Public health microbiology laboratories are on the cusp of unprecedented improvements in pathogen identification, antibiotic resistance detection, and outbreak investigation by using whole-genome sequencing (WGS). However, considerable challenges remain due to the lack of common standards and absence of the guidelines from the regulatory agencies specifically addressing microbiological WGS applications. The goal of this presentation is to share the approach that Microbial Diseases Laboratory of the California Department of Public Health took to validate the WGS on the Illumina platform for routine use to meet Clinical Laboratory Improvements Act (CLIA) requirements for laboratory-developed tests (LDTs). The study was undertaken to establish performance specifications for clinical WGS applications according to CLIA guidelines, design modular templates for validation of the next generation sequencing platforms and applications, develop quality assurance and quality control measures, finalize a user-friendly report format, and identify a set of bacterial pathogens that could be used for WGS validation and performance assessments.