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Educational Case: Regulatory Issues With Laboratory Testing

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, diagnostic medicine, Clinical Laboratory Improvement Amendments (CLIA), Food and Drug Administration, laboratory-developed testing, body fluids, waived testing, provided-performed microscopy

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Primary Objective

Objective GP1.7: Regulatory Issues. Explain the broad differences between Food and Drug Administration (FDA)-approved tests and laboratory-developed tests, including Clinical Laboratory Improvement Amendments (CLIA) waived and nonwaived tests, and discuss the regulatory issues involved in physician office laboratories, home testing, and provider-performed microscopy.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic GP: General Principles; Learning Goal 1: Laboratory Tests.

Patient Presentation

A multispecialty physician office practice that previously performed only waived laboratory testing (pregnancy tests, rapid streptococcal antigen, and urine dipsticks) recently added testing for clinical chemistry, hematology, and microscopy for urine sediment. The clinical chemistry and hematology analyzers added to the physician office laboratory perform Food and Drug Administration (FDA)-approved assays that are classified as moderate complexity under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. The physician group upgraded their CLIA license to cover moderate complexity testing. The clinical chemistry analyzer is a compact near point-of-care model that uses whole blood (lithium heparin anticoagulated) as the specimen.

One of the physicians in the group sees a 65-year-old male patient with an inflamed knee joint and aspirates some of the fluid for cell count, chemistry, and crystal analysis. The physician practice is affiliated with a medical center, and this type of testing would normally be sent to the medical center central clinical laboratory. However, the physician requests that the laboratory technician for the office laboratory analyze the joint fluid for basic cell counts and chemistries (eg, glucose, protein) on the newly acquired instruments to get a faster turnaround time while the patient is still in the office.

Diagnostic Findings

The joint fluid is cloudy and more difficult to pipette than whole blood. Analysis of the fluid on the office laboratory chemistry analyzer returns multiple error flags, with no value

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output for glucose concentration. The protein concentration is 3.1 g/dL but with an absorbance warning flag. The white blood count on the hematology analyzer returns an error message with a high count warning.

Questions/Discussion Points

What Are the Clinical Laboratory Improvement Amendments Test Complexities for the Laboratory Tests Run in the Physician Office Laboratory and How Did This Change When They Added the New Testing?

Under the CLIA regulations, clinical laboratories are certified at the highest level of test complexity. The Centers for Medicare and Medicaid Services (CMS) oversees the CLIA regulations and can grant ("deem") authority to other organizations (eg, The Joint Commission, College of American Pathologists) to carry out surveys/inspections and offer accreditation. The CLIA test complexities are waived, provider-performed microscopy (PPM), moderate complexity, and high complexity. The 3 categories other than waived are collectively referred to as "nonwaived" testing and will be the main subject of the discussions below. The physician group previously performed only waived testing, the lowest complexity under CLIA. Examples of waived testing include point-of-care testing such as fingerstick glucose, pregnancy kits, urine dipsticks, and some urine drug of abuse screening strips. The clinical chemistry and hematology testing added to the physician group is moderate complexity, a broad category that includes many FDA-approved tests commonly performed in clinical laboratories. Microscope examination of urine sediment by physicians or other providers is PPM, a subgroup of moderate complexity. Other examples of PPM include potassium hydroxide preparations, pinworms preparations, Fern tests, nasal smears for granulocytes, fecal leukocyte examinations, and qualitative semen analysis (limited to presence or absence of sperm and the detection of motility).

Joint fluid, surgical drain fluid, or other nonblood body fluids (eg, peritoneal, pleural) would almost certainly not be specimen types FDA-approved for assays performed on standard clinical chemistry and hematology analyzers.[1] Analysis of these specimens would be considered laboratory-developed tests (LDTs) that would fall under CLIA high complexity and also require validation by the laboratory. In addition, as evident in the patient case, analysis of these body fluids can result in errors or erroneous results if the assay is not suitable for the type of body fluid.

There are 5 types of CLIA certificates.[2] Certificates of waiver are issued to laboratories performing only waived tests. Certificate for provider-performed microscopy procedures (PMPP) is issued to laboratories in which a physician, midlevel practitioner, or dentist performs no tests other than the microscopy procedures. Laboratories with the PMPP certificate can also perform waived testing. There are 3 certificates that apply to laboratories performing moderate or high complexity testing. The certificates also cover PPM and waived testing. Certificate of registration is issued to a laboratory until the entity is determined by a survey to be in compliance with CLIA regulations. A certificate of compliance is issued after an inspection finds a laboratory to be in compliance with all applicable CLIA requirements. A certificate of accreditation is issued to a laboratory that achieves accreditation by an organization approved by CMS.

What Are the Personnel Requirements for the Various Clinical Laboratory Improvement Amendments Licenses?

Clinical Laboratory Improvement Amendments personnel requirements are found in Subpart M of the Code of Federal Regulations (CFR), which details qualifications and responsibilities for laboratories performing PPM, moderate complexity, and high complexity testing.[3] Under CLIA, clinical laboratories performing only waived testing do not have specific personnel requirements. The requirements and categories of personnel required are more complex with moderate and high complexity testing. Provider-performed microscopy classification has specific requirements for testing personnel and laboratory director. Moderate complexity testing has requirements for testing personnel, laboratory director, clinical consultant, and technical consultant. High complexity testing has requirements for general supervisor in addition to the personnel listed above for moderate complexity.

What Are Some of the Key Differences in Requirements for Laboratory Director for the Various Clinical Laboratory Improvement Amendments Classifications?

The Laboratory Director for PPM can be any of the following: DDM/DDS, MD, DO, or DPM licensed to practice in the state in which the laboratory is located, or midlevel practitioner (eg, nurse midwife, nurse practitioner, or physician assistant) who is authorized to practice independently in the state in which the laboratory is located. For PPM, there is no requirement for laboratory director to have prior experience supervising or directing nonwaived testing.

There are multiple routes to meet the requirements for laboratory director for moderate complexity testing.[3] For pathologists (MD or DO), the requirement can be met by being a board-certified pathologist through the American Board of Pathology or the American Osteopathic Board of Pathology. For nonpathologist physicians (MD or DO), the following can suffice: 1 year of supervising or directing nonwaived testing, 20 hours of continuing medical education (CME) commensurate with laboratory director duties, or 20 hours of clinical laboratory training during medical residency. For the 20 hours of CME, there are commercially available courses that offer content to meet this requirement. Individuals with doctoral degrees in science can meet requirements to be laboratory director for moderate complexity testing by obtaining certification from boards such as the American Board of Medical Microbiology or the American Board of Clinical Chemistry. This route generally involves approved fellowship training

Table 1. Examples of CLIA Test Complexities and Regulatory Requirements.

Category	Examples	Requirement for Non-pathologist MD or DO to Serve as Laboratory Director Other Than Valid Medical License in State of the Laboratory Testing
Waived	Fingerstick glucose Pregnancy kit Rapid streptococcal antigen Urine dipstick And many other point-of-care tests	None
Provider-performed microscopy	Fern test Potassium hydroxide preparations Qualitative semen analysis Urine sediment examination	None
Moderate complexity	Many FDA-approved clinical chemistry, hematology, and microbiology tests	20 hours CME, or 20 hours laboratory training in residency, or 1 year supervising or directing nonwaived testing
High complexity	Any laboratory-developed test Test requiring pathologist interpretation	2 years supervising or directing nonwaived testing

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; CME, continuing medical education; FDA, Food and Drug Administration.

after doctoral training (eg, in clinical chemistry or medical microbiology) or documented experience in clinical laboratories. There are also routes for individuals with bachelor's or master's degree in the sciences to qualify as laboratory director if they have prior experience supervising or directing nonwaived testing. For those with only a bachelor's or master's degree, CME cannot replace the prior experience requirements.

The requirements for laboratory director for high complexity testing are more stringent than moderate complexity. One of the key differences is that the nonpathologist MD or DO cannot use 20 hours of CME to meet the laboratory director requirements and instead needs 2 years of experience supervising or directing nonwaived testing. Similar to moderate complexity testing, individuals with doctoral degrees in science and certification from boards such as the American Board of Medical Microbiology or the American Board of Clinical Chemistry meet requirement for laboratory director for high complexity testing. Table 1 summarizes CLIA test complexities and also some of the laboratory director requirements. An additional stipulation is that any one person can serve as laboratory director for no more than 5 CLIA certificates for nonwaived testing. There is currently no limit for the number of waived licenses that an individual can be laboratory director.

What Are the Technical and Regulatory Implications for Running Nonblood Body Fluids on Clinical Chemistry and Hematology Analyzers?

Body fluids from nonblood or urine sources present a difficult challenge for clinical laboratories.[1,4] Examples of these fluids include bile, cerebrospinal fluid, cyst contents, gastric aspirates, joint fluid, peritoneal fluid, pleural fluid, surgical drain fluid, vitreous fluid, and wound exudates. With few exceptions, FDA-approved tests for these fluid types are unavailable. It is important to carefully examine the package insert for FDA-approved tests to see what specimen types are approved. For example, some tests may be approved for urine and/or cerebrospinal fluid in addition to serum/plasma. The heterogeneous nature of body fluids leads to technical difficulties in analysis. Some fluid types can be thick and viscous and difficult to pipette and analyze. Other fluids, especially cyst contents, may have analyte concentrations far in excess of what is typically encountered with serum or plasma. An example of this would be amylase from a pancreatic cyst containing high amounts of pancreatic enzymes.

The key regulatory point is that analyzing a nonapproved specimen type changes the classification of the test to an LDT, which is automatically high complexity and with expectations for thorough validation prior to performing the test for clinical purposes.[5] Laboratory-developed tests are a broad category and also include highly labor-intensive tests such as gene or exome sequencing in molecular diagnostics.[6] Laboratories considering LDTs should thoroughly review the validation and regulatory requirements to be sure these can be met.

What Should be Done in Follow-Up to the Patient Case?

The request by the physician to analyze the joint fluid on the office laboratory instrumentation was not appropriate. There are multiple key issues and action items that should follow from this incident. The performance of LDTs in a laboratory with only a moderate complexity CLIA license is not acceptable and opens the laboratory up to regulatory penalties. The results obtained from the analysis are not reliable and should not be reported in the patient chart or used for clinical decision-making. That the instruments returned error or warning flags is fortunate in alerting that the results may not be valid. However, some assays will return a result even if the specimen type is inappropriate, opening up the possibility that these results can provide misleading information. The physicians and office laboratory personnel should review and emphasize procedure that the clinical chemistry and hematology analyzers are to be used only as directed in the package inserts for the assays. Nonapproved specimen types should not be analyzed. Compliance with regulations and acceptable laboratory practice is ultimately the responsibility of the laboratory director.

Teaching Points

- Clinical laboratories (including physician office laboratories) are regulated under CLIA, with the details in the

CFR. Centers for Medicare and Medicaid Services oversees the CLIA regulations and deems authority to other organizations (eg, The Joint Commission, College of American Pathologists) for activities such as surveys, inspections, and accreditation.

- Clinical Laboratory Improvement Amendments defines 4 categories for laboratory testing in ascending order of complexity: waived, PPM, moderate complexity, and high complexity. The last 3 categories are collectively referred to as "nonwaived" testing.
- Clinical laboratories must meet CLIA regulations for the highest complexity testing performed in the laboratory. For example, a laboratory performing almost all waived testing but some moderate complexity testing needs to meet the moderate complexity requirements.
- Each of the laboratory test categories entail specific requirements for laboratory director and testing personnel. Moderate and high complexity testing has some additional personnel category requirements. Clinical laboratories performing testing should thoroughly review and be in compliance with CLIA regulations.
- Laboratory-developed tests are category of tests that are not FDA-approved and are classified as high complexity. Simple examples include using specimen types other than those approved in the assay package insert. More technically involved examples are genomic molecular diagnostic tests. Laboratory-developed tests have demanding validation requirements.
- Body fluids other than blood and urine are often not specimen types that are FDA-approved for laboratory assays, making their analysis high complexity under CLIA. There are a number of technical and validation challenges with these fluids. Clinical laboratories interested in performing analysis on body fluids should thoroughly review the literature and regulatory requirements.

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