REVIEW

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2026.2025-153
Cyprus J Med Sci 2026;11(1):1-9

Unmasking *Candidozyma auris*: Whole Genome Sequencing-Driven Discoveries in Pathogenesis and Treatment Innovation

Ayşe Seyer

DESAM Research Institute, Near East University, Nicosia, North Cyprus

Abstract

Candidozyma auris (formerly known as *Candida auris*, *C.auris*) is a pathogenic yeast that can cause invasive candidiasis and hospital outbreaks. It is considered an emerging global health issue due to its high mortality, high transmissibility, resistance to extreme environmental conditions, and resistance to multiple antifungal agents. This fungal pathogen is distributed worldwide across its six clades. Due to these features, in 2022 the World Health Organisation listed *C.auris* on the Fungal Priority Pathogens List. The diagnosis is quite challenging to establish using conventional techniques. Despite the limitations of conventional diagnostic tests, f whole-genome sequencing (WGS) provides a wide range of information, from phylogenetic characterisation to genotypic analysis, with implications for guiding appropriate therapeutic and infection-control strategies. This review summarises current WGS-based studies on *C.auris*, focusing on phylogenetic analysis, epidemiology, outbreak control, and antifungal resistance-associated mutations.

Keywords: *Candidozyma auris*, *Candida auris*, whole genome sequencing, antifungal resistance, fungal infection, candidiasis

INTRODUCTION

An overall increase in the number of infectious disease outbreaks was observed worldwide. Between 1996 and 2023, there were 3013 documented outbreaks. These outbreaks included 1305 respiratory outbreaks, 484 direct-contact outbreaks, 469 foodborne or waterborne outbreaks, 436 vector-borne outbreaks, and 319 miscellaneous outbreaks.[1] Furthermore, invasive and opportunistic fungal infections have emerged as a significant public health concern in recent years, particularly among immunocompromised populations, due to antifungal resistance, global spread, increased incidence, and high mortality.[2] According to the 2025 report issued by the World Health Organization (WHO), the annual incidence of invasive fungal infections (IFIs) was estimated as 6.5 million cases worldwide and 3.8 million deaths. Among these deaths, around 2.5 million were considered directly attributable to IFIs, underscoring the significant contribution of these infections to global morbidity and mortality.[3]

Examples of IFIs of serious concern include those caused by the fungal pathogens identified as critical priorities. According to the WHO Fungal Priority Pathogen List published in 2022, the fungal pathogens identified as critical priorities are *Cryptococcus neoformans, Aspergillus fumigatus,* and *Candida albicans*. Due to rapid spread, multidrug resistance, and high mortality rates (30%-60%), *Candidozyma auris* (formerly known as *Candida auris*) is prioritised in this list as well beside the other medically essential fungi.[4]

C.auris was first isolated from the external ear canal of a patient in Japan in 2009, resembling *Candida haemulonii*,[5] and was later isolated in 2011 from a blood culture.[4] Within 10 years, *C.auris*

To cite this article: Seyer A. Unmasking *Candidozyma auris*: whole genome sequencing-driven discoveries in pathogenesis and treatment ınnovation. Cyprus J Med Sci. 2026;11(1):1-9

ORCID ID of the author: A.S. 0000-0002-5096-898X.

Corresponding author: Ayşe Seyer
E-mail: ayse.seyer@neu.edu.tr, seyerayse@gmail.com
ORCID ID: orcid.org/0000-0002-5096-898X

Received: 16.12.2025
Accepted: 08.01.2026
Publication Date: 17.02.2026

spread globally, causing invasive healthcare-associated infections and outbreaks; however, incidence rates remain poorly understood because conventional diagnostic tests are insufficient. The Pan American Health Organisation reported a dramatic increase in *C.auris* cases during the coronavirus disease 2019 pandemic in the WHO Region of the Americas, with a 318% rise compared with case numbers from 2015-2017.[4] This increase has underscored the limitations of conventional diagnostic methods, which are often unavailable or lack sufficient accuracy to identify *C.auris*. As a result, molecular approaches, particularly next-generation sequencing (NGS), have become increasingly important for species identification and epidemiological investigation. NGS in clinical microbiology enables the detection of pathogens, the characterisation of virulence and resistance-associated genes, and the study of the resistome. When applied to *C.auris*, f whole-genome sequencing (WGS) provides information on resistance, virulence, and clades, which are crucial for outbreak management.[6-9]

This review focuses on the applications of WGS in the diagnosis of *C.auris*, its contribution to understanding antifungal resistance, its role in informing treatment strategies, and its utility in investigating and managing healthcare-associated outbreaks. The literature search was performed from 2016 to 2025 for data on *C.auris* using PubMed and Google Scholar. Publications in English and Turkish were accepted. The search terms included: "*Candida auris*", "*Candidozyma auris*", "*C.auris*", "identification", "diagnosis", "NGS", "WGS", "antifungal resistance", "fluconazole resistance", "treatment", "novel therapeutic approaches", "hospital outbreak", and "outbreak management".

C.auris: A Global Health Threat

This multidrug-resistant fungus is highly transmissible and can survive in the environment.[10] After its discovery, *C.auris* was rapidly, simultaneously, and independently reported from 6 continents and more than 50 countries. WGS has identified six clades based on geographic origin: clade I (Southern Asia), clade II (Eastern Asia), clade III (Africa), clade IV (South America), clade V (Iran), and clade VI (Indo-Malaysian).[4]

Clades I, III, and IV, which are most commonly associated with outbreaks, emerged 36 to 38 years ago. This information indicates recent divergence and the possibility that *C.auris* originated from a non-pathogenic environmental ancestral lineage.[10] A retrospective study found that the earliest *C.auris* outbreak occurred in 1996, involving a clade II isolate that had previously been misidentified.[11] Since it was not reported until 2009, its sudden global emergence suggests that its incidence may be increasing due to climate change. In fact, *C.auris* was recently isolated from aquatic environments, apples in stores, and other surfaces. Viable *C.auris* was isolated from two dogs with otitis externa in India and from the oral cavity of a dog in Kansas. These findings indicate the potential for zoonotic transmission in the context of global warming.[12]

Currently, four major classes of antifungal agents are prescribed to treat fungal infections. These are azoles, polyenes, echinocandins, and antimetabolites, each with a unique mode of action. Azoles target the ergosterol biosynthesis pathway. Polyenes bind ergosterol and damage the fungal cell wall. Echinocandins block the enzyme beta-(1,3)-D-glucan synthase, while antimetabolites inhibit nucleic acid synthesis. *C.auris* isolates are reported to be resistant to at least one of the four major antifungal classes.[12] The halotolerance of the isolates, in addition to their multidrug resistance profiles, suggests that they may have originated in saline environments. Subsequently, detection of *C.auris* in public swimming pools, hospital wastewater, and sewage water demonstrates its adaptability to aquatic environments.[10] It can grow slowly at high temperatures, such as 42 °C. This thermal tolerance enables it to withstand fever responses in humans and to survive in animals with high body temperatures, such as birds.[13]

Prolonged intensive care unit stay, prior use of antifungals or antibiotics, renal impairment, colonisation and persistence on surfaces, environmental persistence, and invasive medical procedures such as mechanical ventilation or parenteral nutrition are risk factors for developing *C.auris* infections in healthcare settings.[4] The transmission of *C.auris* isolates within and between health care settings has been clarified, indicating that abiotic factors can also contribute to the spread. *C.auris* can originate from environmental sources, such as plants or aquatic environments. The widespread use of triazoles in agriculture can contribute to increased antifungal resistance, and international travel and trade can facilitate its global spread.[13]

Delayed diagnosis, misidentification, multidrug resistance, and underlying comorbidities dramatically increase the mortality rates associated with *C.auris* infections. Therefore, developing effective infection control measures, understanding genetic and virulence factors, and establishing standardised methods for antifungal susceptibility testing are essential to combat the rapid spread of these infections and their high mortality rates.[4]

C.auris can cause invasive candidiasis, a severe, life-threatening nosocomial infection with high mortality that mainly affects immunocompromised patients. The incidence and mortality rates of fungal infections are tentative estimates.[14] Countries of the European Union and the European economic area reported 4,012 cases of *C.auris* colonization or infection between 2013 and 2023. Spain, Greece, Italy, Romania, and Germany are the countries that reported the highest number of cases.[15] The United Kingdom reported its first large-scale *C.auris* outbreak in 2016, involving 72 cases.[16] In Latin America, the first reported cases occurred in 2012 in Venezuela, where 18 patients had bloodstream infections (BSI) with a mortality rate of around 27.7%. Colombia was the second country to identify *C.auris* cases in 2013, with a total of 1,720 cases reported according to the most recently published surveillance data. As of 2021, Panama had reported 239 confirmed *C.auris* infections, while other countries, such as Mexico, Peru, Brazil, and Argentina, had also reported sporadic cases or outbreaks with varying incidence rates.[17] Recently, in September 2025, Cyprus and France reported an increase in *C.auris* cases and outbreaks. Although the number of *C.auris* infections is rising significantly, the true scale of the problem is likely underreported because of the lack of systematic surveillance and mandatory reporting.[15]

This multidrug-resistant fungus is typically resistant to fluconazole and may exhibit high amphotericin MIC-B values. In mycological cultures, they grow within 3 days at 25-37 °C, but most can grow at 42 °C. Colonies on sabouraud dextrose agar (SDA) appear smooth and cream-coloured, whereas colonies on CHROMagar range from pink to purple. There are no sufficiently morphological or biochemical properties of *C.auris* that strictly differentiate it from other *Candida* species; therefore, it can be misidentified as *C.haemulonii, C.duobushaemulonii, Saccharomyces cerevisiae,* and *Rhodotorula glutinis*. In this case, confirmation by MALDI-TOF, polymerase chain reaction (PCR), or sequencing is advised.[18]

Conventional Diagnosis

Direct microscopy, mycological culture, blood culture, and histopathology are conventional diagnostic methods widely used to detect IFIs. They remain the gold standard due to their advantages. However, these techniques have some disadvantages: they are time-consuming and exhibit low sensitivity, specificity, or both.[14] Direct microscopy gives rapid results. This low-cost technique allows direct visualisation of fungal elements from patient samples. Some require specific staining techniques and experts to evaluate the results. A disadvantage of this technique is that it has low sensitivity (50%) and limited specificity.[14,19] Mycological culture allows the isolation of fungal pathogens and provides a basis for species-level identification and the assessment of antifungal susceptibility. Fungi can grow on commonly used culture media, such as blood agar, but specific mycological agar media, such as SDA, are better suited for their growth. However, cultural sensitivity is low (50%).

Mycological histopathology is not widely used because it is insufficiently sensitive to distinguish among pathogenic fungi with similar morphology in tissue sections. Furthermore, it is time-consuming and may cause fatal delays.[14,19]

Serological tests are suitable for detecting fungal antigens specific to *Candida* spp. and *Aspergillus* spp. Beta-1,3-D-glucan, mannan, galactomannan, and glucuronoxylomannan antigens and antibodies (anti-mannan and anti-germ-tube antibodies) can be detected in blood and sterile body fluids.[14,19]

Because of limited sensitivity delays, the above-mentioned diagnostic methods are sometimes insufficient for diagnosing fungal infections. In such cases, serological, molecular, or more advanced techniques should be applied.[14] Among these techniques, molecular tests are preferred due to their high sensitivity, culture independence, and rapid results. Numerous PCR-based molecular techniques are available to detect pathogenic fungi. Conventional PCR, nested PCR, real-time PCR, PCR-enzyme-linked immunosorbent assay, multiplex PCR, and direct deoxyribonucleic acid (DNA) sequencing are techniques used in molecular fungal diagnosis. The PCR technique provides rapid, sensitive results, with sensitivity ranging from 75% to 95% and specificity ranging from 80% to 90%.[15,19] In a study, PCR was the most appropriate diagnostic method for routine laboratories among evaluated tests [WGS, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF), and PCR], because PCR equipment is available in most health-care settings.[20]

C.auris lacks specialised phenotypic features that differentiate it from other *Candida* species. Therefore, it is challenging to identify *C.auris* in routine clinical laboratories using conventional phenotypic methods. Many misidentifications have been reported by automated diagnostic tools such as VITEK2, BD Phoenix, RapID Yeast Plus, and API 20C.[13,14] Due to diagnostic issues, the National Centre for Emerging and Zoonotic Infectious Diseases published an algorithm in 2019 for the accurate identification of *C.auris*, advising further testing if *C.haemulonii, C.duobushaemulonii,* or *Candida* spp. are detected by conventional phenotypic methods.[21]

Therefore, emerging diagnostic methods such as metagenomic sequencing, MALDI-TOF mass spectrometry (MALDI-TOF MS), and NGS are preferred.[19] Metagenomic sequencing is also preferred for rare fungal species or mixed infections, while loop-mediated isothermal amplification can be considered because it does not require specialised equipment.[14]

After the discovery of *C.auris* in 2009, identification is performed using MALDI-TOF MS in several countries. However, this method has some limitations, as it can misidentify *C.auris* as other *Candida* species. Amplified fragment length polymorphism and multilocus sequence typing (MLST) have been used to detect clonality, but, because of their low discriminatory power, genetic relatedness could not be determined.[16]

Deoxyribonucleic Acid Sequencing

Hospitals worldwide are facing a rising incidence of difficult-to-treat infections, with *C.auris* among the most challenging pathogens. To cope with these threats, early identification of strains and rapid detection of virulence and antifungal resistance profiles are essential. Determining the chains of transmission of infections in hospitals and identifying environmental sources are crucial steps in preventing these infections. However, conventional fungal diagnostic tests lack these features.[22] In contrast, NGS technologies possess high discriminatory power, thereby eliminating the disadvantages associated with laborious, time-consuming, and expensive diagnostic tests.[6,9,22] Figure 1 provides an overview of the three NGS workflows used in BSI diagnostics. NGS is widely used for outbreak management, pathogen characterisation, pathogen surveillance, taxonomy, and metagenomics.[6,9,22] Here, WGS has the potential to analyse the relatedness of isolates, characterise profiles of nosocomial infections, and map the global distribution of *C.auris*.[16] Therefore, WGS is a good alternative for fungal diagnosis if it can overcome major scientific and logistical issues and meet the criteria for clinical diagnosis.[22]

Whole Genome Sequencing for *C.auris*

WGS enables species- and subtype-level characterisation of clinical isolates and offers substantially higher resolution than genetic marker-based approaches such as MLST. WGS provides improved discriminatory power for lineage differentiation when compared with pulsed-field gel electrophoresis, variable-number tandem repeat analysis, and MALDI-TOF MS. In addition, the comprehensive genomic information generated by WGS allows analysis of genetic features associated with antifungal resistance, virulence, biofilm formation, and environmental persistence. This approach further supports the characterisation of outbreak-associated *C.auris* lineages and provides epidemiological and phylogenetic insights relevant to the investigation of transmission dynamics.[22]

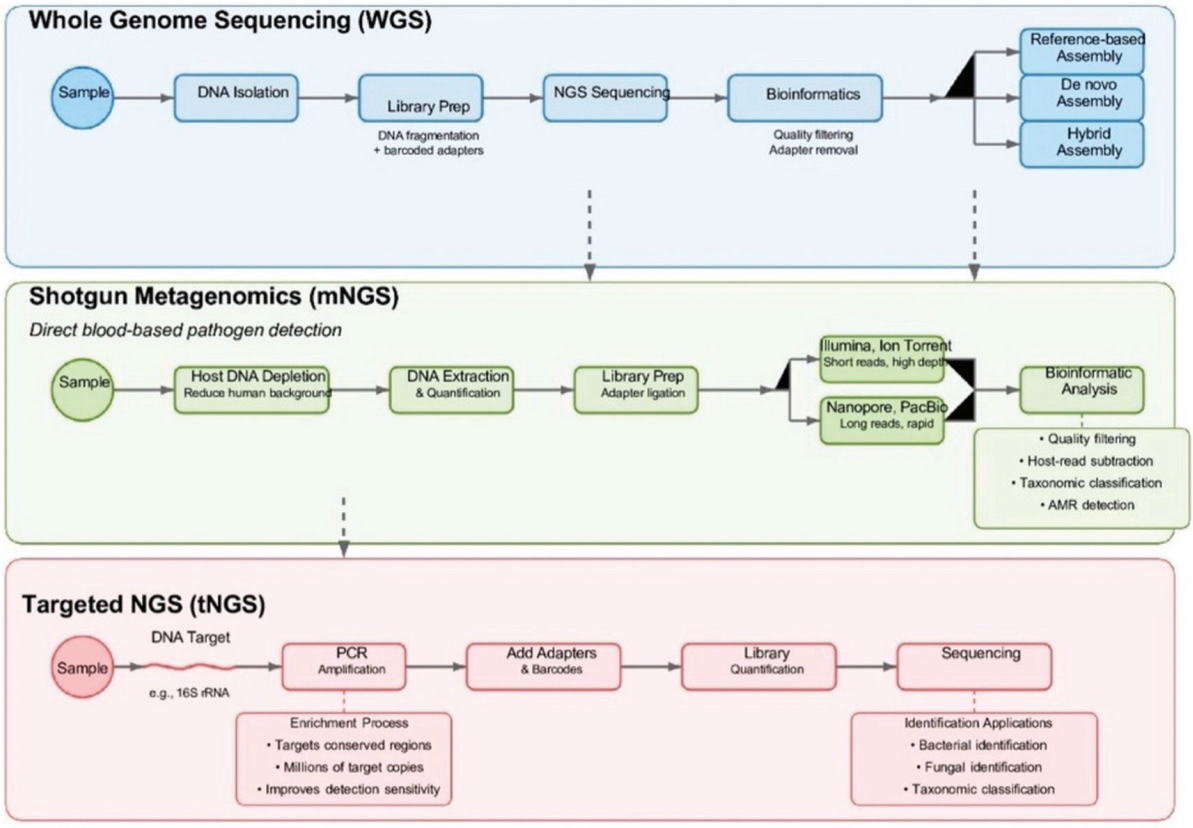

Figure 1. Genomic sequencing approaches for blood stream infections diagnostics.[23]

DNA: Deoxyribonucleic acid, NGS: Next-generation sequencing, PCR: Polymerase chain reaction.

Although many studies demonstrate the effectiveness of NGS-based technologies in clinical diagnosis, their use in clinical diagnostic laboratories remains limited.[9] Despite logistical constraints, WGS is commonly used in medical mycology research and surveillance. Within a more focused framework, *C.auris* WGS studies are thematically organised to address key areas, including phylogenetic structure and global emergence, molecular mechanisms of antifungal resistance, nosocomial transmission and outbreak investigation, and the development of resistance under antifungal treatment pressure.[5,24] These topics are discussed in detail below and summarised in Table 1.

Clinical Aspects of Whole Genome Sequencing

Antifungal Resistance

Sharma et al.[5] conducted the first study in India following the detection of five cases of candidemia across four hospitals. They used WGS (Illumina MiSeq platform) and reported clonal similarity, with only 0.2% genome-wide variation. They also identified the ergosterol (*ERG*) biosynthesis genes and *FKS* genes in the *C.auris* genome; these genes are associated with antifungal resistance. The *ERG* and *FKS* genes of *C.auris* showed 78-85% similarity to those of *C.albicans* and *C.glabrata*. All isolates were resistant to fluconazole; some were also resistant to voriconazole, amphotericin B (AmB), flucytosine (5FC), and echinocandins.[5]

During a large-scale, multidrug-resistant *C.auris* outbreak at a specialist London hospital between 2015 and 2016, Rhodes et al.[16] conducted a study to characterise the epidemiology of outbreak isolates, their genetic diversity, and antifungal resistance patterns. Both Oxford Nanopore Technologies (MinION) and Illumina sequencing are used for WGS. Based on WGS analysis of single-nucleotide polymorphisms (SNPs), they discovered that the UK outbreak strains were of Indian or Pakistani origin. These strains were genetically heterogeneous, indicating that the outbreak resulted from multiple introductions of *C.auris* into the hospital. In addition, 14 isolates were multidrug-resistant, and one isolate was resistant to both 5FC and echinocandins. In some isolates, resistance to posaconazole, 5FC, and echinocandins was also detected. Moreover, in this study, two novel antifungal-resistance alleles were discovered. One was a serine-to-tyrosine substitution in the *FKS1* gene, and the other was a phenylalanine-to-isoleucine substitution in the *FUR1* gene.[25]

Between 2012 and 2015, Lockhart et al.[26] conducted a study to determine whether the emergence of *C.auris* originated from a single strain or occurred independently in several countries. They included 54 patients from Pakistan, India, South Africa, Venezuela, and Japan. Antifungal susceptibility test results showed that 93% of the isolates were resistant to fluconazole, 35% to AmB, and 7% to echinocandins. 41% of isolates were resistant to two or more antifungal agents, whereas 4% were resistant to three antifungal classes. Using WGS, distinct amino acid substitutions in *ERG11* associated with azole resistance were identified in each clade: Y132F in Venezuela, India, and Pakistan; K143R in India and Pakistan; and F126T in South Africa. The WGS analysis strongly suggested the simultaneous and independent emergence of distinct clonal populations of *C.auris* on at least three continents, rather than a global spread from a single source.[26]

In a comprehensive study conducted across different hospitals in Colombia, samples were collected from patients, healthcare personnel, and hospital surfaces. They investigated antifungal resistance profiles and the genetic relatedness of *C.auris* isolates. The results indicated that 41% of patients and healthcare staff were colonised with *C.auris*, whereas 11% of environmental samples were positive for *C.auris*. All isolates were genetically identical. 14% of the isolates were resistant to fluconazole, while 31% were resistant to AmB. Isolates from the northern part of the country showed higher resistance to AmB than isolates from Central Colombia. This is explained by the four novel non-synonymous mutations (utg4_968953: T/C, utg5_821828: C/T, utg4_160118: G/A, utg4_352365: G/A), which are associated with resistance to AmB.[27]

Chowdhary et al.[28] conducted the most comprehensive study of antifungal resistance patterns in *C.auris*. They collected 350 *C.auris* isolates from various hospitals over eight years (2009-2017). Antifungal susceptibility testing showed resistance rates of 90% to fluconazole, 8% to AmB, and 2% to echinocandins. Y132 and K143 substitutions are found in the *ERG11* gene, and a novel mutation (S639F) is found in the *FKS1* gene.[28]

Another study was a global collaboration involving 19 countries and 304 *C.auris* isolates from hospitalised patients and the hospital environment. WGS analysis identified four *C.auris* clades: clade I was the most widespread; clade II included isolates from Canada, Japan, South Korea, and the United States; clade III included isolates from Australia, Canada, Kenya, South Africa, Spain, and the United States; and clade IV included isolates from Colombia, Israel, Panama, the United States, and Venezuela. Researchers reported that these clades have undergone phylogeographic mixing, and distinct genetic clades now overlap geographically. According to antifungal susceptibility testing results, 80% of the isolates were resistant to fluconazole, 23% to AmB, and 7% to micafungin. In this study, they used WGS to identify mutations associated with antifungal resistance. The results showed that the prevalent mutation associated with azole resistance was Y132F, present in 53% of clade I isolates and 40% of clade IV isolates. In contrast, fluconazole resistance in clade III isolates was associated with the F126L substitution. Copy-number variation in the *ERG11* gene was associated with fluconazole resistance. These findings highlighted two crucial points: clade-specific mechanisms of antifungal resistance, and the non-intrinsic nature of resistance in *C.auris* isolates, since both resistant and susceptible isolates are present in the same population.[29]

C.auris is also a significant risk factor for solid-organ transplant patients. A 2022 study reported the emergence of pan-drug-resistant *C.auris* isolates. These isolates were resistant to four major antifungal groups: azoles, echinocandins, polyenes, and 5FC. Using the Illumina WGS sequencer, they identified genetic mutations in the ERG11 (K143R) and CDR1 (V704L) genes, which are both associated with azole resistance. S639Y and F635C mutations in *FKS1* were associated with echinocandin resistance, whereas mutations in *FCY1*, *FUR1*, and *ADE17* were associated with 5FC resistance. A critical finding of this study was that drug combinations had no effect on these pan-drug-resistant *C.auris* isolates.[30] Treatment strategies for pan-drug-resistant cases have not yet been established; therefore, such cases should be monitored through active surveillance programs.[4]

In 2022, a study was conducted in Lebanon to characterise phylogenetic types and transmission dynamics of *C.auris* isolates. A total of 28 *C.auris* isolates were included in the study. Phylogenetic analysis indicated that all isolates belonged to the South Asian clade I and that they exhibited limited genetic diversity, with a minimum of 6 SNPs between isolates. The limited number of SNPs indicates that the outbreak was hospital-associated and that person-to-person transmission may have occurred. All isolates harbor a mutation in the *THR1* gene, which encodes homoserine kinase. Additionally, a Y132F mutation in the *ERG11* gene and the novel D709E mutation in the *CDR1* gene were identified. The results showed that these isolates were resistant to fluconazole and AmB, but susceptible to echinocandins.[31]

Spruijtenburg et al.,[32] who confirmed the existence of the fifth clade of *C.auris*, reported similar findings in a study in another study investigating echinocandin resistance in *C.auris* isolates. The WGS-based SNP analysis identified up to 11 SNPs among resistant isolates obtained from the same patient, demonstrating that resistance develops during antifungal therapy. Most detected substitutions were in *FKS1*; however, a novel substitution, *FKS1*M690V, was also associated with echinocandin resistance. Extremely low SNP differences among patient isolates indicated clonality and a common source of the outbreak within the hospital.[33]

Another study, which used WGS and bioinformatics for epidemiologic investigation, reported significant findings. Three WGS bioinformatic pipelines, Nullarbor, MycoSNP, and TheiaEuk, were used. The results were evaluated in terms of SNP detection, analysis time, and genome assembly. All of these pipelines are capable of analysing WGS data from *C.auris* isolates and can be used to assist disease control efforts.[34]

A genome-wide association study in 2024 on three major *C.auris* clades (I, III, and IV) was performed to identify SNPs associated with differences in antifungal susceptibility. The results of the study indicated 15, 42, and 13 antifungal-susceptibility-related SNPs in clades I, III, and IV, respectively. These findings indicated that SNPs can act as biomarkers for rapid diagnosis of drug susceptibilities; therefore, genetic variations can significantly influence antifungal susceptibilities.[12]

Between 2020 and 2024, 66 *C.auris* isolates were collected from a tertiary care center in New York. WGS was performed on the Illumina platform, and genomic analysis was conducted using the Genome Analysis Toolkit-based pipeline. The results of the study indicated that all isolates belonged to clade I and had mutations in the *ERG11*, *TAC1b*, and *CDR1* genes. Resistance to fluconazole among isolates was 100%. Across all isolates, five missense variants in the *FKS1* gene were identified: one isolate with p.Ser639Tyr, one isolate with both p.Arg1354Ser and p.Asp642His, seven isolates with p.Met690Ile, and nine isolates with p.Val1818Ile. Mutations p.Ser639Tyr and p.Arg1354Ser were associated with micafungin and anidulafungin resistance in echinocandin-resistant isolates, while Met690Ile, detected in two isolates, was associated with caspofungin resistance.[35] As mentioned above, WGS has been widely employed to study the epidemiology, transmission, and outbreak monitoring; resistance mechanisms and the emergence of new resistance; clade determination; and population genetics of *C.auris*.

Novel Therapeutic Approaches

Beyond surveillance and outbreak tracking, WGS also plays an increasingly important role in antifungal drug development. WGS enables systematic identification of antifungal resistance mechanisms and thereby defines the genetic constraints that next-generation members of existing drug classes must overcome.[26] Usually, repurposing existing drugs or using

Table 1. Characteristics of the studies included

Study	Focus	Geographic scope	WGS approach
Sharma et al.[5]	Resistance analysis	India (10 hospitals)	Illumina MiSeq: SNP/phylogenomic analysis
Rhodes et al.[25]	Outbreak investigation and resistance detection	United Kingdom	Oxford Nanopore (MinION), Illumina; SNP/ phylogenomic analysis
Lockhart et al.[26]	Clade structure and resistance detection	Pakistan, India, Venezuela, South Africa, Japan	PacBio, Illumina, HiSeq; SNP/phylogenomic analysis
Escandón et al.[27]	Resistance, outbreak mapping and molecular epidemiology	Colombia (4 hospitals)	Illumina HiSeq 2500; SNP/phylogenomic analysis
Chow et al.[29]	Clade evolution and global population genomics	19 countries	Not specified; SNP/phylogenomic analysis
Jacobs et al.[30]	Pan-drug-resistance evolution	USA	Not specified; SNP/ phylogenomic analysis
Reslan et al.[31]	Clade assignment and resistance profiling	Lebanon	PacBio; SNP/phylogenomic comparative analysis
Spruijtenburg et al.[33]	Echinocandin resistance	Kuwait	Not specified; SNP analysis
Gorzalski et al.[34]	Outbreak tracking, clade identification, resistance detection	Southern Nevada, USA	Illumina (MiniSeq, NovaSeq 6000)
Wang and Xu[12]	Resistance mapping	22 countries	Not specified; public data (meta-analysis)
Smithgall et al.[35]	Intra-clade resistance variation	NYC, USA	Illumina (NextSeq2000)

WGS: Whole-genome sequencing, SNP: Single-nucleotide polymorphism.

combination therapies are ways to overcome this limitation and combat resistance. Tetrazoles, rezafungin, and encochleated AmB (MAT2203) are examples of new members of existing classes. Tetrazoles (VT-1161, VT-1598) are azole-like compounds designed for higher specificity to fungal Erg11p, reducing off-target effects,[36] while rezafungin is a novel echinocandin with a much longer half-life, allowing weekly dosing and improved tissue penetration.[37] On the other side there is one more alternative drug member encochleated AmB (MAT2203), which is an oral formulation of AmB using a cochleate lipid bilayer to improve tolerability and delivery. Ibrexafungerp (a triterpenoid) is a new class of drug with same target. It inhibits β-1,3-glucan synthase but binds to a site distinct from that of echinocandins.[36,37]

Also, there are some drug candidates with novel mechanisms of action. Among these candidates fosmanogepix is an inhibitor of fungal glycosylphosphatidylinositol biosynthesis, a novel, fungal-specific target. It is active against multidrug-resistant species, such as *C.auris*.[36,37] ATI-2307 which is an arylamidine, is thought to collapse mitochondrial membrane potential, inhibiting respiration. Hydrazycins (BHBM, D0, D13) target the synthesis of fungal sphingolipids while trehalose inhibitors target the trehalose pathway, which is essential for fungal growth and virulence. In addition turbinmicin is classified as a broad-spectrum fungicidal compound that disrupts endoplasmic reticulum-golgi vesicular transport to the plasma membrane, showing promise as an anti-biofilm drug.[36]

Repurposed drugs and adjunctive therapies also seem likely to be effective. AR-12 (a celecoxib derivative) is one of these drugs, which inhibits fungal acetyl CoA synthetase and enhances host antifungal immunity. 5FC, an older antifungal agent, is typically used in combination with other antifungal agents and is being re-evaluated at lower doses. Calcineurin and Hsp90 inhibitors (Cyclosporin A, Tacrolimus, Geldanamycin, Efungumab) inhibit stress-response pathways and can synergise with current antifungals. Similarly MGCD290 (a histone deacetylase inhibitor) synergises with azoles and echinocandins *in vitro* by inhibiting fungal Hos2 and Hsp90. Colistin has also been shown to potentiate fluconazole and echinocandin activity, particularly against tolerant or resistant strains, by enhancing ergosterol depletion.[36]

Monoclonal antibodies, vaccines, and antifungal peptides are other innovative agents being considered as alternatives for treatment. It is reported that antifungal mAbs, such as Mycograb, can enhance the fungicidal effects of conventional agents like AmB and can improve survival rates in invasive candidiasis. Also, live-attenuated and pan-fungal recombinant vaccines can target common fungal proteins to elicit host immune protection, while nanoparticles, such as lipid-based and metal-based systems, can enhance the bioavailability and antifungal efficacy of drugs and show promise in inhibiting biofilm formation. However, the majority of studies on these alternative strategies have been conducted *in vitro*, and further investigation is needed to validate their efficacy and safety *in vivo* or in human research.[37]

Drug repurposing of commercially available non-antifungal drugs, such as sertraline, pitavastatin, and the antibiotic sulfamethoxazole, is also under investigation as a potential antifungal strategy. In addition, silver and bismuth nanoparticles and caspofungin-loaded zinc oxide nanoparticles have demonstrated antifungal activity against *C.auris*.[38]

In clinical microbiology, WGS is used extensively for strain-level identification, antimicrobial resistance profiling, and the investigation of recurrent infections and transmission routes.[9,22] In the context of *C.auris*, delayed or missed identification in hospital settings can facilitate unnoticed transmission and lead to healthcare-associated outbreaks, underscoring the importance of accurate strain characterisation for patient safety and outbreak control. Although conventional mycological methods remain the gold standard for diagnosing fungal infections, these approaches frequently fail to identify *C.auris*, thereby limiting the reliable implementation of infection-control interventions. Centers for Disease Control and Prevention notes that diagnosis of *C.auris* by traditional phenotypic methods can be challenging, as these methods often misidentify it. Reports indicate that *C.auris* can be misidentified as *C.haemulonii, C.lusitaniae, C.famata,* or *C.duobushaemulonii* by some identification algorithms. In this case, further workup is advised to confirm a possible *C.auris* case.[21] Sequence analysis allows us to determine genetic relationships, identify mutations that lead to antibiotic resistance, and identify fungi (18S ribosomal DNA) or bacteria. Therefore, such advanced molecular methods have become increasingly common in microbial diagnosis. In clinical microbiology

laboratories, NGS approaches are used for outbreak management, molecular case finding, characterisation of pathogens, surveillance, taxonomy, metagenomics, and modes of pathogen transmission.[6]

On the other hand, enabling the use of a wide range of samples (humans, animals, food, and the environment) offers significant advantages. Therefore, NGS is increasingly preferred in medical microbiology laboratories.[6] However, the availability of fungal genome sequences for analysis is limited relative to bacterial genome databases.[9] WGS analysis tracing transmission dynamics and detecting novel mutations associated with antifungal resistance.[39] Moreover, WGS SNP phylogenetic analysis is critical for outbreak management.[24] Despite the achievements and significant potential of WGS, advancements are still required in this field. In medical microbiology, the routine implementation of WGS is influenced by several practical and methodological considerations, including turnaround time, cost, bioinformatic requirements, standardisation, quality assurance, validation, and reporting. The cost of WGS remains variable and context-dependent, influenced by sequencing throughput, personnel expertise, and computational resources, although it has decreased substantially over time. Another significant challenge in WGS implementation is the lack of universally standardised bioinformatic pipelines, reference databases, and interpretative frameworks, which can compromise inter-laboratory comparability and reproducibility of results.[40] Bioinformatics pipelines must offer user-friendly interfaces that enable direct input of data from sequencing instruments and retrieval of top matches against comprehensive, well-curated reference genome databases.[41] Harmonised reporting standards are also essential to ensure that genomic findings are interpretable and clinically meaningful.[42] These considerations are highlighted in guidance documents and surveillance frameworks issued by the WHO, the European Centre for Disease Prevention and Control, the Clinical and Laboratory Standards Institute, and the International Organisation for Standardisation.

From the One Health perspective, WGS provides a unifying framework for integrated surveillance across human, animal, and environmental reservoirs, enabling high-resolution comparison of isolates and supporting the investigation of potential zoonotic and zooanthroponotic transmission pathways. Without a collaborative approach, it will not be possible to clarify transmission patterns across human, animal, and environmental sources.[10]

It is known that most WGS-based studies have focused on antifungal resistance and transmission mechanisms. However, to combat this fungal pathogen comprehensively, we need to focus on the survival of *C.auris* in the hospital environment. A recent study by Kalkanci et al.[43] reports, for the first time in the *C.auris* literature, complex resistance phenotypes to both antifungals and biocides. They showed that biofilm formation, several virulence factors, and environmental adaptability support the survival of this fungal pathogen in healthcare settings. Therefore, the study indicated that control of *C.auris* requires a multipronged strategy that incorporates targeted biocide use, environmental decontamination, and careful screening of colonised patients.[43]

CONCLUSION

In conclusion, WGS has fundamentally reshaped *C.auris* research by enabling a detailed understanding of its evolution, population structure, transmission dynamics, and resistance mechanisms. The integration of WGS into surveillance programs and clinical diagnostics is recommended to track outbreaks, identify novel mutations, monitor the emergence of resistance under antifungal pressure, and design alternative therapeutic agents. For future studies in this field, the global implementation of standardised WGS protocols and the expansion of open-access genomic databases are essential. Collaboration among surveillance, antifungal stewardship, and infection-control programs will enhance our ability to mitigate the spread of *C.auris* and reduce the global burden of antifungal resistance.

MAIN POINTS

- Whole-genome sequencing (WGS) is the most informative method for the identification of the *C.auris* at the clade, outbreak and resistance levels.
- Genomic analyses have clarified the global population structure of *C.auris* and its independent emergence across multiple geographic regions.
- WGS enables detection of antifungal resistance-associated mutations, supporting improved interpretation of susceptibility patterns in clinical isolates.
- Integration of WGS with epidemiological data strengthens outbreak investigation and infection prevention strategies in healthcare settings.
- Broader implementation and standardisation of WGS approaches are needed to translate genomic data into routine clinical microbiology practice.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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