Letter re: Marr editorial

To the Editor—We appreciate the thoughtful review provided by Dr Marr [1] in response to our paper [2]. Marr raises several important issues, and we support her conclusion that we have uncovered the tip of the iceberg with respect to C. gattii infections in the United States. Future data may provide additional insight into seemingly counterintuitive findings, such as the association between central nervous system symptoms and patient survival. We also agree that there are likely as-yet-unrecognized areas of C. gattii endemicity outside the Pacific Northwest, which are associated with infections elsewhere.

We would, however, like to clarify points regarding our definition of the outbreak and outbreak strains. Outbreaks, as Marr correctly notes, are defined by a greater-than-expected number of cases of a disease within a given time period and geography. Case definitions differ for each outbreak, but genetic typing increasingly plays a role in that definition. A Salmonella outbreak today, for example, would not be defined as all Salmonella isolates identified in the United States during a specific time period, but rather all Salmonella typhimurium isolates with 1 or a few specific pulsed-field gel electrophoresis pattern(s) and epidemiologic links between case patients during that time period. In our article, we defined outbreak strains based not on exposure, as Marr states, but on genotyping results for C. gattii isolates. Three clonal groups of isolates (VGIIa, VGIIb, and VGIIc) represented 81% of all human isolates identified at the Centers for Disease Control and Infection (CDC) since 2004. That no VGIIa/b/c strain infections were found in persons without Pacific Northwest exposure is the factor that delineated these strains as belonging to
a localized outbreak. Most non-VGIIa/b/c isolates were from patients outside the Pacific Northwest without a single common exposure history and were genetically dissimilar to each other. The small number of patients from the Pacific Northwest with non-VGIIa/b/c infections likely represents a low level of endemic, nonoutbreak-associated *C. gattii* disease, which was detected by enhanced surveillance.

In addition, site of acquisition was determined for all patients by detailed travel history. The patient from Hawaii was considered to have acquired his infection outside the Pacific Northwest because he had no travel history to the Pacific Northwest. His isolate (VGII-other) was considered a nonoutbreak strain because no other genetically similar isolates were identified at the CDC, and thus we had no reason to suspect that this infection was associated with the ongoing Pacific Northwest outbreak.

Marr notes the potential importance of regular identification of cryptococcal isolates to the species level. Differentiation of cryptococcal species is relatively simple but rarely done in clinical practice: It currently requires collection of isolates (a practice that may not be consistently carried out during patient care) and plating of the isolates on canavanine-glycine bromothymol blue agar [3], which is not always found in clinical microbiology laboratories. We encourage clinicians and laboratories to consider identifying cryptococcal infections as *C. gattii, Cryptococcus neoformans*, or other species, regardless of patient type or location. Learning more about all *C. gattii* infections in the United States may help us both optimize patient care and uncover more of the iceberg.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.