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Candida guilliermondii, an Opportunistic Fungal Pathogen with Decreased Susceptibility to Fluconazole: Geographic and Temporal Trends from the ARTEMIS DISK Antifungal Surveillance Program

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Although a rare cause of invasive candidiasis, *Candida guilliermondii* has been reported to exhibit decreased susceptibility to antifungal agents. Aside from case reports and small surveys, there is little information regarding the epidemiology and antifungal susceptibility profile of *C. guilliermondii*. We report geographic and temporal trends in the isolation and antifungal susceptibilities of 1,029 *C. guilliermondii* clinical isolates collected from 127 medical centers as part of the ARTEMIS DISK Antifungal Surveillance Program. In addition, we report the in vitro susceptibility of 132 bloodstream isolates of *C. guilliermondii* to caspofungin. *C. guilliermondii* represented 1.4% of the 75,761 isolates collected from 2001 to 2003 and was most common among isolates from Latin America (3.7% versus 0.6 to 1.1%). Decreased susceptibility to fluconazole was noted (75% susceptible; range, 68 to 77% across regions), and voriconazole was more active in vitro against *C. guilliermondii* than fluconazole (91% susceptible; range, 88 to 93% across regions). Fluconazole was least active against isolates from dermatology (58%) and surgical (69%) services and against isolates associated with skin and soft tissue infection (68%, compared to 85% susceptible for bloodstream isolates). There was no evidence of increasing azole resistance over time among *C. guilliermondii* isolates tested from 2001 to 2003. Of 132 bloodstream isolates of *C. guilliermondii* tested against caspofungin, most were inhibited by ≤2 μg/ml (96%; MIC_{50}/MIC_{90}, 0.5/1.0 μg/ml). *C. guilliermondii*, a species that exhibits reduced susceptibility to fluconazole, is the sixth most frequently isolated *Candida* species from this large survey and may be an emerging pathogen in Latin America.

Candida guilliermondii is an uncommon species of *Candida* that is most often associated with onychomycosis (3) and is rarely seen as a cause of invasive fungal infection (1, 2, 4, 6, 10, 12, 17, 25, 27). Dick et al. (2) previously reported a case of disseminated candidiasis due to *C. guilliermondii* in which the patient died despite amphotericin B therapy. The organism was shown by in vitro testing to be resistant to amphotericin B. Resistance to fluconazole was reported in a case of osteomyelitis of the finger caused by *C. guilliermondii* (25). The infection did not respond to prolonged treatment with fluconazole (400 mg/day) and ultimately required amputation of the affected digit. The isolate of *C. guilliermondii* obtained from infected bone was resistant to both fluconazole and itraconazole. Masala et al. (6) previously reported a nosocomial cluster of *C. guilliermondii* catheter-related fungemia among five surgical patients in an Italian hospital. The isolates were all resistant to flucytosine and susceptible to fluconazole and amphotericin B. All of the patients were successfully treated with fluconazole and removal of the vascular catheters. No obvious clinical or environmental source was identified; however, the isolates shared a common randomly primed polymorphic DNA pattern, and nosocomial transmission stopped following a reinforcement of infection control measures. Most recently, Girmenia et al. (4) described an increased frequency of candidemia due to *Candida guilliermondii* (29 of 243 episodes; 11.7%) among patients with hematologic malignancies in an Italian hospital over a 22-year time period. Molecular typing revealed no evidence of a common infection source; however, at least 65% of the 29 episodes were considered to be catheter related. The isolates were generally susceptible to amphotericin B (100%), fluconazole (91%), and voriconazole (95%).

Those reports suggest that although rare, *C. guilliermondii* may exhibit decreased susceptibility to several different classes of antifungal agents, may be transmitted from patient to patient in the hospital setting, and may be associated with the presence of an intravascular foreign body. Recent in vitro survey data confirm the decreased susceptibility of this species to fluconazole, although the numbers of isolates tested were generally small (1, 10, 12, 26, 27). Likewise, the MICs of caspofungin, anidulafungin, and micafungin have been observed to be 2- to 16-fold higher for *C. guilliermondii* than for other species of *Candida*, with the exception of *Candida parapsilosis* (4, 10, 15, 18).

Aside from these limited observations, there is little information regarding the epidemiology, frequency of occurrence, and antifungal susceptibility profile of this rare species of *Candida* (4, 12). Given the fact that the data available suggest the potential for decreased susceptibility of *C. guilliermondii* to

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TABLE 1. Variation in frequency of *Candida guilliermondii* by geographic region[a]

Region	Total no. of *Candida* species isolates	Total no. (%) of *C. guilliermondii* isolates
Asia-Pacific	17,183	190 (1.1)
Europe	41,187	392 (1.0)
Latin America	11,280	413 (3.7)
North America	6,111	34 (0.6)
Total	75,761	1,029 (1.4)

[a] Data were obtained from the ARTEMIS DISK Global Antifungal Surveillance Program, 2001 to 2003. Isolates represent all incident isolates from all sites of infection.

TABLE 2. Geographic variation in susceptibility of *Candida guilliermondii* to fluconazole and voriconazole

Region	Antifungal agent	No. of isolates tested	% of isolates[a]		
			S	SDD	R
Asia-Pacific	Fluconazole	190	77.4	14.7	7.9
	Voriconazole	105	87.6	2.9	9.5
Europe	Fluconazole	392	73.0	14.0	13.0
	Voriconazole	220	92.8	3.6	3.6
Latin America	Fluconazole	413	77.0	12.8	10.2
	Voriconazole	274	91.6	4.0	4.4
North America	Fluconazole	34	67.7	23.5	8.8
	Voriconazole	34	88.2	8.8	3.0
Total	Fluconazole	1,029	75.2	14.0	10.8
	Voriconazole	633	91.2	3.9	4.9

[a] All isolates were tested by the disk diffusion method performed in accordance with CLSI standard M44-A. S, susceptible, with zone diameters of ≥19 mm for fluconazole and ≥17 mm for voriconazole; SDD, susceptible-dose dependent, with zone diameters of 15 to 18 mm for fluconazole and 14 to 16 mm for voriconazole; R, resistant, with zone diameters of ≤14 mm for fluconazole and ≤13 mm for voriconazole.

polyenes, azoles, flucytosine, and the echinocandins, it seems prudent to gather additional information regarding this opportunistic fungal pathogen. In the current study, we use the extensive database provided by the ARTEMIS DISK Antifungal Surveillance Program (16) to describe the geographic and temporal trends in the isolation of *C. guilliermondii* from clinical specimens collected from 127 medical centers between 1997 and 2003, the types of specimens and clinical services in which *C. guilliermondii* infections are recognized, and the in vitro susceptibilities of 1,029 clinical isolates, including 307 bloodstream infection (BSI) isolates, of this species to fluconazole and voriconazole as determined by standardized disk diffusion testing. This report will serve as the largest study of *C. guilliermondii* isolates to date.

MATERIALS AND METHODS

Organisms and test sites. A total of 134,715 isolates of *Candida* spp. from 127 different medical centers in Asia (23 sites), Latin America (16 sites), Europe (74 sites), the Middle East (2 sites), and North America (12 sites) were isolated and identified between June 1997 and December 2003. In addition, 75,761 isolates of *Candida* spp. from 115 study sites in 35 countries were tested for susceptibility to fluconazole and voriconazole. All *Candida* spp. considered pathogens from all body sites (e.g., blood, normally sterile body fluids [NSBF], deep-tissue biopsy, genital tract, gastrointestinal tract, skin, and soft tissue) and isolates from all in-hospital and outpatient locations during the study period from 2001 to 2003 were tested. Of the 307 BSI isolates collected, 132 were sent to the University of Iowa for testing against caspofungin.

Data for *C. guilliermondii* were stratified by year of isolation, geographic region, clinical service (hospital location), and specimen type. *Candida* spp. considered by the local-site investigator to be colonizers, that is, not associated with an obvious pathology, were excluded, as were duplicate isolates (the same species and the same susceptible-resistant biotype profile within any 7-day period). Identification of isolates was performed in accordance with each site's routine methods.

Susceptibility test methods. Disk diffusion testing of fluconazole and voriconazole was performed as described previously (16) and in accordance with Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) document M44-A (9). Plates (150-mm diameter) containing Mueller-Hinton agar (obtained locally at all sites) supplemented with 2% glucose and 0.5 μg of methylene blue per ml at a depth of 4.0 mm were used. The agar surface was inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of a 0.5 McFarland standard. Fluconazole (25-μg) and voriconazole (1-μg) disks (Becton Dickinson, Sparks, Md.) were placed onto the surfaces of the plates, and the plates were incubated in air at 35 to 37°C and read at 18 to 24 h. Zone diameter endpoints were read at 80% growth inhibition by using the BIOMIC image analysis plate reader system (version 5.9; Giles Scientific, Santa Barbara, Calif.) (5, 13, 16, 17).

MICs of caspofungin were determined by broth microdilution (BMD) as described previously (18). All isolates were tested in RPMI broth with 24 h of incubation and a prominent reduction in growth relative to control (MIC-2) endpoint criteria.

The interpretive criteria for the fluconazole and voriconazole disk diffusion tests were those of the CLSI (9, 19, 20) and are as follows: susceptible (S), zone diameters of ≥19 mm (fluconazole) and ≥17 mm (voriconazole); susceptible-dose dependent (SDD), zone diameters of 15 to 18 mm (fluconazole) and 14 to 16 mm (voriconazole); resistant (R), zone diameters of ≤14 mm (fluconazole) and ≤13 mm (voriconazole). The corresponding MIC breakpoints (8, 19, 20) are as follows: S, MIC of ≤8 μg/ml(fluconazole) and ≤1 μg/ml (voriconazole); SDD, MIC of 16 to 32 μg/ml (fluconazole) and 2 μg/ml (voriconazole); R, MIC of ≥64 μg/ml (fluconazole) and ≥4 μg/ml (voriconazole).

QC. Quality control (QC) was performed in accordance with CLSI document M44-A (9) by using *Candida albicans* ATCC 90029 and *C. parapsilosis* ATCC 22019. A total of 5,865 and 5,484 QC results were obtained for fluconazole and voriconazole, respectively, more than 99% of which were within the acceptable limits. External quality assurance was performed by testing more than 2,900 isolates from blood and NSBF against both fluconazole and voriconazole by ARTEMIS participating laboratories and by the central reference laboratory (13, 17). Excellent agreement was seen between participating and reference laboratories, ensuring the accuracy of the ARTEMIS data.

Analysis of results. All disk zone diameters were read by electronic image analysis and interpreted and recorded with a BIOMIC Plate Reader system (Giles Scientific Inc.). Test results were sent by e-mail to Giles Scientific for analysis. The zone diameter susceptibility category (S, SDD, or R), and QC test results were all recorded electronically. Patient and doctor names, duplicate test results (the same patient, the same species, and same biotype results), and uncontrolled results were automatically eliminated by the BIOMIC system prior to analysis.

RESULTS

Isolation rates of *C. guilliermondii* over time and by geographic region. A total of 134,715 isolates of *Candida* spp. were isolated and identified at 127 study sites between June 1997 and December 2003 (16). *C. guilliermondii* ranked sixth among more than 16 species of *Candida*, accounting for approximately 1% of all isolates (16). The frequency of isolation of *C. guilliermondii* did not change over the course of the study.

Data on the various sites that contributed isolate results to the study were available for the time period of 2001 through 2003 (Table 1). *C. guilliermondii* represented 1.4% of the 75,761 isolates collected during this time period and was most common in the Latin American region (Table 1), accounting for 3.7% of the isolates from the region.

Geographic variation in susceptibility of *C. guilliermondii* to fluconazole and voriconazole. Table 2 presents the in vitro susceptibilities of *C. guilliermondii* to fluconazole and voricon-

TABLE 3. Susceptibility of *Candida guilliermondii* to fluconazole and voriconazole by clinical service

Clinical service (total no. of isolates)[a]	Antifungal agent	No. of isolates tested (%)[b]	% of isolates from service[c]	% of isolates		
				S	SDD	R
Hematology-oncology (4,635)	Fluconazole	47 (4.6)	1.0	78.7	6.4	14.9
	Voriconazole	32 (5.1)		96.9		3.1
Medical (17,408)	Fluconazole	159 (15.4)	0.9	79.9	13.2	6.9
	Voriconazole	124 (19.6)		93.5	3.2	3.2
Surgical (5,126)	Fluconazole	51 (5.0)	0.9	68.6	23.5	7.8
	Voriconazole	47 (7.4)		91.5	4.3	4.3
Intensive care unit (10,052)	Fluconazole	67 (6.5)	0.7	79.1	11.9	9.0
	Voriconazole	55 (8.7)		90.9	1.8	7.3
Dermatology (1,457)	Fluconazole	158 (15.3)	10.8	57.6	24.1	18.4
	Voriconazole	121 (19.1)		90.9	6.6	2.5
Urology (649)	Fluconazole	14 (1.4)	2.2	78.6	7.1	14.3
	Voriconazole	6 (0.9)		83.3	16.7	
Outpatient (6,414)	Fluconazole	47 (4.6)	0.7	74.5	10.6	14.9
	Voriconazole	25 (3.9)		84.0	8.0	8.0
Other, NOS (30,020)	Fluconazole	486 (47.2)	1.6	79.2	11.5	9.3
	Voriconazole	223 (35.2)		90.1	3.2	6.7

[a] Total number of *Candida* isolates from each service.
[b] Percentage of all *C. guilliermondii* isolates tested.
[c] *C. guilliermondii* as a percentage of all isolates from that clinical service.

azole stratified by geographic region of origin, as determined by CLSI disk diffusion testing. These isolates were obtained from 115 institutions in 35 countries. Overall, it is apparent that *C. guilliermondii* exhibits decreased susceptibility to fluconazole (75.2%), especially compared to that of *C. albicans* (97.8%) (data not shown). Little variation in the susceptibility to fluconazole was apparent across the four broad regions, although the isolates from North America were the least susceptible to this agent (67.7%).

Voriconazole was always more active against *C. guilliermondii* than fluconazole, irrespective of geographic region. Only a slight variation in voriconazole activity was observed across the different regions, ranging from a low of 87.6% S in the Asia-Pacific region to a high of 92.8% in Europe. The overall level of susceptibility (91%) compared favorably to that seen for other species of *Candida* and was superior to that reported for *Candida glabrata* (81.7% S) and *Candida krusei* (83.2% S) (data not shown) (16).

Trends in resistance to fluconazole and voriconazole among *C. guilliermondii* isolates over time. There was no evidence of increasing resistance to the azoles among *C. guilliermondii* isolates tested between 2001 and 2003. Resistance to fluconazole ranged from 11.7% in 2001 to 8.1% in 2003, and resistance to voriconazole ranged from 4.2% (2001) to 5.0% (2003) (data not shown).

Variation in the frequency of isolation and antifungal susceptibility profile of *C. guilliermondii* by clinical service. The clinical services reporting the isolation of *C. guilliermondii* from patient specimens included the hematology-oncology service, medical and surgical services, intensive care units (medical, surgical, and neonatal), the dermatology service, the urology service, and the outpatient service (Table 3). Those strains from services with only a few isolates and those for which a clinical service was not specified were included in the category "other, not otherwise specified" (NOS).

C. guilliermondii was isolated most frequently from patients hospitalized from the dermatology service and was much less common from all other services. In contrast to data reported previously by Girmenia et al. (4), we did not observe an increased frequency of isolation of *C. guilliermondii* among cancer patients. Fluconazole was least active against isolates from the dermatology (57.6% S) and surgical (68.6% S) services and varied little across the other services (range, 74.5 to 79.9%). Voriconazole was active against at least 90% (range, 90.9 to 96.9%) of isolates from all services, with the exception of isolates from the urology (83.3% S) and outpatient (84.0% S) services.

Variation in the frequency of isolation and antifungal susceptibility profile of *C. guilliermondii* by clinical specimen type. The major specimen types yielding *C. guilliermondii* as a putative pathogen included blood, NSBF; urine, respiratory, skin, soft tissue, and genital specimens (Table 4). Those isolates from uncommon specimen types and those for which a specimen type was not recorded were grouped under the category "miscellaneous (Misc.), NOS."

Aside from the Misc., NOS category, *C. guilliermondii* was isolated most frequently from blood specimens, followed by skin and soft tissue specimens. It was isolated infrequently from urine and genital specimens. Interestingly, isolates of *C. guilliermondii* from blood were generally susceptible (85.0%) to fluconazole, whereas those from skin and soft tissue specimens were considerably less so (67.7% S). Voriconazole showed a high degree of activity (>90% S) against isolates from blood (93.4% S), NSBF (96.7% S), skin and soft tissue (93.4% S), and genital (95.0% S) specimens. Voriconazole was least active against isolates from urine (80.4% S and 15.7% R).

Activity of caspofungin against bloodstream isolates of *C. guilliermondii*. Previously, we and others have shown that echinocandin MICs are consistently higher for *C. guilliermondii* and *C. parapsilosis* than for *C. albicans* when tested by BMD methods (10, 15, 18). When tested against caspofungin using the recently optimized BMD method (14, 18), 96% of the 132 bloodstream isolates of *C. guilliermondii* were inhibited by ≤2 μg/ml, a concentration that is exceeded throughout the dosing interval following the administration of caspofungin at stan-

TABLE 4. Susceptibility of *Candida guilliermondii* to fluconazole and voriconazole by specimen type

Specimen type/site (total no. of isolates)[a]	Antifungal agent	No. of isolates tested (%)[b]	% of isolates from site[c]	% of isolates		
				S	SDD	R
Blood (8,256)	Fluconazole	307 (29.8)	3.7	85.0	9.1	5.9
	Voriconazole	198 (31.3)		93.4	1.5	5.1
NSBF (3,155)	Fluconazole	36 (3.5)	1.1	72.2	22.2	5.6
	Voriconazole	30 (4.7)		96.7	3.3	
Urine (9,722)	Fluconazole	78 (7.6)	0.8	71.8	12.8	15.4
	Voriconazole	51 (8.1)		80.4	3.9	15.7
Respiratory (20,274)	Fluconazole	136 (13.2)	0.7	77.2	10.3	12.5
	Voriconazole	72 (11.3)		88.8	4.2	7.0
Skin/soft tissue (4,986)	Fluconazole	127 (12.3)	2.5	67.7	24.4	7.9
	Voriconazole	103 (16.3)		93.4	5.8	1.0
Genital (15,831)	Fluconazole	44 (4.3)	0.3	84.1	6.8	9.1
	Voriconazole	20 (3.2)		95.0	5.0	
Misc., NOS (13,537)	Fluconazole	301 (29.3)	2.2	67.4	16.6	16.0
	Voriconazole	159 (25.1)		89.9	5.7	4.4

[a] Total number of *Candida* isolates from each specimen type.
[b] Percentage of all *C. guilliermondii* isolates tested.
[c] *C. guilliermondii* as a percentage of all isolates from that specimen type.

dard doses (24, 28). Limited clinical data suggest that this species may respond to treatment with caspofungin (7).

DISCUSSION

The results from this extensive survey of *C. guilliermondii* both confirm and extend previous observations regarding this species (1–4, 6, 10, 12, 15, 25, 27). First of all, it is clear the *C. guilliermondii* is an uncommon clinical isolate throughout most of the world (Table 1). The increased frequency of isolation in Latin America is curious and not readily explained. This is even more striking when one considers only bloodstream isolates from Latin America, where *C. guilliermondii* ranks fourth behind *C. albicans*, *Candida tropicalis*, and *C. parapsilosis* and ahead of both *C. glabrata* and *C. krusei* (15). As reported in several smaller studies (1, 10, 12, 27), *C. guilliermondii* does appear to exhibit decreased susceptibility to fluconazole, and this pattern is seen in all geographic regions (Table 2). This observation is in contrast with the considerable geographic variation in fluconazole activity seen with *C. glabrata* (16) and *C. rugosa* (21).

Prior to this survey, there was very little known about the activity of voriconazole against this species. In a large U.S. survey of 2,000 BSI isolates of *Candida*, Ostrosky-Zeichner et al. (10) found only nine isolates of *C. guilliermondii* and reported a median MIC of voriconazole of 0.06 μg/ml (range, 0.03 to 0.13 μg/ml). A previous report from our laboratory demonstrated that 96.7% of 92 BSI isolates were susceptible to voriconazole at ≤1 μg/ml (16). Likewise, Girmenia et al. (4) found that 20 of 21 isolates (95%) were susceptible to voriconazole (MIC range, ≤0.03 to 4 μg/ml). The data reported herein (Table 2) indicate an overall susceptibility to voriconazole of 91.2% among 633 isolates tested by the disk diffusion method. The difference in activity noted between fluconazole and voriconazole for this species is similar to that seen with *C. glabrata* (12, 16) and suggests that voriconazole may be effective against some fluconazole-resistant *C. guilliermondii* isolates.

Given that this species is best known as a cause of onychomycosis and superficial cutaneous infections (3), it is not surprising that we found it to be isolated fairly commonly from isolates from skin and soft tissue infections obtained from patients of the dermatology service (Tables 3 and 4). We could not confirm the increased incidence of *C. guilliermondii* infections among cancer patients as reported previously by Girmenia et al. (4).

Although the role of *C. guilliermondii* as a pathogen when isolated from nonsterile sites such as the respiratory, urinary, and genital tracts is debatable, isolates from blood and NSBF must be considered significant. Thus, it is worth noting that the single most common specimen to yield *C. guilliermondii* on culture was blood (Table 4). This finding lends support to the few clinical reports of invasive fungal infection due to this species, indicating that it may indeed cause significant infections (2, 4, 6, 25).

Although little geographic variation in fluconazole susceptibility was observed (Table 2), this was considerably more pronounced across the different clinical services, where the lowest activity was seen with isolates from the dermatology service (57.7% S) and the highest activity was seen with isolates from the medical service (79.9%). This could be related to the frequent use of both oral and topical azoles to treat dermatologic infections (3). The activity of voriconazole did not vary significantly by clinical service, although it should be noted that it was most active against isolates from the hematology-oncology service, where azole drug pressure is often very high.

Perhaps the most encouraging information from this survey is the finding that bloodstream isolates of *C. guilliermondii* remain generally susceptible to both fluconazole and voriconazole (Table 4). These findings are similar to those reported previously by Girmenia et al. (4) for Italian bloodstream isolates. Although voriconazole appears to be reliably active against isolates from other specimen types, this is not the case with fluconazole. Given the low cost and low toxicity of fluconazole, it remains a first-line treatment for most candidal infections; however, the variable activity of this agent against *C. guilliermondii* suggests that treatment may be best guided by accurate species identification and judicious use of antifungal susceptibility testing (11, 22, 23).

TABLE 5. In vitro activity of caspofungin against 132 bloodstream isolates of *Candida guilliermondii*[a]

Organism	MIC (μg/ml)			Cumulative % of isolates at MIC (μg/ml) of:						
	Range	50%[b]	90%[b]	0.12	0.25	0.5	1	2	4	8
C. guilliermondii	0.03–>8	0.5	1	21	39	81	95	96	96	96

[a] Isolates tested in RPMI 1640 broth with 24 h of incubation and a prominent reduction endpoint criterion (MIC-2).
[b] MIC encompassing 50% and 90% of isolates tested, respectively.

Very few isolates of *C. guilliermondii* have been tested against the echinocandins and other antifungal agents (10, 12, 15). Our results for caspofungin versus BSI isolates (Table 5) indicate that although MICs for this species may be elevated compared to those seen with *C. albicans* (18), they remain in a range that should allow infections due to this species to be treated effectively. Likewise, despite the original report of amphotericin B resistance described previously by Dick et al. (2), resistance to this agent has not been documented in subsequent studies (1, 4, 6, 10, 26). In a previous report (12), we found only 2 of 102 BSI isolates of *C. guilliermondii* showing possible resistance to amphotericin B (MICs of 2 and 32 μg/ml, respectively).

In summary, we have used the extensive and validated database of the ARTEMIS DISK Antifungal Surveillance Program (16) to increase our understanding of *C. guilliermondii* as an opportunistic pathogen. Our findings suggest that this species may be an emerging pathogen in Latin American but not in other regions of the world. This species clearly exhibits decreased susceptibility to fluconazole and is generally susceptible to clinically achievable concentrations of voriconazole and caspofungin. Although uncommon, it is most likely to be isolated from blood and may be associated with intravascular catheters. When isolated from skin and soft tissue infections, it often exhibits decreased susceptibility to fluconazole. These data provide significant new information regarding this rare opportunistic fungal pathogen. Such information is uniquely available from longitudinal global surveys such as ARTEMIS.

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