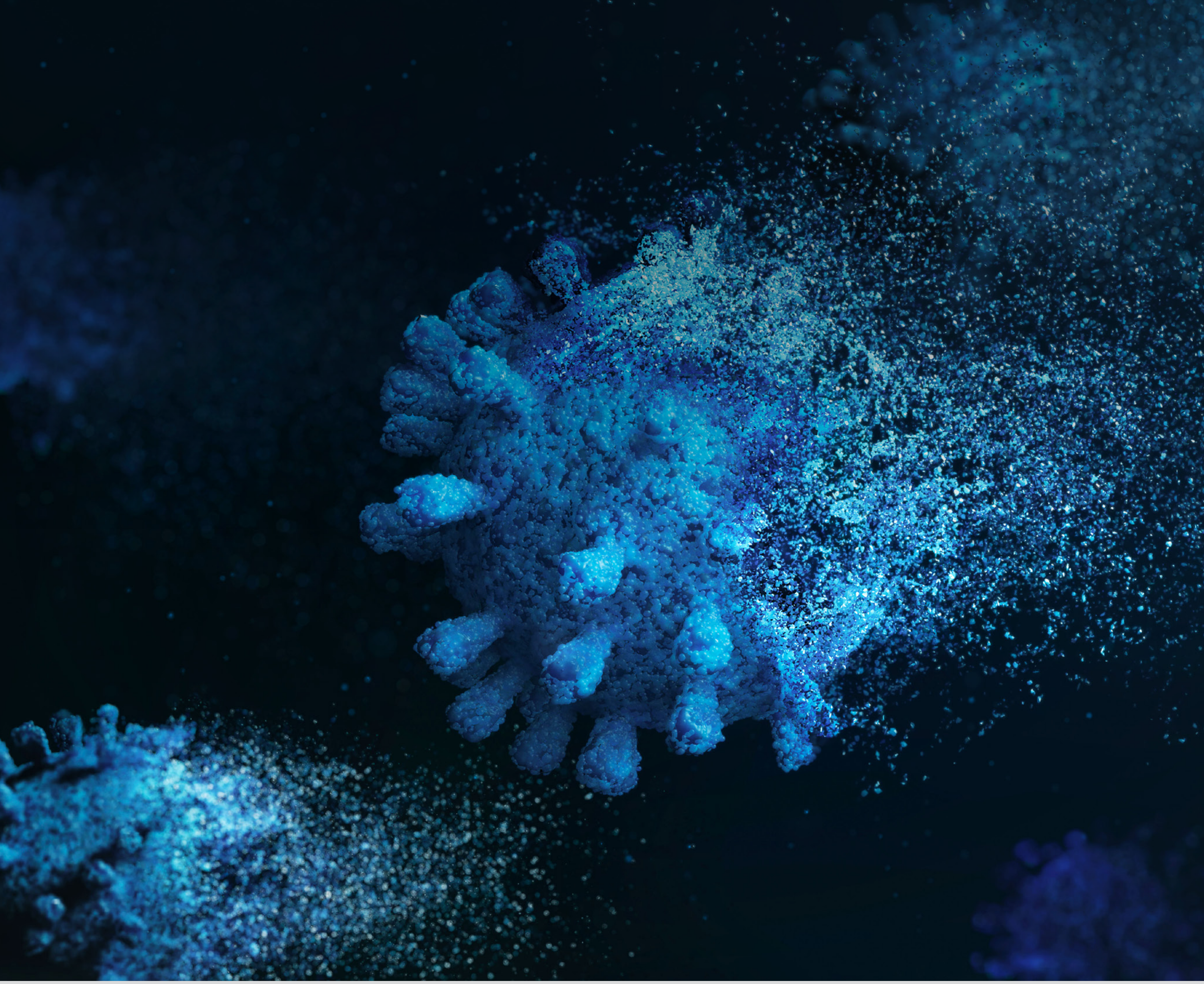

GENOME SEQUENCING TO STOP SUPERBUG TRANSMISSION

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GENOME SEQUENCING TO STOP SUPERBUG TRANSMISSION

Infections in health-care settings continue to rise. Scientists and health-care providers are turning to next-generation sequencing to detect outbreaks and guide IMPLEMENTATION OF TARGETED INTERVENTIONS.

SORRASAK JAR TINYO / GETTY IMAGES

▲ **Any medical device or procedure that opens the skin, such as an intravenous catheter, is a potential site for infection.”**

Genomic surveillance has proven its value during the COVID-19 pandemic. Sequencing is indispensable for monitoring SARS-CoV-2 evolution and detecting mutations that could make the virus more contagious or virulent, or evade the immune protection from prior infection and vaccination. Researchers are applying this genomic approach in other settings to reduce the spread of pathogenic microbes.

“Sequencing of SARS-CoV-2 during the pandemic has broadened our minds to what is possible — and shown us the kind of infrastructure and organizational bodies that are needed to apply it to health-care associated infections (HAIs),” says Daria Van Tyne, comparative genomics expert, working in the Infectious Disease Division at the University of Pittsburgh School of Medicine, Pennsylvania.

As part of the NIH-funded Enhanced Detection of Hospital-Associated Transmission (EDS-HAT) project, she has been combining routine whole-genome sequencing (WGS) surveillance of bacterial pathogens with machine learning and data mining of electronic medical records to identify outbreaks not detected by traditional methods. “We are mainly focused on bacteria but expanding to monitor virus transmission, including SARS-CoV-2, and fungal pathogens,” Van Tyne explains.

HAIs include central line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia and surgical site infections. Up to 87% of HAIs are caused by just 17 microorganisms[1]. Worryingly,

> **“SEQUENCING OF SARS-COV-2 DURING THE PANDEMIC HAS BROADENED OUR MINDS TO WHAT IS POSSIBLE.”**

among those pathogens, 20% include strains that have acquired multidrug resistance.

"The problem has got worse during the pandemic," says John Fallon, Chair of East Carolina University's Department of Pathology & Laboratory Medicine and chief of Vidant Medical Center's hospital laboratory in North Carolina. Nationwide, both drug-resistant HAIs and deaths increased by at least 15% during 2020[2]. "There are more resistant infections, possibly due to the increased use of antibiotics before vaccines and treatments were widely available, upending previous progress in tackling HAIs," he explains.

These findings highlight the urgent need for hospitals and public health systems to be able to monitor multiple threats simultaneously and take effective action to prevent, contain and combat HAIs. Fallon says genomic surveillance using WGS will be crucial for improved responses to both antimicrobial resistance and new pathogens with pandemic potential.

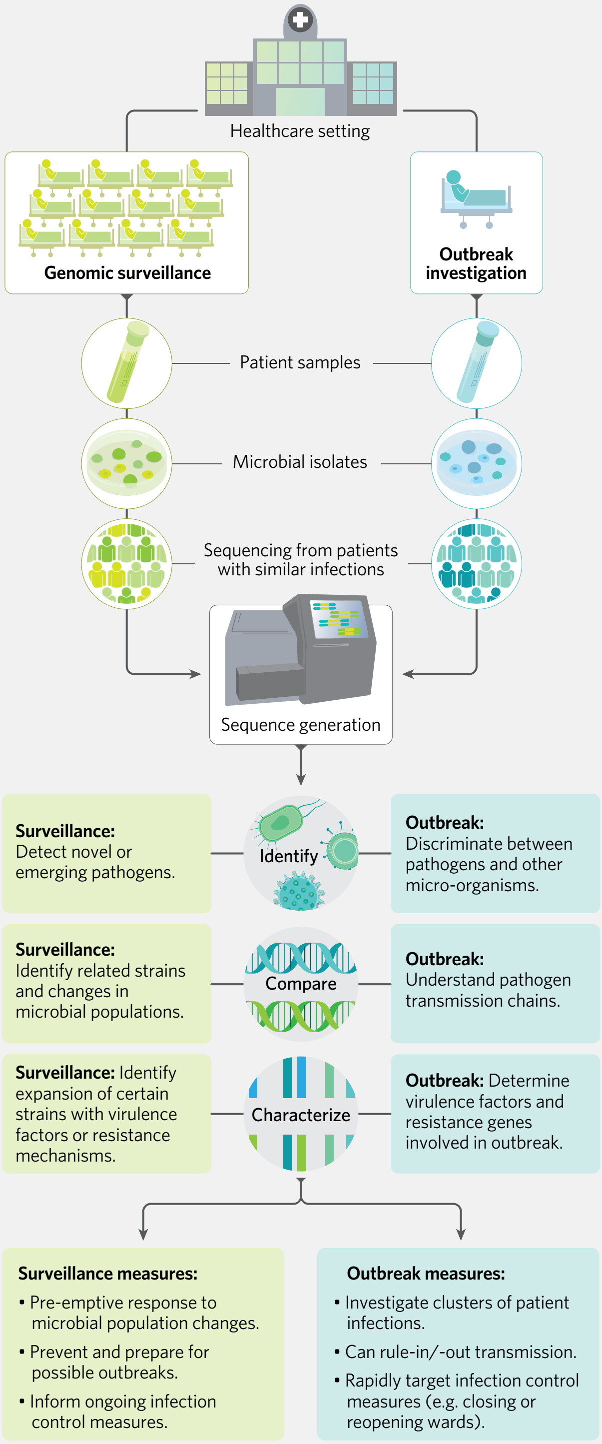
HIGH-RESOLUTION HAI DETECTION

HAIs occur in patients being treated for other conditions. They are a major cause of morbidity and mortality, particularly in patients who are critically ill or immunocompromised. Data from the Centers for Disease Control and Prevention indicate that, on any given day, about one in 31 hospital patients in the United States has at least one HAI.

Typically, doctors diagnose HAIs based on patient signs and symptoms, and start treatment after taking into account the patient's risk of HAI infection and mortality. To control the spread of HAIs, infection-prevention teams in hospitals review epidemiological data, including patient records and clinical-isolate culture results, to attempt to find the causative agent and potential route of transmission. Clinical isolates suspected to be part of an outbreak undergo phenotypic and molecular typing at reference laboratories; finding a similar microorganism in samples from different patients may indicate transmission has taken place. This process can result in substantial delays in the detection of outbreaks and miss some altogether.

GENOMIC SEQUENCING FOR MANAGING HEALTH-CARE ACQUIRED INFECTIONS

Whether it's routine surveillance or outbreak investigation, genomic analysis provides invaluable information.



Surveillance: Detect novel or emerging pathogens.

Outbreak: Discriminate between pathogens and other micro-organisms.

Surveillance: Identify related strains and changes in microbial populations.

Outbreak: Understand pathogen transmission chains.

Surveillance: Identify expansion of certain strains with virulence factors or resistance mechanisms.

Outbreak: Determine virulence factors and resistance genes involved in outbreak.

Surveillance measures:

- Pre-emptive response to microbial population changes.
- Prevent and prepare for possible outbreaks.
- Inform ongoing infection control measures.

Outbreak measures:

- Investigate clusters of patient infections.
- Can rule-in/-out transmission.
- Rapidly target infection control measures (e.g. closing or reopening wards).

"Traditional typing methods lack resolution and granularity," says Ben Parcell, consultant microbiologist at Ninewells Hospital and Medical School in Dundee, Scotland. These methods cannot identify all microorganisms and are unable to show whether individual strains from different patients are related or have concerning genetic resistance markers. "WGS provides greater discrimination compared to standard typing tests, and by using WGS we have more confidence in confirming that transmission has or hasn't taken place."

Most methods currently used in HAI investigation rely on the interpretation of microbial species identification and phenotypic susceptibility test results. Genetically sequencing clinical isolates, provides unprecedented and unequivocal information on species identity and the presence of antimicrobial resistance genes, allowing for targeted infection treatment and prevention measures. Moreover, analysing the sequence similarity between microorganisms can definitively reveal whether transmission has occurred and inform the best infection control response (see 'Genomic sequencing for managing health-care acquired infections').

“WGS is a very powerful tool as it allows us to ask whether two bacterial isolates that came from separate patients are related to each other and, if so, whether there is a high likelihood of transmission,” Van Tyne says.

CONTINUOUS HAI MONITORING

Thanks to substantial decreases in the cost of WGS and new sequence analysis tools, it is now feasible to apply genomics for routine HAI surveillance. Various projects are already proving the cost-effectiveness of this approach and improving patient safety.

Over a two-year period, Van Tyne and colleagues sequenced the genomes of more than 3,000 bacterial isolates collected from patients at UPMC Presbyterian Hospital. Systematic analysis of these genomes revealed that 14 different groups of related species were causing the HAIs, and that they were evolving at different rates[3,4]. The researchers were also able to detect multiple outbreaks that had been missed using traditional infection prevention methods, and identify transmission routes for most of them, decreasing the number of transmission events and potentially saving the hospital more than US$600,000.

For example, they found an outbreak of vancomycin-resistant *Enterococcus faecium* (VRE) associated with an interventional radiology procedure that would not have been identified without WGS[5]. “If we had used traditional methods that rely on geo-temporal clustering of cases, we would never have discovered how patients in different units of the hospital were acquiring the same strain of VRE,” she explains.

WGS surveillance for HAI outbreak detection is still uncommon and is usually limited to large hospitals as it requires specific infrastructure and experience. In some settings, it may be more practical to prioritize sequencing of samples from more vulnerable patients or from high-risk hospital units, such as neonatal intensive care.

Resources and time can also be saved by confining the use of WGS to HAI outbreak investigation. In 2014, the Scottish Healthcare Associated Infection Prevention Institute (SHAIPI) established a clinical WGS service to confirm or refute HAI outbreaks in real time[6]. Parcell, who is part of this initiative, outlined the benefits of this approach.

> **“MY DREAM IS THAT WE WILL SOON BE ABLE SEQUENCE SAMPLES FROM INFECTED PATIENTS AND OBTAIN INFORMATION ON THE PATHOGEN’S IDENTITY AND RESISTANCE GENES IN JUST A FEW HOURS.”**

“When outbreaks are suspected, we sequence the isolates. If the outbreak is confirmed, targeted measures are put in place — such as screening the environment and patients,” he says. “When outbreaks are ruled out by sequencing, the measures are stepped down and wards re-opened.” Hospitals are able to avoid unnecessary disruption of services, and staff can focus on preventive measures to stop the occurrence of further outbreaks[6].

Parcell also highlights the importance of getting results in an actionable time frame for outbreak management. With advances in WGS technology, it is possible to produce sequencing results that can inform outbreak measures and interventions while the outbreak is still happening — days before traditional typing results are available[7]. “Having sequencing facilities close to hospitals helps get the results faster and could replace the need for multiple routine laboratory tests,” he adds. Parcell envisages WGS becoming a standard approach for outbreak investigation.

INCREASING SURVEILLANCE

Sequencing efforts for surveillance of SARS-CoV-2 have become relatively common in high-income countries. Fallon has been involved in the Coronavirus Variant Sequencing (CORVASEQ) project, which has sequenced 14% of all positive samples in eastern North Carolina since the start of the pandemic. “We are tracking the spread and development of the virus across the state, and look at variant breakthroughs, re-infections, hospitalizations and deaths by age, race, county and so on,” he says.

However, when it comes to HAIs, the systems are still underdeveloped. “There is not much incentive for US hospitals to do sequencing-based surveillance of HAIs, and therefore to invest in the resources required,” says Van Tyne. Projects like EDS-HAT are helping to demonstrate improvements in patient safety and the cost-effectiveness of the approach. “Ultimately, a system of incentives and penalties will be required to make WGS surveillance as widespread as it needs to be”.

Finding ways to speed up data generation, interpretation and management will undoubtedly help. “My dream is that we will soon be able sequence samples from infected patients and obtain information on the pathogen’s identity and resistance genes in just a few hours,” says Fallon. “Then we can get them started on the most appropriate treatment right away.”

Maintaining the sequencing consortia that were established in the pandemic will support routine surveillance for novel and re-emerging pathogens. Of the UK, Parcell says: “If there is a positive outcome of the pandemic, it is that our sequencing capabilities for pathogen surveillance have improved.”

More hospital laboratories are gaining the ability to easily sequence microorganisms, which means that patients and health-care systems will benefit from earlier, definitive outbreak detection, reduced transmissions and cost savings. Illumina is committed to providing tools to perform HAI genomic surveillance and better understand pathogen transmission to inform effective control and prevention measures. ■

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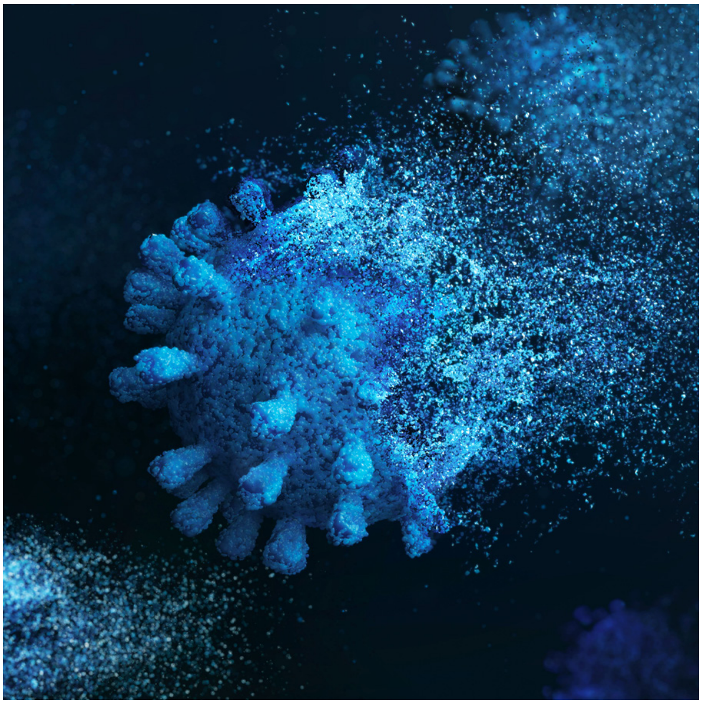

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