

scalable and automated analysis pipeline already in use for rapid (days) characterization of genomic-relatedness in small and large sets of isolates. Mapping and SNP calling was performed against high-quality, best-match reference genomes. Sets of samples with pairwise distance of 2 persons with genomically related isolates and were denoted as “clusters.” Separately, we also investigated within-patient diversity by quantifying the genomic relatedness of isolates collected from individual patients. **Results:** Isolates represented 28 distinct species. We identified 10 *Escherichia coli* clusters (range, 2–4 patients; median, 2 patients), 2 *Klebsiella pneumoniae* clusters (range, 2–4 patients), and 1 *Enterococcus faecium* cluster (3 patients). All but 1 involved genomically matched isolates from multiple hospital locations. There were 4 *Escherichia coli* ST131 clusters spanning 4 months, including 1 with 4 patients across 3 different hospital locations. At a species level, there were distinct differences between the observed SNP distances between samples isolated from the same versus different patients (Fig. 1). All identified clusters had not been flagged by routine outbreak detection methods used by the UCI infection prevention program. **Conclusions:** Comprehensive WGS-based surveillance of hospital clinical isolates identified multiple potential transmission events between patients not in the same unit at the time cultures were taken. Combining WGS detection and real-time epidemiologic investigation may identify new avenues of transmission risk and could provide early warnings of clonal transmission to prevent larger outbreaks. High-volume surveillance of hospital isolates can also provide species- and context-specific clonality.

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Whole-genome sequencing cluster analysis reveals complex healthcare-associated COVID-19 dynamics

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Background: Identifying and interrupting transmission of severe acute respiratory syndrome coronavirus 2 and resulting disease (COVID-19) in acute-care settings can be challenging due to incubation period, asymptomatic infection, and prevalent community disease. To elucidate routes of infection and interrupt COVID-19 outbreaks with uncertain epidemiological chains of transmission, UPMC utilized reactive whole-genome sequencing (WGS) of viral specimens. **Methods:** UPMC infection prevention teams identified healthcare-associated COVID-19 clusters with uncertain transmission pathways among patients and/or healthcare personnel (HCP) in acute-care hospitals. Nasopharyngeal samples preserved in viral transport media were obtained for genetic analyses. Nucleic acids were extracted and WGS libraries were prepared by targeted enrichment or multiplex PCR methodologies. Resulting sequencing reads were aligned to the Wuhan-1 reference genome, followed by identification of single-nucleotide polymorphisms (SNPs) among the genomes and construction of a phylogenetic tree. Specimens were considered genetically similar if there were ≤ 2 SNP differences between viral genomes within a cluster.

Results: Between May 2020 until August 2022, infection prevention teams requested WGS for 17 healthcare-associated clusters of COVID-19 involving 182 individuals across 8 UPMC facilities (median outbreak size, 9 individuals; range, 2–26). Of the 182 individuals, 36 lacked clinical specimens and 30 did not pass WGS quality-control criteria of $\geq 95\%$ of the reference genome with a minimum of $10\times$ coverage. Of the 116 sequenced genomes, 94 (81%) had virus genetically similar to ≥ 1 other specimen, including 87 (83.6%) of 104 patient viruses and 7 (58.3%) of 12 HCP viruses, comprising 22 clusters (Fig. 1). The remaining 22 (20.6%) specimens were genetically unrelated. In total, 16 (94.1%) of the 17 epidemiologically identified clusters had 2 or more individuals with a genetically similar virus. Also, 7 (41.1%) of these clusters had genetically similar viral genomes for every individual within each cluster. Also, 9 (52.9%) clusters



contained both genetically related and unrelated specimens: 5 of these had more complex genomic profiles (including 4 clusters containing 2 distinct subclusters of ≥ 2 genetically related viruses) and 1 cluster contained 3 sub-clusters of ≥ 2 genetically related viruses. In the outbreak with 3 clusters, 3 SNPs separated specimens from 2 temporally proximal clusters, suggesting possible propagation between clusters (cluster B-3 in Fig. 1). **Conclusions:** WGS can complement traditional epidemiological investigations of healthcare-associated COVID-19 outbreaks, revealing complex transmission dynamics. Future investigations will characterize the impact of WGS on determining specific transmission pathways in acute-care facilities.

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Factors associated with SARS-CoV-2 and community-onset invasive *Staphylococcus aureus* coinfection, 2020

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Figure 1. Timing from first SARS-CoV-2 positive test collection to initial invasive *Staphylococcus aureus* specimen collection, community-onset coinfection cases, 11 US counties, March 1–December 31, 2020.

