



Comment for CLIAC Meeting November 7, 2019  
Submitted October 30, 2019

The Association of Public Health Laboratories (APHL) appreciates the opportunity to advise the Clinical Laboratory Improvement Advisory Committee (CLIAC) workgroup on how new technologies, workflows and bioinformaticists are changing the current and future practice of laboratory science. Updates to CLIA in these areas will offer clarification and consistency where it is currently lacking.

Our members routinely work at the leading edge of innovative developments in laboratory practice, and thus have valuable perspective on how emerging technologies benefit public health. APHL encourages CLIAC to provide recommendations to CMS allowing for regulatory language that is broad yet flexible, allowing CLIA to adjust to emerging technologies promptly, while ensuring quality and preventing delays in diagnostic and surveillance activities.

*Question 1: Are bioinformaticists needed in clinical and public health laboratories? If so, what are the current roles, responsibilities, and competencies of bioinformaticists in these settings?*

Bioinformaticists play a vital role in public health laboratories as they are critical to modern day disease detection and surveillance. In a rapidly changing field, bioinformaticists are responsible for identifying and building appropriate programs and analytical pipelines, helping to interpret results, identifying outbreaks, conducting disease surveillance, and implementing quality metrics. They are important for successful collaboration with Information Technology staff, helping build greater computing capacity and ensuring data security, migration and integrity.

Bioinformaticists are necessary for any public health laboratory utilizing Next Generation Sequencing (NGS) in areas such as human genetics, molecular subtyping surveillance, or molecular microbial testing, or other technologies that generate large data sets. The particular skill set required may be different across laboratories. For some public health applications that provide data to a national program, bioinformatics can sometimes be handled offsite by a reference entity. However, for programs working locally, including foodborne outbreak surveillance, newborn screening or region-specific disease outbreak detection, a dedicated bioinformaticist may be needed within the public health laboratory. Laboratories may sometimes find it more efficient to utilize staff sharing arrangements to equip them with necessary tools and skills to meet bioinformatics needs.

The "Competency Guidelines for Public Health Laboratory Professionals: CDC and the Association of Public Health Laboratories,"<sup>11</sup> developed in 2015, address basic competencies for progressing in a career as a bioinformaticist. A CLIAC recommendation for an expert group to update these competency guidelines, including considerations for biology and public health expertise, would improve the characterization of the skillsets required for bioinformaticists.

---

<sup>11</sup> MMWR Supplements May 15, 2015 Vol. 64 No. 1 Pg. 1 – 95. Competency Guidelines for Public Health Laboratory Professionals: CDC and the Association of Public Health Laboratories

*Question 2: What areas exist in CLIA where specific requirements or guidance might be needed to ensure the accuracy and reliability of new and emerging laboratory technologies and nontraditional testing workflow models, including next generation sequencing, biomarker testing, metagenomics, and others?*

A few suggestions for where recommendations are needed are outlined below, however APHL concurs with the April CLIAC meeting report, that a thorough review of the CLIA regulations is needed to define all areas where updates related to these fields are necessary. New technologies, such as NGS, could have separate specialties, however if placing new guidance in existing specialties would allow more expeditious release, this may be preferable.

Guidance is recommended for qualifications for high complexity testing personnel and bioinformaticists, commensurate to the complexity and responsibility of the work. Laboratory leadership provisions should also be reviewed to account for knowledge in these areas.

Our member laboratories have and need a spectrum of expertise in bioinformatics, from qualified users to leaders in the field. Given the breadth of the field, bioinformaticists currently have an array of backgrounds. Some have a strictly computer science background, with hands on biological science training in the laboratory. Others have degrees in microbiology or molecular biology with thesis projects and/or training utilizing bioinformatics. In some instances, laboratory personnel are trained to perform basic analyses, however they cannot perform the full scope of bioinformatics work. In other situations, a deeper understanding of the biology is required than can be ascertained by training a computer scientist on the job. Education and experience requirements need to account for the scope of work and diversity of backgrounds and training.

Emerging technologies often cannot follow the same validation strategies used in traditional testing and require a dynamic framework for validations as these technologies evolve. For example, a method-based validation is likely more appropriate than validating each of the genes on a disease-specific screening panel. NGS requires independent validation for the wet-lab, bioinformatics and reporting, therefore, recommendations for handling validation of distinct yet linked portions of a protocol that may even be performed in separate laboratories, are needed. In-house developed bioinformatics pipelines need rigorous validation but with flexibility in interpreting results since previous standards may be less sensitive and specific. Guidance would also need to address how best to validate pipelines and analysis tools previously validated by an outside entity. For example, tools and services provided through the BioNumerics software and the Calculation Engine used by PulseNet contain analysis parameters that cannot be altered by the laboratory that generated the sequences.

QA/QC guidance will need to be carefully considered for emerging technologies. The use of traditional positive and negative controls are not always applicable in NGS workflows as numerous other measures, including in silico methods, can be used to assess quality and acceptability of data generated. Non-targeted analysis through High Resolution Mass Spectrometry that, for example, quickly identifies emerging drugs, such as designer opioids or

cannabinoids in clinical samples, also does not lend itself to traditional approaches. Bioinformatics does not fit clearly into the QC requirements under the current CLIA guidelines. Guidance related to documenting development of bioinformatics pipelines, version control, and database usage is needed.

The amount of data generated by NGS is unlike any other biological test to date. Data management, including storage mechanism/location, duration of storage, curation and sharing is a substantial challenge. The database and pipeline used can vary the output, so guidance on how to implement and maintain version control is essential. Guidance addressing storage of raw versus processed data is also needed. Guidance should also reflect the different needs of microbial and human data, also allowing for extension to other "omics" methods, where data may contain sequences of both human and microbial origin.

In biomonitoring programs and other public health surveillance programs where biomarkers of exposure are measured in clinical samples, the applicability of results to patients' health conditions may be unclear. CLIA should consider providing recommendations for guidance on whether these tests should require an ordering provider, reasonable reference ranges and the PHLs responsibility to provide context and patient education.

*Question 3: What data are available that could assist in answering how CLIA may need to be revised or where guidance may be needed to ensure the accuracy and reliability of emerging technologies?*

To successfully gather and learn from available data, CLIA will need to continue to collaborate with partners, subject matter experts, and laboratories using new emerging technologies in a multistage process to develop consistent guidance. There are some data on use and challenges with emerging technologies in PHLs, including the need for data standards, for example "Next Generation Sequencing in Public Health Laboratories, 2014 Survey Results".<sup>2</sup>

Since updates of this level to CLIA would reasonably be expected to take years, it is suggested that CMS consider the release of Interpretive Guidelines for Laboratories to serve as a reference when seeking clarification regarding how the existing regulations apply to new emerging technologies. These guidelines could serve as a reference for both laboratories and inspectors to ensure consistency across CLIA in these innovative areas in a shorter timescale.

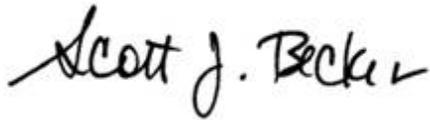
Addressing how CLIA interacts with technological advances is an enormous undertaking. APHL commends the CLIA for beginning the conversation. Updates to the current regulations will need to be an iterative

---

<sup>2</sup> APHL. 2015. Next generation sequencing in public health laboratories, 2014 survey results. Association of Public Health Laboratories, Silver Spring, MD:  
[https://www.aphl.org/AboutAPHL/publications/Documents/ID\\_NGSSurveyReport\\_52015.pdf](https://www.aphl.org/AboutAPHL/publications/Documents/ID_NGSSurveyReport_52015.pdf)

process, performed in consultation with informed stakeholders. APHL looks forward to providing whatever further expertise the committee needs as it prepares recommendation for the Secretary.

Sincerely,



Scott J. Becker, MS

Executive Director



Grace Kubin, PhD

President

*APHL works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.*