The introduction of next generation sequencing platforms and continual decrease in the cost for sequencing has enabled many laboratories to implement these valuable tools and methods to transform their laboratory workflows and advance many areas of research. We are currently using NGS platforms to address drug resistance, molecular epidemiology and clinical diagnostics for *Mycobacterium tuberculosis*. The rapid detection of drug-resistant tuberculosis (TB) is critical to ensure patients are treated with an effective drug regimen and prevent acquisition of further resistance and transmission. Molecular-based assays play a pivotal role for rapid diagnosis, but the targets and mutations must be known to design many of these assays. Unfortunately, the mechanisms of resistance are not fully understood for all drugs used to treat TB. We are using whole genome sequencing (WGS) and functional genetics to address this area to close the knowledge gap and improve the accuracy of these tests. We are also implementing WGS within our national surveillance system to detect outbreaks and possible transmission networks to help local TB programs focus their limited resources to stop ongoing transmission within their community.