academic center with a Department of Diagnostic Medicine, combining radiology and pathology, however the outcomes of this new arrangement need to be scrutinized.

D. Multiphoton imaging

Skin and accessible mucus membrane lesions could be subjected to multiphoton imaging for diagnosis, without removal of tissues. Such imaging can be done through endoscopy. This modality could be used for diagnosis of malignant as well as premalignant lesions [24-26]. Deeper tissues have been examined by this technique in experimental settings [27].

Conclusion

Improvements in non-invasive diagnostic testing, through advances in transcutaneous and trans-mucus membrane spectrometry, breath analysis through mass-spectrometry, and higher resolution imaging has the potential to alter the current diagnostic paradigms. It would be prudent for Pathology leadership and national organization to address this issue preemptively and in a proactive manner, preferably through collaboration with radiology.

Conflict of Interest and Disclosures

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