Technology innovations in genomics that reduce sequencing time and cost have created new opportunities for biological research. Since the mid 2000's, large scale sequencing of bacterial genomes using Illumina technology has become a standard for pathogen epidemiology studies, resulting in very large data sets for some species. Genome data has been generated faster than can be properly analyzed and integrated with results of classical experimental approaches to microbiology. My group has concentrated on analyzing the tens of thousands of *S. aureus* genome in the public domain. Antibiotic resistance prediction is an area of great interest currently that falls at the interface of bioinformatics and laboratory culture based analysis. I will discuss the challenges and successes of genome-based antibiotic prediction. I will also discuss the linkages between classical molecular genetics, shotgun metagenomics and comparative megagenomics of bacterial species.