



GENOME WATCH

Through the gut, down the drain

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This month's Genome Watch highlights how metagenomics could link the gut microbiota and COVID-19 disease outcomes and track emerging SARS-CoV-2 variants, with the potential to inform clinical practice and public health policy.

Heterogeneity in clinical outcomes of COVID-19 demands a better understanding of the underlying factors to improve prognostic and therapeutic approaches. The COVID-19 pandemic has also highlighted the necessity of accurate, real-time epidemiological surveillance to inform public health policy for effective pandemic management. When applied to the human gut microbiota, shotgun metagenomic and metatranscriptomic sequencing provide insights into gut bacterial-viral interactions in patients with COVID-19. When applied to environmental samples such as municipal wastewater, these approaches support community-level epidemiological surveillance in epidemic and pandemic contexts.

It has been proposed that differences in the gut microbiota composition between individuals might be associated with the severity of COVID-19 disease symptoms¹. Yeoh et al. applied shotgun metagenomic sequencing of faecal DNA obtained from patients with COVID-19. They found that the gut microbiomes of patients differed significantly compared to healthy

controls, and that these microbial signals stratified with clinical disease severity and correlated with biomarkers of inflammation. Specific changes in the microbiota following COVID-19 included decreased relative abundance of known immunomodulatory microorganisms that the authors suggest could provide a potential biological explanation for the observed heterogeneity in disease severity. These differences in the microbiota remained significant for at least 30 days after viral clearance, which hints at a potential role of the gut microbiota in the post-infection autoinflammatory syndrome known as 'long COVID'. It is important to emphasize that these findings are based on association and not causation, due to the limitations of small sample size and confounding factors such as antibiotic usage and hospitalization. More definitive studies are needed in longitudinal, population-based cohorts to determine the role of the gut microbiota in COVID-19 or vice versa. Understanding associations of the gut microbiota with COVID-19 outcomes could offer new avenues for developing prognostic indications and therapeutic targets for COVID-19.

Current research provides evidence for the gastrointestinal manifestations of COVID-19. The SARS-CoV-2 virus infects intestinal organoids, and large titres of viral RNA are commonly seen in stool samples of patients³. Persistent faecal shedding of viral RNA has been leveraged for epidemiological surveillance through wastewater sequencing. In comparison to conventional genomic surveillance based on clinical samples of symptomatic individuals that may lag behind the true viral spread and underestimate the prevalence of circulating variants, wastewater-based genomic surveillance could potentially identify all viral variants actively shed by both symptomatic and asymptomatic individuals within a community. In a preliminary study, Jahn et al.³ used deep shotgun

sequencing of wastewater samples and identified mutations that corresponded to the novel B.1.1.7 variant in Switzerland two weeks before it was first found in local patient populations, indicating that this approach could detect recently introduced genomic variants.

Although the resolution of metatranscriptomic sequencing is limited by the presence of multiple variants and low viral RNA titres in wastewater samples, method development efforts have led to the recovery of complete consensus SARS-CoV-2 genomes, thus enabling phylogenetic analysis of the predominant variant. These new methods, which include oligonucleotide capture enrichment⁴ and targeted amplification⁵ with long-read sequencing⁶, also enabled the rapid detection of minor circulating variants that were underrepresented or not yet detected by local clinical sequencing. Given the concerning emergence of multiple clinically important variants complicating COVID-19 vaccination and mitigation strategies, shotgun sequencing of wastewater samples could be considered as a surveillance tool that can facilitate comprehensive, real-time tracking of emerging SARS-CoV-2 variants locally and across the globe.

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