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A Review of the Genetic Features of *Staphylococcus aureus* Based on Whole-Genome Sequencing

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مراجعة السمات الوراثية للمكورات العنقودية الذهبية بناء على تسلسل الجينوم الكامل

انفال نافع عبدالله : قسم الاحياء المجهرية /كلية الطب/ جامعة الانبار/ رمادي -العراق

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الخلاصة

أصبحت إمكانية دراسة ديناميكيات مسببات الأمراض البكتيرية والتطور الجينومي بعد التطور في انواع العدوى والنمو ممكنة بواسطة تسلسل الجينوم الكامل. بكتريا المكورات العنقودية الذهبية هي أحد مسببات الأمراض البشرية الشائعة. يمكن أن تتسبب بحمى خفيفة أو أمراض خطيرة تهدد الحياة. إن التحدي في علاج والسيطرة على المكورات العنقودية الذهبية ينبع من انتشارها ومقاومتها المتزايدة للمضادات الحيوية المستخدمة سريريا. المكورات العنقودية الكاملة. نشر اول جينوم للمكورات العنقودية الذهبية في عام ٢٠٠١ وقدمت أول عرض لبنية الجينوم ومحتوى الجينات. يركز هذا البحث على العدوى ، وعوامل الفوعة ، والتنوع الجيني ، والجينات المقاومة، والتباين الوراثي في قاعدة واحدة، والاكشافات الجديدة، والدراسات المقارنة الخاصة ببكتريا المكورات العنقودية الذهبيه.إن الغرض من هذه الدراسة هو لفت الانتباه إلى السمات الوراثية للمكورات العنقودية الذهبية بناء على تسلسل الجينوم الكامل.

Abstract

The possibility of studying bacterial pathogens' dynamics and genomic evolution during human colonization and infection has been made possible by whole-genome sequencing. Staphylococcus aureus bacteria is a common human pathogen. It can cause mild erythema or serious life-threatening ailments. A challenge in treating and controlling Staphylococcus. aureus stems from its prevalence and increasing resistance to clinically used antibiotics. The full Staphylococcus. aureus genomes published in 2001 and provided the first view of genome structure and gene content. This research focuses on infections, virulence factors, genetic diversity, resistant genes, Single nucleotide polymorphism, novel identification, and comparative studies of Staphylococcus. aureus. The purpose of this study is to draw attention to the genetic features of Staphylococcus aureus based on Whole-Genome Sequencing, a bacterium that is frequently found in clinical microbiology labs .
Journal of Al-Farabi University College Keywords: Staphylococcus aureus, MRSA, Whole-genome sequencin

.١Introduction Staphylococcus aureus remains one of the leading causes of infections worldwide. It is the second most common pathogen causing resistance-related deaths and one of the most often isolated bacteria in nosocomial and community-acquired infections linked to a high rate of mortality and morbidity. In both the hospital (HA-MRSA) and community (CA-MRSA) environments, the rise and spread of MRSA with

supplementary resistance to other antimicrobial drugs is a major concern (Gregorio et al., 2023) .As a human pathogen, S. aureus depends not only on its ability to become resistant to many antimicrobial agents used in clinical settings, but also on its ability to generate a wide range of virulence factors, such as elements that facilitate host colonization, toxins, and immune evasion mechanisms. Global public health is being threatened by several epidemic S. aureus lineages. These referred to as high-risk clones (HRCs) typically change in frequency across time and space, and they have the potential to combine increased virulence or transmission potential with resistance to several antibiotic families (Gregorio et al., 2023). Conventional typing techniques, which have relatively low discriminatory power and make it challenging to distinguish between closely related strains, restrict thorough epidemiological examinations of S. aureus. Some examples of these techniques include phage typing, antibiotic susceptibility, and plasmid analysis (Rodriguez et al., 2015) .Some transmission instances can only be identified by whole-genome sequencing (WGS), which has a better resolution than other typing techniques such as spa typing and epidemiologic review. Interpreting data from standard typing methods for S. aureus strains is challenging due to the lack of a clear consensus on the degree of genetic variation that defines a different strain. Most normal healthcare settings cannot effectively utilize traditional typing methods due to their time-consuming, expensive, and technically difficult characteristics (Rodriguez et al., 2015; Lakhundi and Zhang, 2018). Comparing whole-genome sequencing (WGS) to conventional typing techniques, WGS offers significantly higher resolution and discriminatory power, making it possible to identify transmission instances and outbreak sources with greater accuracy. Crucial information for controlling and preventing outbreaks can be obtained from WGS's ability to map the spread of diseases within a population and reconstruct transmission chains (Gilchrist et al., 2015). WGS enables more flexible and exact definitions for outbreak cases, enhances the effectiveness of epidemiological tracebacks, and provides accurate in silico prediction of antimicrobial resistance profiles, improving surveillance and treatment methods for drug-resistant organisms such as MRSA (Struelens and Sintchenko, 2020) .The history of S. aureus and its genome are reviewed in this paper. The purpose of this study is to draw attention to the genetic features of Staphylococcus aureus based on Whole-Genome Sequencing, a bacterium that is frequently found in clinical microbiology labs .

.٢ Infections and Virulence Factor of S. aureus The name Staphylococcus was introduced by Ogston in 1883 for the group of micrococci obtained from pus from surgical abscesses (Lowy, 1998). Following that, Friedrich Julius Rosenbach added the species name (aureus) in 1884. S. aureus is a cluster-forming bacterium that forms yellow colonies, its name is derived from two Greek words: (staphyle and kokkos), which mean "the bunch of grapes," and aureus, which means "golden" (Srisuknimit, 2019).The major cause of nosocomial bacteremia, surgical site, prosthetic joint, and cardiovascular infections in addition to pneumonia and other respiratory tract infections. Other moderately severe S. aureus infections, such as furuncles, abscesses, and wound infections, are typically not fatal, but they can cause a great deal of pain and morbidity. They constitute a significant public health burden because of their frequency (Tong et al., 2015). Additionally, S. aureus can opportunistically advantage the initial damage caused by other infections or predisposing factors. This happens, for instance, in lung infections brought on by viral diseases like the flu, where a subsequent S. aureus infection is frequently the final cause of mortality (McCullers, 2014). Multiple factors that contribute to S. aureus has been reported to produce add to its pathogenicity. Toxins, immune evasion factors, exoenzymes, and antimicrobial resistance determinants .These factors include Antigens (such as capsules and adhesins) ,enzymes (such as coagulase and lipase), and toxins (such as hemolysins, leukocidins, enterotoxins, and exfoliative toxins. Another significant virulence feature linked to S. aureus survival in food-processing environments and persistence in clinical settings is its ability to form biofilms. Multiple additional virulence determinants acquired through MGEs (Oogai et al., 2011). WGS analysis detected a total of 116 virulence genes in S. aureus isolates, Common virulence genes found in all isolates included adsA, aur, cap8A-G, cap8L-P, esaAB, essAB, esxA, icaADR, isd, lip, and sspBC (Mikhaylova et al., 2022).

.٣Evolutionary history of the population structure of S. aureusFigure 1 shows a review detailing the molecular genetic mechanisms and events that have shaped the species' evolutionary history, and the population structure of S. aureus was published in 2016 (Fitzgerald and Holden, 2016).

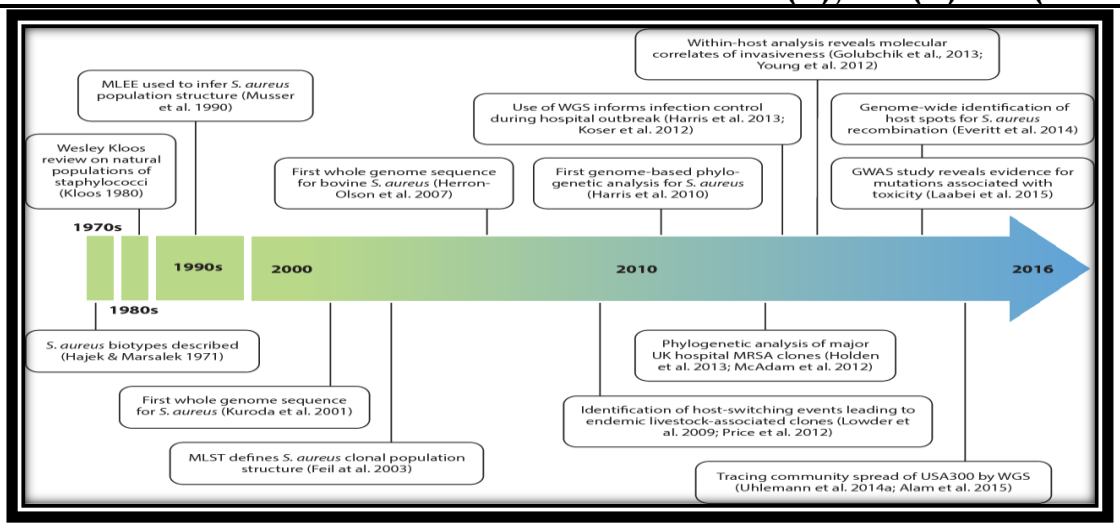

Figure 1: Chronology of discovery in S. aureus population biology. Abbreviations: GWAS, genome-wide association study; MLEE, multilocus enzyme electrophoresis. MLST, multilocus sequence typing; MRSA, methicillin-resistant Staphylococcus aureus; WGS, whole-genome sequencing (Fitzgerald and Holden, 2016).

4. Genetic diversity The two main parts of bacterial genomes are the accessory and core parts. The genes that are shared by all isolates are referred to as the core genome; these genes typically carry crucial genetic information about cellular metabolism and replication. About 75% of *the S. aureus* genome is comprised of the core, which is highly conserved between strains. Within the accessory genome, which is frequently home to immune evasion, antibiotic resistance, and virulence mediators, lies a large portion of the genetic diversity present in MRSA and other infections. The accessory component makes up about 25% of the entire genome of *S. aureus*. It is made up of mobile genetic elements (MGEs) that are acquired via horizontal transfer between strains, including plasmids, bacteriophages, transposons, chromosomal cassettes, and pathogenicity islands. As a result, compared to the core genome, the accessory genome is typically more varied and strain-specific (Malachowa and DeLeo, 2010). Figure 2 shows the major genomic elements in methicillin-resistant *Staphylococcus aureus*.The full genomes of two methicillin-resistant S. aureus (MRSA) strains were made public in a ground-breaking study by (Kuroda *et al.*, 2001). It contained the first genomes of staphylococci being released. The genome size was 2.8Mbp, average G+C content was 33% while in a study in Western Australia, the genome size was 3.05 Mb with the same average (Monecke *et al.*, 2013). The most common genome size in the *S. aureus* genome was 2.8Mbp (Gordon *et al.*, 2014; Raven *et al.*, 2019; Monecke *et al.*, 2021).

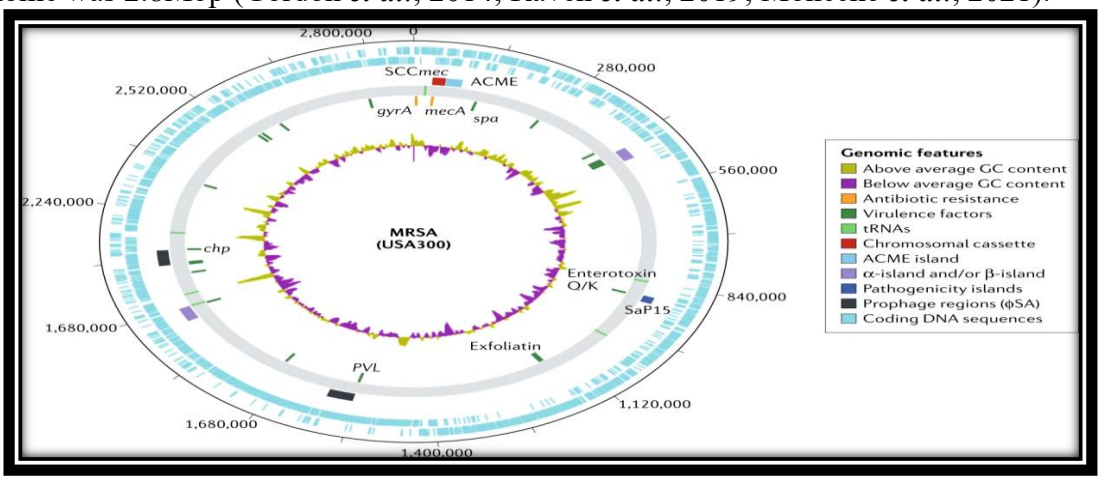

Figure 2: Major genomic elements in methicillin-resistant Staphylococcus aureus .

Representative genomic map of the USA300 strain FPR3757. The innermost circular track (track1) represents GC content. Moving outwards, track 2 displays select antibiotic resistance genes in orange and virulence factors in green. Track 3 shows the location of tRNAs. Track 4 displays select mobile genetic elements, with chromosomal cassettes in red, various pathogenicity islands in shades of blue through violet, and prophages in black. The outer two tracks (5 and 6) represent coding sequences in blue. PVL, Panton–Valentine leukocidin. Selected annotation created using Artemis/DNA Plotter. MRSA, methicillin-resistant Staphylococcus aureus (Turner et al., 2019).

.٥Epidemiology of MRSA

There is an increased probability of contracting MRSA infection in the following groups: children, the elderly, athletes, military personnel, drug injectors, people from indigenous backgrounds or living in underprivileged urban areas, people with HIV or cystic fibrosis, people who visit the doctor frequently, and incarcerated populations. While the exact causes of the fluctuating rates of MRSA infection are still unknown, developments in molecular epidemiology are providing increasingly detailed insights into the dynamics of the MRSA population (Algammal et al., 2020 The emergence of MRSA infections in people without a history of hospitalization led to the development of separate nomenclatures for HA-MRSA and CAMRSA .Initially, strain types ST5 or ST8 (REFS), a predominance of SCCmec type IV or type V, lower rates of clindamycin resistance, and an enhanced chance of PVL expression were used to identify CA-MRSA isolates. But during the 1990s, site-specific genotypic differences have started to converge, indicating that both CA-MRSA and HA-MRSA are capable of encroaching on one other's niche (Popovich et al., 2017).

.٦Drug Resistance Genes

MRSA has obtained MGEs containing genes for antibiotic resistance on multiple different occasions. In both MRSA and methicillin-susceptible Staphylococcus aureus (MSSA), resistance to penicillin (blaZ), trimethoprim (dfrA and dfrK), erythromycin (ermC), clindamycin (constitutively expressed ermC), and tetracyclines (tetK and tetL) has been found on insertion sequences, transposons, and sometimes plasmids. Antibiotic resistance is frequently genetically linked to disinfectant or heavy metal resistance (for example, quaternary ammonia compounds, mercury, or cadmium) in HA-MRSA bacteria, most likely reflecting the high selective pressures found in hospital environments (Pulingam et al., 2022).The most important and risk-resistant gene is mecA gene. Methicillin-resistance gene mecA (SCCmec) was carried by an SCC element. A study by Kurado found mecA gene in two strains with vanA, rimM, ssaA2, rpsK, rpoB, walk, Pbp4, varT, and ATPase genes (Kuroda et al., 2001). In 2004 the genomes of two clinical isolates: MRSA252, representative of EMRSA-16, an effective epidemic clone in the United Kingdom, and MSSA476, MRSA252 carry the mecA gene but MSSA476 Does not carry the mecA gene but it carries a CDS (SAS0043) encoding a protein similar (43.7% amino acid identity) to the plasmid-borne fusidic acid-resistance (Holden et al., 2004). Also in The United Kingdom, Resistance was defined as 30% relative coverage for blaZ, fusB, and as 80% relative coverage for the remaining mobile genes. This resulted in the optimum balance between overall sensitivity and specificity (Gordon et al., 2014). In Saudi Arabia identify mecA, norA, norC, MgrA, tet , APH-IIIa, blaZ, tetK, and AAC-APH (Snoussi et al., 2023). V036-V64 (VRSA) strain carries vanA gene which means resistant to vancomycin but in V036 (VSSR) the gene was absent (Kim and Lee, 2020).

.٧Single Nucleotide Polymorphism (SNPs)

Single Nucleotide Polymorphisms identified by Whole-Genome Sequencing (WGS) in Staphylococcus aureus provide crucial genetic variations that aid in understanding the evolutionary and transmission dynamics of the bacteria. SNPs are specific changes in a single nucleotide base within the genome sequence, allowing for precise genetic differentiation and tracking of strains over time and space. These SNPs play a vital role in high-resolution typing, surveillance, and outbreak investigations of Staphylococcus aureus, providing insights into the genetic diversity and relatedness of isolates. In 2001, 159 SNPs Were identified (Kuroda et al., 2001). Holden and others found 285 (SNPs) in common or core protein-coding regions (CDS) separate MSS476 and MW2 both belong to ST (Holden et al., 2004). The first study to evaluate the diversity of S. aureus using next-generation sequencing (NGS). Discovered 35 SNPs in 31 loci that distinguished the first vancomycin-sensitive sample from the last vancomycin-resistant isolate (Mwangi et al., 2007). Analyzed a global collection of isolates linked to ST239 using the Illumina sequencing platform and multiplex index tags for the sequencing libraries, just 14 SNPs were required to distinguish 5 of the isolates (Harris et al., 2010). Thirty-five diverse strains were sequenced, and 29 whole genome sequences were included to create a single nucleotide polymorphism (SNP)-based phylogenetic tree encompassing 11 distinct lineages. A consistent index of 0.59 was found in the maximum-parsimony tree of isolates from different strains of S. aureus based on 80,836 SNPs (Driebe et al., 2015).A study in France found SNP numbers ranged from 0 to 22 SNPs within the Bordeaux–Limoges clade and from 80 to 232 between the Bordeaux–Limoges clade and the other group. and the mutation rate in the core genome of three to six SNPs per year (Durand et al., 2018). 115 core genome SNPs different from the mapping reference (Raven et al., 2019). Comparative between two strains VRSA (V036-V64) and VSSA (V036) by

using the complete genome sequences analyzed SNPs. they detected eight SNPs differing between V036-V64 and V03 (Kim and Lee, 2020).

٨. Identification of S. aureus Strains Based on WGS

Compared to previous methods of strain identification, whole-genome sequencing (WGS) has made it possible to identify and characterize a higher number and diversity of S. aureus strains. According to the investigations, at least six different S. aureus strains were found using WGS analysis. HV (high virulence) strains belonging to ST121 and t645 spa type, AHV (attenuated high virulence) strains with a novel MLST allele combination, mostly t4770 spa type, LV (low virulence) strains with 5 different MLST patterns, ST59 strains, the predominant clonotype including MRSA, ST398 strains, mainly MSSA with high biofilm formation and ST5527 strains, a newly emerging clonotype with high antimicrobial resistance (Német et al., 2020). In contrast, traditional strain typing methods like MLST, and spa typing would have identified a more limited set of S. aureus strains. Therefore, the evidence indicates that whole-genome sequencing has enabled the discovery and characterization of a significantly larger number and broader range of S. aureus strains compared to other strain identification approaches.

٩. Novel Identification in Some of the Studies

Three classes of new pathogenicity islands were identified in the genome a toxic-shock-syndrome toxin island family, exotoxin islands, and enterotoxin islands. The analysis also identified 70 candidates for new virulence factors (Kuroda et al., 2001). Nineteen additional virulence genes were recorded, The remaining new poisons were discovered in the νSaα and νSaβ genomic island regions (Baba et al., 2002). The most significant observation was evidence of gene transfer between the staphylococci and bacilli (Gill et al., 2005). Identified three novel blaZ frameshift mutations that were associated with susceptibility despite the presence of the gene (Gordon et al., 2014). In Saudi Arabia, C15-MRSA shows a novel SCCmecV/ SCCfus composite element (Senok et al., 2017). This study demonstrates that, under selective pressure, by the accumulation of mutations in genes related to cell wall synthesis, vancomycin-susceptible S. aureus can develop thicker cell walls and, hence, develop high vancomycin resistance. That highlights a novel vanA-negative mechanism for VRSA emergence (Kim and Lee, 2020). Reported for the first time, a pvl-positive ST152-t355 MRSA clone from SSIs in Ghana (Egyir et al., 2021).

١٠. Comparative Studies

Comparative studies between Staphylococcus aureus genomes and other bacteria using whole-genome sequencing (WGS) have revealed valuable insights. Research has focused on the genetic connection between S. aureus isolates from different sources, highlighting shared antibiotic resistance and virulence genes (Alkuraythi et al., 2024), This study investigated and compared the genomic characteristics of S. aureus isolates from retail meat and patients in Saudi Arabia. The results show that 43% of the S. aureus isolates from meat and 100% of the patients' isolates were MDR. Virulence genes such as cap, hly/hla, sbi, and isd were found in all S. aureus isolates from both sources (Alkuraythi et al., 2024). The presence of these genes in meat-derived isolates underscores its role as a reservoir. Genomic relatedness also suggests the potential transmission of resistance between different settings. These findings emphasize the necessity for a comprehensive approach to monitor and control S.aureus infections in both animals and humans. Antibiotic-resistant strains of Staphylococcus aureus and Staphylococcus haemolyticus, particularly methicillin-resistant Staphylococcus aureus, are common in Egyptian hospitals. They used publicly available genome assemblies from strains isolated in the Middle East (Kuwait, Lebanon, Tunisia, Palestine, United Arab Emirates, Morocco, and Suda) along with whole-genome sequencing on 56 S. aureus and 10 S. haemolyticus isolates from Alexandria Main University Hospital to shed light on the strains that are currently in circulation in Egypt. Atl, a gene required for biofilm formation, is present in the core genomes of S. haemolyticus and S. aureus. Four new MLSTs have been identified by researchers (Montelongo et al., 2022). This study was important because it highlights the use of WGS in the Middle East. These studies showcase the power of WGS in understanding bacterial genomics and pathogenicity. Figure 3 shows the phylogenetic trees based on the core genome annotated by continent of origin for S.aureus and S.haemolyticus isolates.

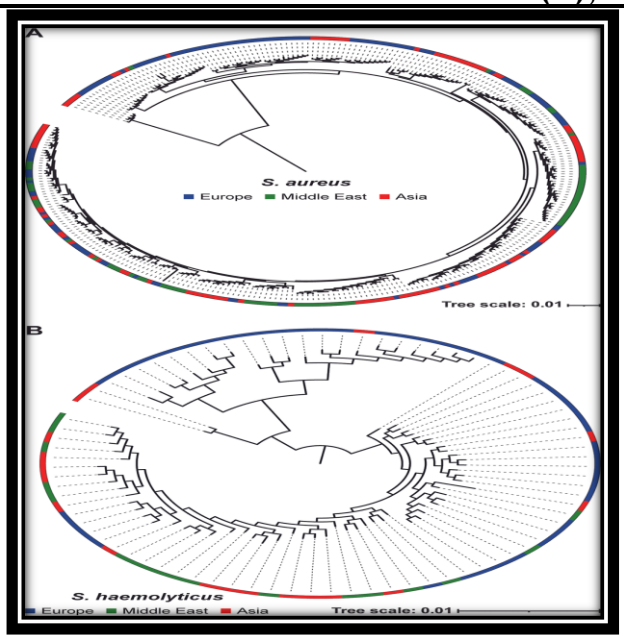

Figure 3: Phylogenetic trees based on core genome annotated by continent of origin for (A) S. aureus and (B) S. haemolyticus isolates. The continent of isolation for each genome included in these analyses is indicated by the color in the outer band of the circular tree with Europe in blue, the Middle East in green, and Asia in red)Montelongo et al., 2022.(

.IIThe most commonly used sequencing platforms for S.aureus genomics

The Illumina Genome Analyzer GAIIx and NextSeq® sequencing systems (Illumina Inc., San Diego, CA, USA) are the most widely used technologies for sequencing S. aureus genomes. To provide high-quality data for further investigations like genome assembly, phylogenetic analysis, and the identification of genetic markers linked to virulence and antibiotic resistance, these systems are frequently employed for whole-genome sequencing (WGS) of S. aureus isolates (Durand et al., 2018; Campbell et al., 2022). A sequencing platform's selection is influenced by the particular research issue, the required level of coverage, and the available resources. On the other hand, Illumina platforms are typically used due to their excellent accuracy, affordability, and accessibility to bioinformatic resources and tools for further research. Table 1 is shown. An overview of the fundamental data from S. aureus genomic research .

CONCLUSION

The genomic properties of Staphylococcal bacteria that were investigated utilizing whole genome sequencing are the main topic of this review paper. WGS is an essential technique in the study of infections. In clinical microbiology and infection control, it is frequently used for the simple and well-known purpose of investigating outbreaks by identifying new bacterial lineages, virulence factors, antibiotic resistance genes, and their population structures. Beyond streamlining processes and providing unmatched economies of scale for laboratory diagnostics, WGS will genuinely become a platform technology by producing information that exceeds that of existing techniques .

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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