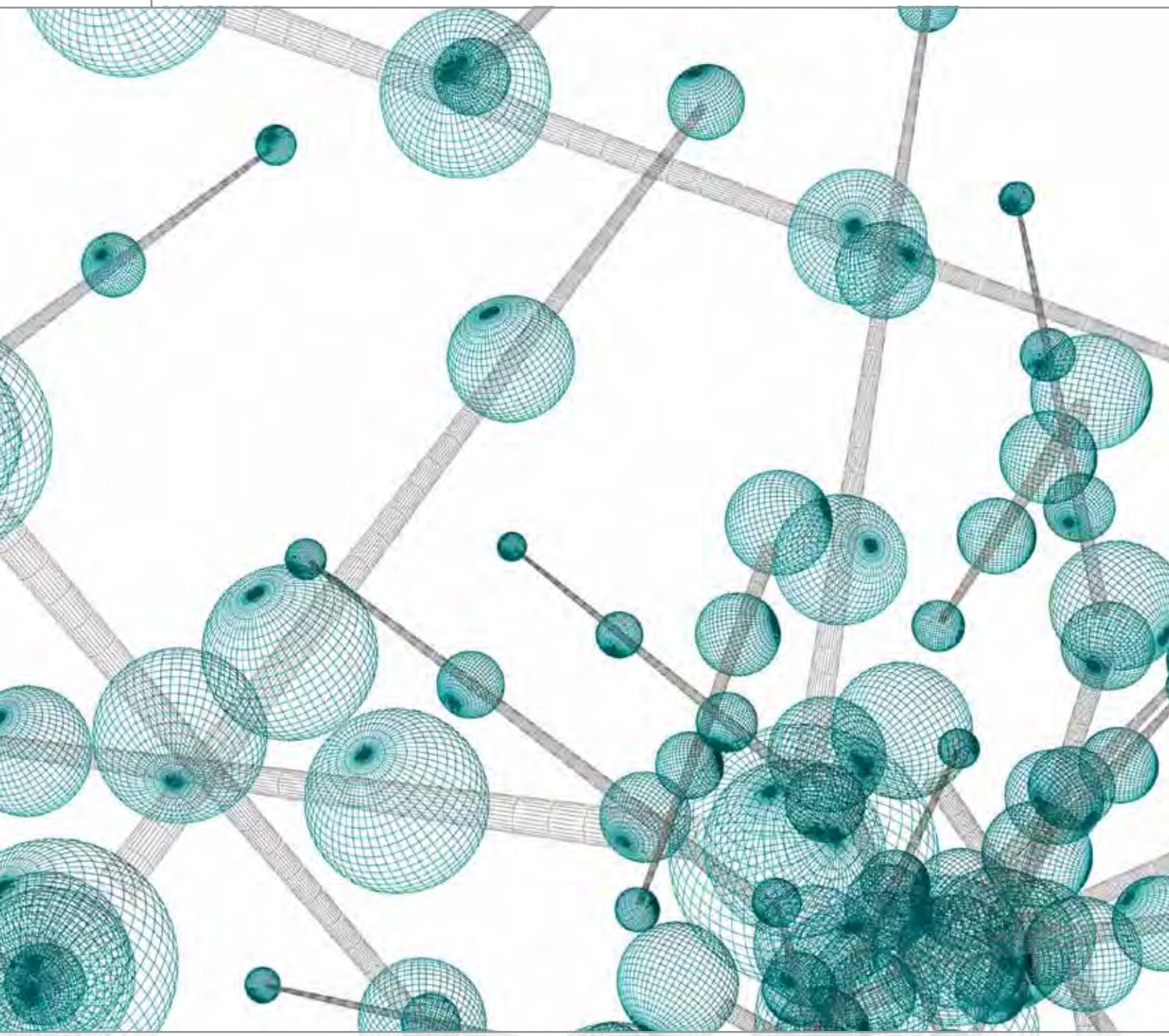
2010

MOLECULAR TESTING CAPACITY SURVEY REPORT



APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

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Background/Introduction

The development of the polymerase chain reaction (PCR) in the 1980s revolutionized molecular biology and has paved the way for technological advances that have improved the ability to detect and monitor disease. The genetic identification of disease-causing microbes, establishment of the Laboratory Response Network (LRN) for the detection of agents of bioterrorism, and enhancements to epidemiology and surveillance activities have all contributed to the implementation of molecular diagnostics into routine laboratory practices in public health laboratories.[1] Classical testing methods such as culture or biochemical tests, although effective, can be slow, laborious, and in some cases, subject to interpretation. Conversely, molecular tests are powerful diagnostic tools that are advantageous in that they are rapid; in some cases, more sensitive and specific than classical methods; and useful for specimens containing fastidious bacteria and viruses.[2] These diagnostics range from assays designed to detect a single target to multiplex assays that can detect multiple analytes within the same specimen.[3] However, molecular diagnostics are not without their challenges and limitations. While many of the molecular tests used in public health laboratories are FDA-cleared, there are numerous assays for rare or emerging diseases that are developed and evaluated within a single laboratory. Laboratories that develop these types of tests need to perform appropriate validation to establish the performance characteristics and develop appropriate quality control (QC) and quality assurance (QA) practices to meet standards and guidelines developed under the Clinical Laboratory Improvement Amendments (CLIA).[4] Molecular diagnostic tests are an important tool used by public health laboratories as they perform specialized testing for the detection, characterization, and surveillance of diseases or conditions of public health significance. As molecular tests become the norm in public health laboratories, it is critical that laboratorians are well trained to perform, troubleshoot, and interpret the results of the assays, as well as understand the limitations (predictive values, contamination issues, inhibition) of the technology and results produced from the molecular tests.[1]

Methods

The Association of Public Health Laboratories (APHL) periodically surveys its member laboratories to assess their testing capacities, capabilities, and practices. A past molecular survey attempted to assess public health laboratory molecular assay capacity, willingness to share protocols, and ability to provide training and assistance related to infectious diseases (*unpublished data*). Since the previous survey performed in 2005, there have been numerous changes in technology and public health laboratory capacities. These include the nationwide use of real-time reverse transcription (RT) PCR capacity for the detection and surveillance of seasonal and pandemic H1N1 influenza, the incentive funding through the Centers for Disease Control and Prevention's (CDC) Cooperative Agreement to incorporate molecular testing for *Mycobacterium tuberculosis*, new FDA-cleared molecular tests available for purchase, and the implementation of other laboratory-developed molecular tests for infectious diseases. In order to better understand public health laboratory capacity for molecular testing of infectious diseases, APHL launched a 2010 Molecular Testing Capacity Survey to assess current capabilities and capacities, identify potential barriers, and understand the needs of public health laboratories related to the development, implementation, and performance of this specialized testing. This 29-question survey was developed by members of the APHL Molecular Diagnostics Advisory Panel and administered through MRInterview, a web-based survey instrument. Respondents were asked to provide data from their laboratory on their current molecular testing practices for infectious diseases. Descriptive statistics were gathered for all variables, and results were reported for the following categories: Workforce, Infrastructure, Laboratory Practices and Capabilities, Research and Development, Barriers, and Needs.

Results

Ninety-three public health laboratories received this survey, and 75 (80%) responded: 49 of 51 (96%) state laboratories and the District of Columbia, and 26 of 39 (67%) local laboratories. In total, 75 (49 state, 26 local) respondents indicated that their laboratory performed molecular testing for infectious disease agents.

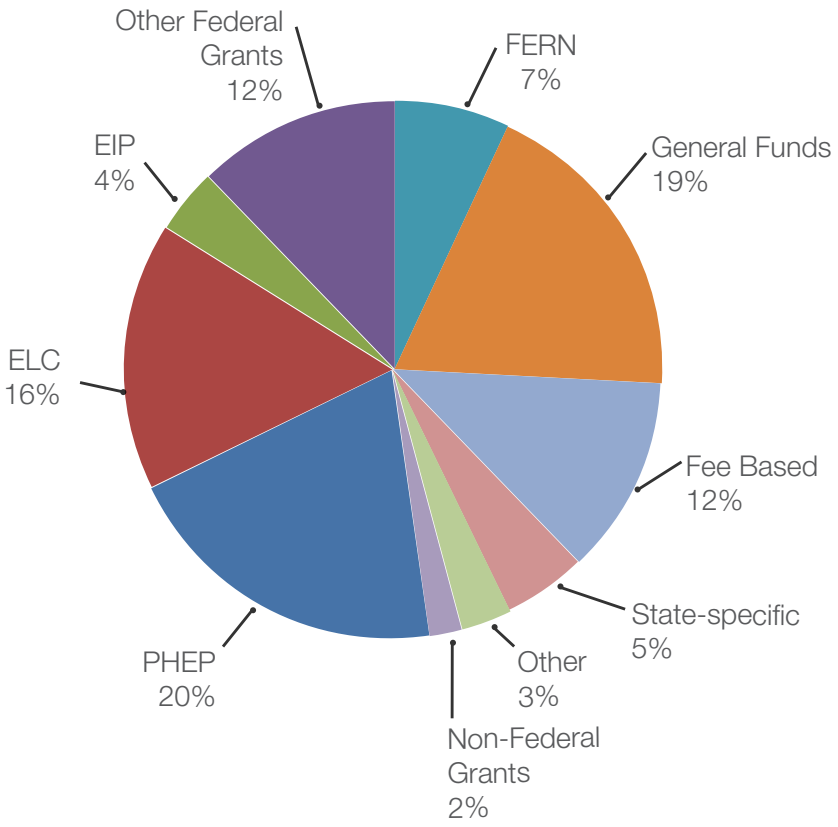
Workforce

It is widely believed that staff who conduct molecular testing need to be well trained to perform and interpret the results from the tests run in their laboratory. Six hundred eighty-nine (70%) staff that perform molecular testing in public health laboratories have earned at least a bachelor's or medical technologist degree, while approximately 11% of the workforce possess a PhD level education. Almost one-third of the staff that perform molecular testing in state public health laboratories possess a graduate level degree, while fewer than one-fourth of the molecular testing staff in local laboratories have earned graduate degrees. On-the-job training and/or prior experience in molecular biology (134 of 268 total responses) appear to be the primary qualifications needed for staff performing molecular testing. Forty-three percent (115 of 268 responses) indicate a degree in molecular biology, certification (e.g., ASCP), or state licensure qualification, while four percent of the responses indicate they have qualified staff who are Emerging Infectious Disease fellows.

Infrastructure

Forty-nine (100%) of the states that responded to this survey perform molecular testing for infectious disease agents. Based on these responses, it can be assumed that molecular testing is performed in all 50 state public health laboratories including the District of Columbia. In addition to the state and local public health laboratories, other governmental laboratories that were reported to perform molecular testing include the

Figure 1. Molecular testing funding source by type



Note: Total responses = 330 (as reported by 75 respondents)

state agriculture laboratory (10 states), the state environmental laboratory (5 states), and the state veterinary laboratory (3 states).

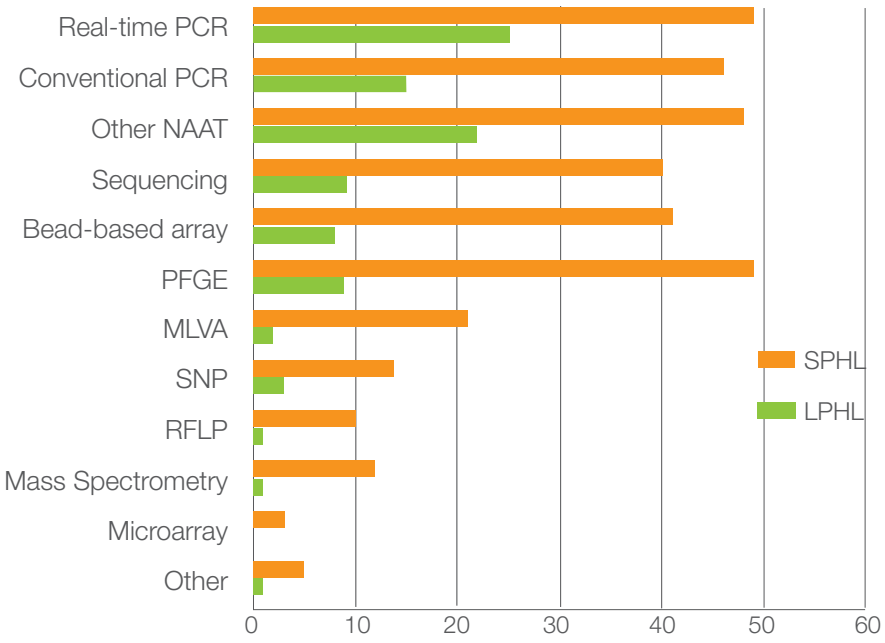
State and local public health laboratories use a variety of sources to fund the cost of molecular testing. While many of the laboratories report using general funds and employ fee-for-service testing, more than half (194 out of 330 responses; see Figure 1) of the funding comes from federal grants and cooperative agreements such as the Public Health Emergency Preparedness (PHEP) and Epidemiology and Laboratory Capacity (ELC) Cooperative Agreements. Local public health laboratories rely heavily on general funds (77%), fee-for-service (73%), and the PHEP Cooperative Agreement (69%) for their molecular testing (data not shown). State public health laboratories report more diversified sources of funding for their molecular testing. Although 43 (88%) state public health laboratories use general funds for this type of testing, nearly all of the state responders reported using the PHEP (n=47; 96%) and ELC (n=47; 96%) grants to support their testing. Seventy-two (96%) of the survey respondents reported that the instruments their laboratories use for molecular testing have been purchased with dedicated funding that can be used for testing activities outside of the original funding source (69 of 72).

Laboratory Capabilities and Practices

More than half (69 of 134 responses) of molecular testing performed in state and local public health laboratories is consolidated into a single laboratory/section or is performed in an agent-specific (e.g., bacteriology or virology) laboratory. In actuality, the survey respondents use a combination of agent-specific laboratories and laboratory sections to perform their molecular testing. For example, several of the survey respondents commented that nucleic acid extractions are performed in agent-specific laboratories, and amplification and detection is performed in the designated molecular laboratory.

Due to the sensitivity of PCR and threat of contamination, workflow is a critical component of molecular testing. Public health laboratories have practices in place to prevent contamination in order to ensure quality laboratory practice. For example, 71 (95%) of the survey respondents report maintaining separate, "clean" pre-PCR rooms or designated areas for handling nucleic acid templates and mastermix setups. Nearly all laboratories (73 of 75) reported practicing unidirectional workflow, from "clean" pre-PCR to "dirty" post-PCR.

Figure 2. Comparison of molecular capacities and capabilities in state and local public health laboratories



Note: Total respondents = 75

Public health laboratories have a variety of technological platforms in place to detect infectious disease causing agents, many of which have the capacity to run multiplex assays that enable the detection/measurement of multiple analytes simultaneously (see Figure 2). Seventy-four (99%) of the laboratories responding to this survey report having real-time PCR capacity; this technology is present in 49 (100%) state public health laboratories and most (n=25;

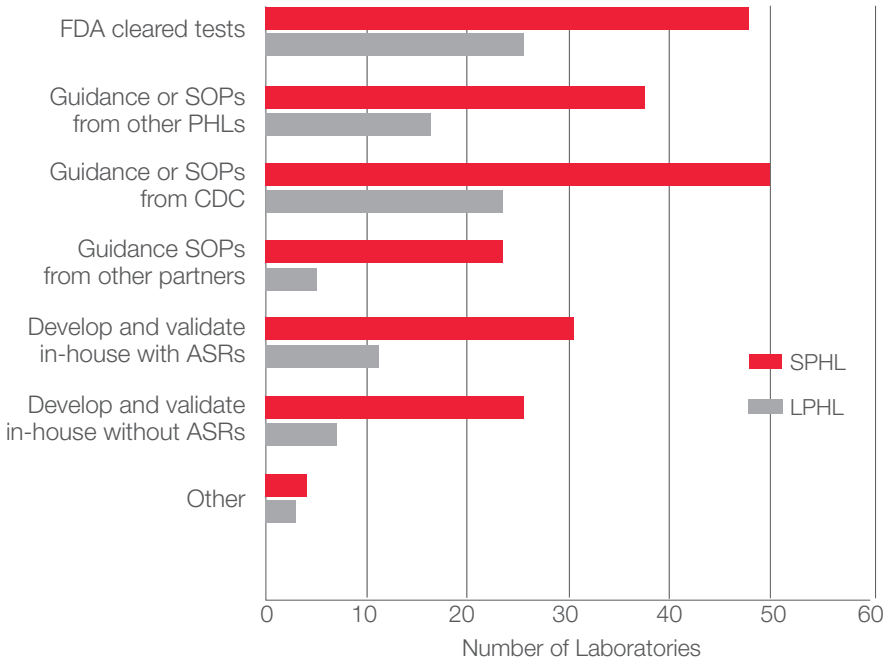
96%) local laboratories. Many of the laboratories continue to use additional nucleic acid amplification tests (NAAT) such as conventional PCR (81%) and/or commercial assays such as automated GC/CT NAAT (93%). Approximately two-thirds of the laboratories have sequencing and/or bead-based array instruments (e.g., Luminex) as part of their molecular testing capacity. Few laboratories have maintained capacity for older test methods such as restriction fragment length polymorphism (RFLP) (11 out of 75) or have adapted other sophisticated technologies such as mass spectrometry (13 out of 75) for infectious disease testing.

The primary molecular testing activities in state and local public health laboratories are tests that employ real-time PCR, automated NAAT, and pulsed field gel electrophoresis (PFGE), which are utilized in greater than 95% of the laboratories on a daily or weekly basis. In local public health laboratories, the primary molecular capacities are real-time PCR (n=25; 96%), followed by other nucleic acid amplification tests (n= 25; 96%) such as automated GC/CT NAAT. At the state level, real-time PCR (49 of 49, 100%); conventional PCR (46 of 49, 94%); other NAAT (48 of 49, 98%); and PFGE (49 of 49, 100%) are embedded into public health laboratory testing services. State public health laboratories are more likely to have additional molecular assays to support infectious diseases testing including sequencing capacity (n=40; 82%) and bead-based arrays (n=41; 84%) compared to local public health laboratories (n=9; 35%) and (n=8; 31%), respectively (see Figure 2).

The emergence or re-emergence of new or rare infectious disease agents as well as improvements in science and technology necessitate the periodic implementation of new assays in the laboratory (see Figure 3). Nearly all public health laboratories (n=72; 96%) use tests that have been approved or cleared by the US Food and Drug Administration (FDA). Other options include technology transferred from CDC into public health laboratories (72 of 75, 96%), and in-house development and validation with analyte-specific reagents (ASRs) that are manufactured under FDA-required Good Manufacturing Practices (41 of 75, 55%). Another testing option is to use laboratory-developed tests (LDTs), which are developed and validated in-house without

the use of ASRs (32 of 75, 43%). Nineteen (25%) of the laboratories that participated in this survey do not use or develop LDTs; ten of these are local public health laboratories. For laboratories that do develop or use LDTs, accuracy (54 of 56, 96%), precision (53 of 56, 95%), analytical sensitivity (52 of 56, 93%), and analytical specificity (51 of 56, 92%) are the parameters used to establish performance when validating new LDTs. The guidance developed by CLIA is used most frequently by public health laboratories (97%) to validate molecular assays.

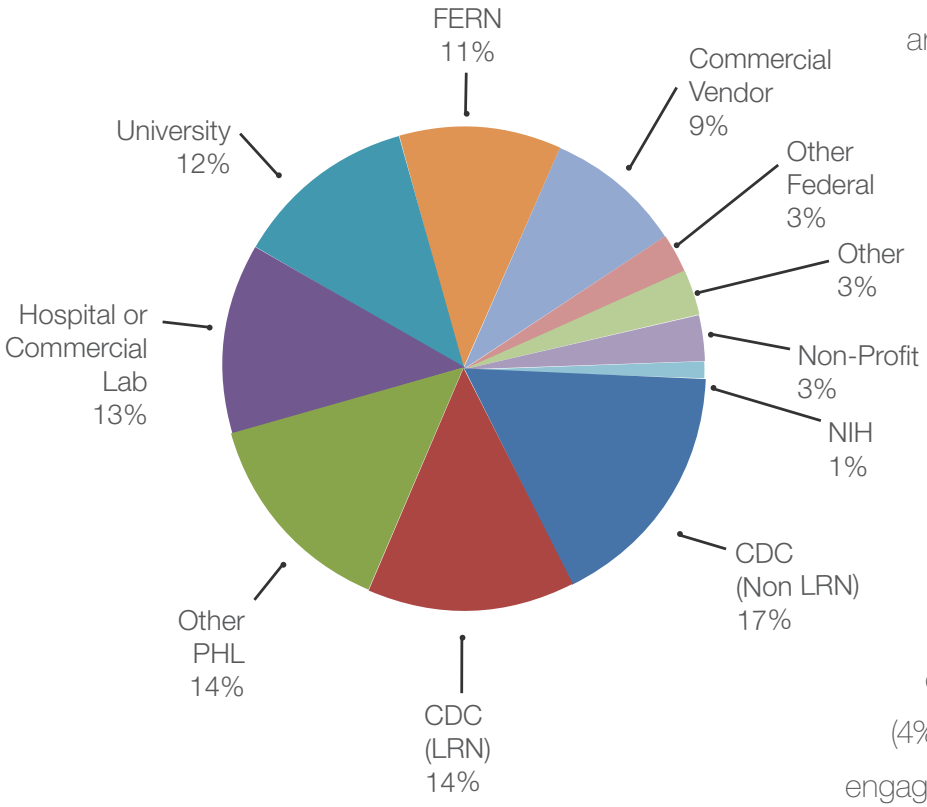
Figure 3. Strategies for implementing new molecular assays in public health laboratories



To maintain testing proficiency, all public health laboratories participate in a proficiency testing (PT) program that is specific to molecular testing. The laboratories reported a number of different mechanisms for meeting their PT needs including the use of a commercial PT from a source such as the College of American Pathologists (CAP) (n=73; 97%), internal panels (n=53; 71%), and participation in a laboratory specimen exchange program (n=37; 49%). Of the laboratories that participate in specimen exchange programs, more than 70% come from CDC or another public health laboratory (48 of 66 responses, 72%). Approximately one-third of these laboratories participate in a regional specimen exchange program to help meet their PT needs.

Research and Development

Figure 4. PHL Collaborative Study Partners



Note: Total Responses = 238 (from 63 respondents)

Sixty-three (84%) state and local public health laboratories have participated in collaborative studies focused on research, assay development, or assay validation. As indicated in Figure 4, CDC and other public health laboratories were reported to be the primary collaborative partners; however, a number of public health laboratories reported performing collaborative studies with hospitals and/or commercial laboratories (30 of 75, 40%), universities (28 of 75, 37%), and commercial vendors (21 of 75, 28%). Local public health laboratories were less likely to participate in collaborative studies: compared to only two (4%) state public health laboratories not engaged in this activity, more than one-third (10 of 26, 38%) of local public health laboratories indicated not participating in collaborative studies.

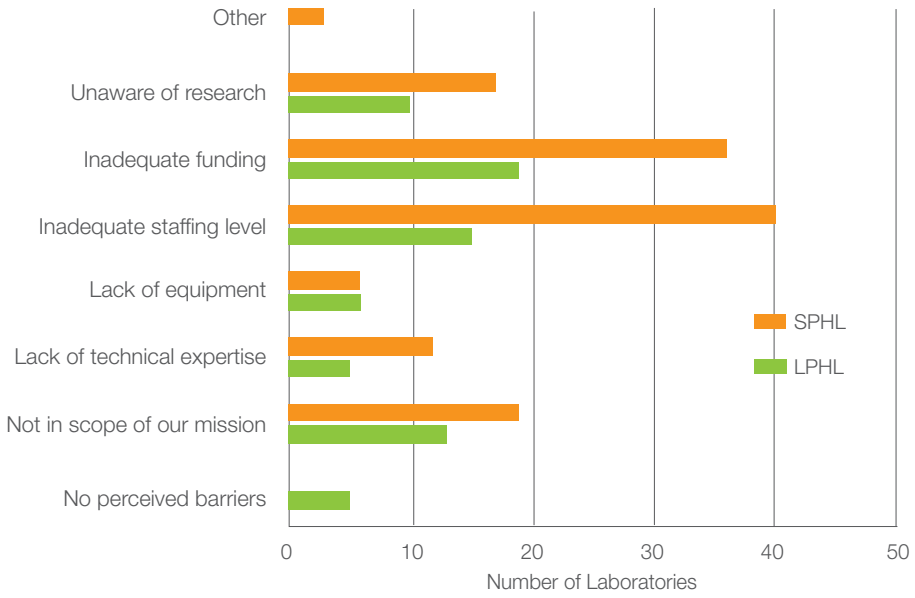
Greater than 70% of the state and local laboratories surveyed have participated in applied research studies including assay development, assay validation, method comparison studies, disease surveillance, and clinical trials. Of this group, 39 (80%) state public health laboratories and 15 (58%) locals have engaged in applied research studies. Assay validation (n=47; 87%) and comparison studies (n=41; 76%), such as PCR vs. culture or EIA, were the most frequent studies performed. Assay development occurs more frequently at the state level (28 of 39, 72%), as less than half (6 of 15, 40%) of the local laboratories engage in this activity.

Barriers

Greater than 80% of the laboratories that participated in this survey identified inadequate staffing levels (60 of 75 laboratories) and inadequate funding (65 of 75 laboratories), accounting for 61% of total responses, as being major barriers to adding additional assays to increase their molecular testing capacity (Figure 5).

Similarly, inadequate staffing levels (55 of 75, 73%) and inadequate funding (55 of 75, 73%) were identified as the top two perceived barriers to the public health laboratory's ability to perform research and development. Despite being identified as one of the core functions and capabilities of public health laboratories,[5] 32 (43%) public health laboratories identified research and development as not in the scope of their mission.

Figure 5. Public health laboratory barriers to conducting research and development



Note: Total respondents = 75

Discussion

These findings provide a snapshot of public health laboratories' current molecular testing capacities and capabilities for infectious disease agents. The incorporation of molecular assays benefits public health laboratories in numerous ways including providing improvements in turnaround time and outbreak response, enhancements in pathogen identification and characterization, the ability to automate assays, and increased throughput. Despite these advantages, the nation's public health laboratories face a number of challenges that impact the use of molecular assays.

The data from the survey suggest that the majority of public health laboratories depend heavily on CDC to transfer technology and other resources to support molecular testing activities. Approximately 40% of the funding for molecular testing comes directly from CDC from the ELC, EIP, and PHEP cooperative agreements/grants, compared to 5% of state-specific funding.

When public health laboratories implement new molecular assays (with the exclusion of FDA-cleared tests), technology transfer from CDC is the most frequently used mechanism to institute new assays. Of the 63 public health laboratories that reported participating in collaborative research and development studies, CDC was identified as the collaborating partner by approximately one-third of the survey respondents, which is more than twice that of the next most frequently reported collaborative partner. While CDC has the expertise and resources to develop tests to detect and monitor infectious disease threats, is this the best scenario? With state budgets and staffing levels continuing to decline, public health laboratories may become even more dependent on CDC to transfer technology. The impending regulatory oversight of LDTs by the FDA has the potential to have a significant impact on how CDC develops tests in-house and how they are rolled out to the states.

In recent years, state budget difficulties have hindered the ability of laboratories to recruit and retain qualified staff in molecular diagnostics. However, as described in this report, a well-trained staff is necessary to develop, perform, and interpret the results of molecular assays. Thus, the development of hands-on training opportunities and protocol/SOP sharing are critical to help laboratories enhance and maintain their molecular testing capacity. Improving collaborations between states and with other partners may help public health laboratories maintain proficiency through specimen sharing, collaborate to develop and validate molecular LDTs, and share model practices to perform molecular testing.

Despite staffing and fiscal challenges, public health laboratories are able to employ a number of molecular technologies to detect and monitor infectious diseases. Each of the laboratories surveyed employ quality molecular biology practices in their testing workflow. Fostering new relationships and improving collaborations with other public health laboratories, federal partners, commercial vendors, and the clinical community may provide opportunities to improve capacity in the future. APHL will continue to work with federal, state, local, and other partners to address these challenges and enhance molecular capacity in the nation's public health laboratories.

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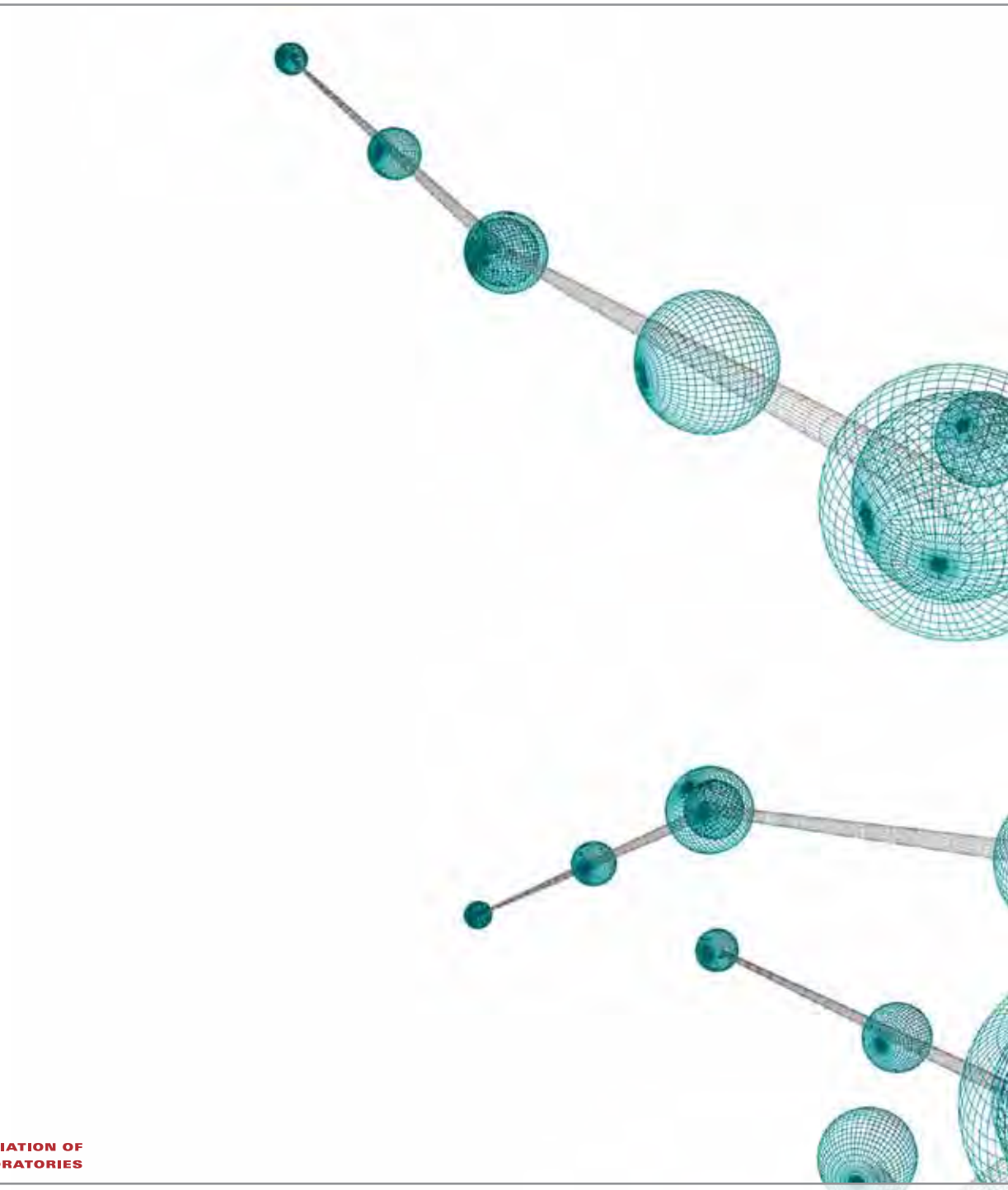

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