

# Name Changes in Medically Important Fungi and Their Implications for Clinical Practice

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**Recent changes in the Fungal Code of Nomenclature and developments in molecular phylogeny are about to lead to dramatic changes in the naming of medically important molds and yeasts. In this article, we present a widely supported and simple proposal to prevent unnecessary nomenclatural instability.**

## ONE FUNGUS, ONE NAME

Until recently, polymorphic higher fungi (*Dikarya*) were allowed to carry multiple names describing sexual (teleomorph) and various asexual (anamorph) stages of their life cycles. These stages could develop independently from each other, and their genetic relationship was often difficult to establish. Today, with the wide application of molecular methods, this problem has largely been solved. With the introduction of molecular genetic approaches, the dual naming system is no longer necessary. Two international expert symposia recently held in Amsterdam, The Netherlands, have been devoted to the fate of dual naming in fungi: One Fungus = One Name symposium on 19 and 20 April 2011 and One Fungus = Which Name symposium on 12 and 13 April 2012. The resulting Amsterdam Declaration on Fungal Nomenclature (1) requested the abolition of Article 59 of the Code of Botanical Nomenclature, the provision that sanctioned multiple names for the same fungus. Under the new Code of Nomenclature of Algae, Fungi and Plants, from 1 January 2013, this system is no longer permitted. One of the consequences of the declaration is that the criteria for naming fungi have changed entirely.

The dual naming system had been useful during the age of the microscope. Today, the main criteria for classification have moved from phenotype to genotype. Analysis of nucleic acid sequence variation now guides taxonomy and has replaced phenotype with the history of phylogenetic relationships and, occasionally, sexual compatibility. The first phase began after the introduction of PCR in the late 1980s and resulted in the discovery of new species by concordance of gene genealogies in several pathogenic fungi. This is now

being expanded following the advent of next-generation sequencing, which is discovering genetically distinct populations that deserve species status. The newly discovered species are genealogically distinct but cryptic in the sense that they were not suspected from morphological phenotype—although after they are recognized, distinguishing phenotypes may be discovered later on. In addition, taxonomy of environmental fungi is developing at a very rapid pace, which has a profound impact on nomenclature of opportunistic fungi. Anatomic morphological categories, such as coelomycetes or hyphomycetes, have become redundant, which implies that all mycological textbooks have become obsolete. Diagnostic laboratories will have to change the type and interpretation of data used to identify fungi. The changes will hopefully contribute to nomenclatural stability in the

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future, but it is obvious that this will not be achieved before the end of a transition phase. Although the shift in identification can be viewed as simply a change in technique from microscopy to DNA sequence analysis, it must also be viewed as a major intellectual shift to a system based on evolution as inferred from comparison of genotypes.

Coincidentally with this process, a significant expansion of the number of etiologic agents of disease is noticed. In the literature, it is often stated that (i) this growth is especially due to the increasing population of immunocompromised patients. A more pertinent cause, however, is (ii) the development of our knowledge, driven by easy access to sequencing technology. The advent of population genomics, which increases the sampled diversity by as many as 4 orders of magnitude, can only increase this trend. A further source of new clinical species to be recognized in diagnostic laboratories is the fact that (iii) also sterile or nonculturable fungi can now be classified according to sequence analysis of PCR-generated amplicons. The expansion of the number of clinically relevant fungi is clearly demonstrated in the *Atlas of Clinical Fungi* of which the first edition (2) contained 320 species, while the 2013 edition of the same book (3) counts a staggering 560 species, and the number of species is still growing at the same pace.

When only a single name should be used for these fungi, most of which bear several names at present, the question is which name has priority? One of the principles of nomenclature is to choose (i) the oldest name, either anamorph or teleomorph, which is also mostly the most widely applied name. The new code has the second rule that if both anamorph and teleomorph names have been widely used, (ii) the teleomorph name is to be maintained unless a formal application in favor of the anamorph name has been made. Both choices are dependent on (iii) the size of the genus and its rank in the taxonomic hierarchy.

### CHANGES AT THE GENUS LEVEL AND ABOVE

Starting with item iii, genus concepts are related to the amount and diversity of available biological material. Nucleic acid variation has provided a means of ensuring that genera are monophyletic, which is a leading principle of modern taxonomy. Species differing at the ordinal or even family level are no longer accepted as members of a single genus. Hence, orders and sometimes families are taxonomically relevant entities. The advantage of the phylogenetic approach is that close relatives come together even if they are morphologically quite different; this may be useful for predictions of pathogenicity or antifungal susceptibility. Conversely, distant relationships are expected to predict large differences in clinically relevant parameters. Until today, most clinical fungi had been grouped in anamorphic form genera based on phenotype that do not necessarily represent phylogenetic relatedness. For example, non-*albicans* *Candida* species comprise a random mixture of species that have been grouped together only because they are morphologically indistinguishable and physiologically similar, but some of them are as distant from each other as humans are from frogs. Applying names that acknowledge this diversity would be logical and medically meaningful. *Candida albicans* and *Candida glabrata* are evolutionary distant species with different antifungal susceptibilities (4). *Penicillium marneffeii* is unrelated to most of the saprobic *Penicillium* species, but it belongs to a group of penicillium-like species classified in the genus *Talaromyces* that possess similar virulence factors. Therefore, reclassification of *P. marneffeii* in *Talaromyces* (5) is useful for the medical mycologist. Similar reasoning can be applied to categories

higher up in the fungal system. Although the Zygomycota appears not to be monophyletic, there has been reluctance to abandon the name, but as the diseases caused by the main groups composing it, the Mucoromycotina and Entomophthoromycotina, are fundamentally different (6), their separation would be a step forward. The novel approach using phylogeny as a main criterion enhances information content of the taxonomy hierarchy.

The above is valid on the assumption that the “real” phylogenetic tree of the fungal kingdom is known. However, it should be realized that only a minor fraction of the existing fungal diversity has been described thus far. Large numbers of novel species are continuously being discovered due to the exploration of new habitats. The main cause of generic instability is material driven; phylogenetic trees are highly sensitive to taxon sampling effects (Fig. 1), and this situation will remain for many decades to come. Description of species on the basis of single sequences from metagenomic data will further complicate the taxonomic system (7). The basis of a genus or of any higher rank in the taxonomic hierarchy is a monophyletic branch of an underlying phylogenetic tree, replacing phenotypic techniques. Fungi may appear to belong to other phylogenetic groups than hypothesized earlier.

The clade approach for naming species, genera, and above has fundamental shortcomings, because of the comparative nature of data and also because no delimitation criterion exists. Determination of all higher taxonomic ranks when they are defined exclusively by sequence data is inherently arbitrary and therefore unstable, leading to numerous transfers of species from one genus to the next. Phylogeny deepens our understanding of the fungal kingdom, but phylogenetic trees are just an approximation of the truth. During the last 10 years, more name changes have been proposed for medical fungi than in the previous 70 years; examples can be found in Table 1. Many clades in a tree can be statistically supported, but what is the level of diversity to recognize a genus? At present, *Aspergillus* contains about 290 species, while genera in the *Scedosporium* lineage, with comparable levels of bar coding gaps between neighboring taxa, contain only 1 to 6 species. If genera become nearly congruent to species, then the genus becomes a redundant category.

A profoundly debated example is the anamorph genus *Aspergillus*. The *Aspergillus* genus was discovered by Micheli in 1753, based on *Aspergillus glaucus*. However, the medically important fungus *Aspergillus fumigatus* is a member of another phylogenetic clade in *Aspergillus* that also bears the teleomorph name *Neosartorya*. In the case of *A. fumigatus*, which was found to have a *Neosartorya* sexual state in 2009 after a concerted effort to generate ascocarps (8), the anamorph name *A. fumigatus* is older and more widely used than *N. fumigata*. However, the *A. fumigatus*/*N. fumigata* clade is phylogenetically remote and phenotypically distinct from the clade that contains the generic type, *A. glaucus* (9). There are two proposals in the literature. One advocates making *Aspergillus* a very large genus covering numerous clades, including those of *A. glaucus* and *A. fumigatus* (9). After careful discussion among the members, this proposal was chosen by the International Commission of *Penicillium* and *Aspergillus*. The other advocates applying existing teleomorph names to all monophyletic branches except one, and that clade alone would retain the name *Aspergillus* (10).

Both proposals have their pros and cons. In the first case, *Aspergillus* would remain the name for all, but as the broad phylogeny includes genera such as *Phialosimplex* and *Polypaecilium*

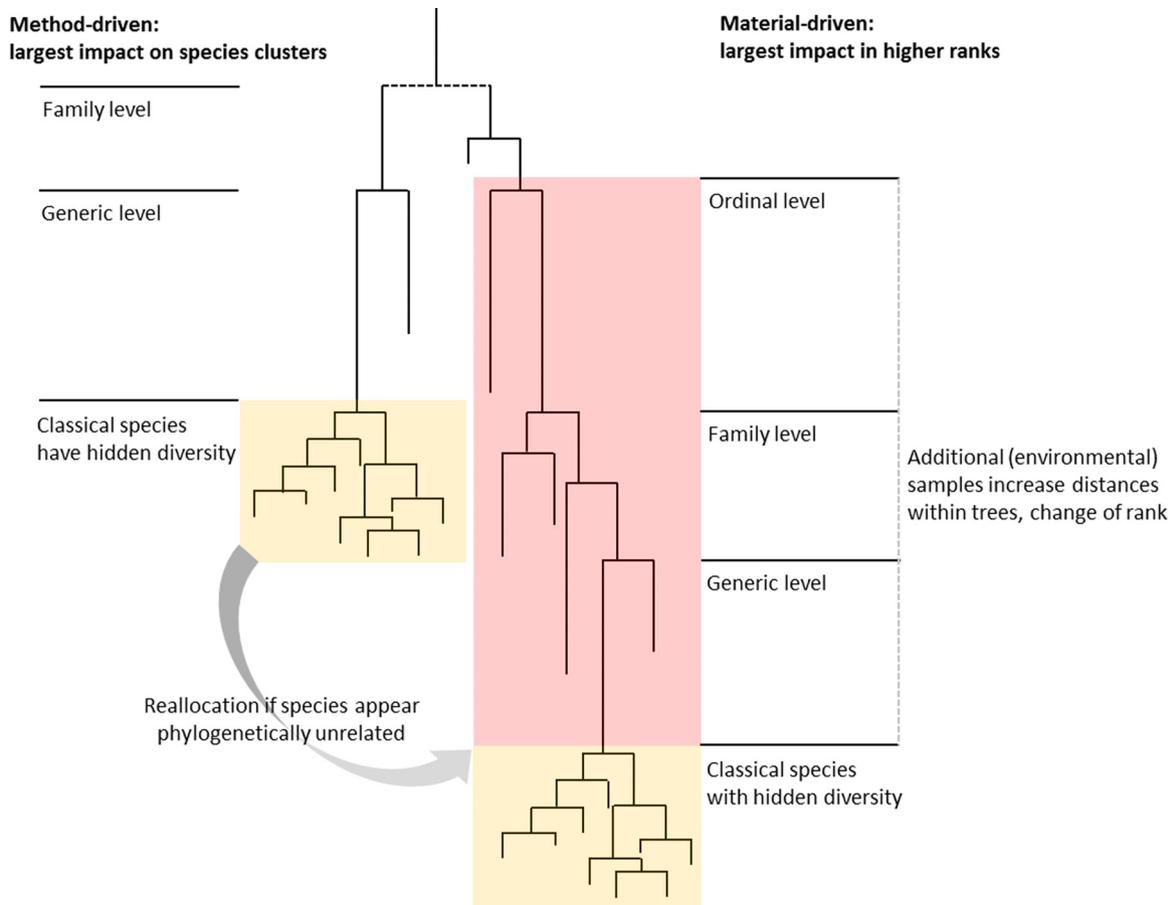


FIG 1 Diagram of name changes driven by methodical advances and sampling effects: subdivisions, reallocations, and rank inflations.

would have to be renamed in *Aspergillus*. The breadth of phenotype embraced by *Aspergillus* would include fungi that have never been associated with *Aspergillus*, but the phylogenetic data supporting this are solid (11), and it should be acknowledged that aspergilli with deviating morphological features do exist. In the second case, *A. fumigatus* would be named *Neosartorya fumigata* because *Neosartorya* species form a distinct monophyletic clade within the exiting genus *Aspergillus*. This may be unpleasant for medical mycologists, but for many other users of the fungal kingdom, this is good news as *Aspergillus* would then be used to refer specifically to *Aspergillus* species in the subgenus *Circumdati*. These include fungi with even more prominent economic value, for example the Asian food fungus, *Aspergillus oryzae*, its close relative, the aflatoxin producer, *Aspergillus flavus*, and the industrial fermentation workhorse, *Aspergillus niger*.

In summary, a major source of potential name changes, in addition to problems of dual nomenclature, is linked to phylogeny as a leading principle, while phylogenetic trees and taxonomic hierarchies are still under construction and subject to change while nature's diversity is better understood.

#### CHANGES AT THE SPECIES LEVEL AND BELOW

Species recognition is primarily method driven, i.e., tied to the method of observation. The shift from recognizing species by observable phenotype to recognizing them by nucleic acid variation has resulted in a proliferation in the number of species. In recent

years, more precision has been achieved in molecular methods by replacing species recognition in single-gene studies by multiple-gene analysis of lineages and populations, leading to molecularly defined taxa (sibling or cryptic species; Table 2). This trend will continue now that whole genomes are becoming available for large numbers of strains within a single species, as has been shown with model fungi (12–14).

When this process is clinically relevant, the novel naming system should rapidly be adopted. For example, *Sporothrix schenckii*, agent of human sporotrichosis, contains a hypervirulent sibling now known as *Sporothrix brasiliensis* causing large epidemics in Brazil (15). In another example, *Scedosporium aurantiacum*, one of the novel species recognized within the former umbrella species *Scedosporium apiospermum* is significantly less susceptible to currently used antifungal agents than the original species (16).

Application of more-variable genes to the same fungi will always lead to discovery of more diversity, again as demonstrated by population genomics. Almost all fungal species that have been examined show evidence of recombination and, therefore, exhibit upper and lower bounds to species recognition. The lower bound has been found using population genomic analysis to identify genetically differentiated populations of interbreeding individuals, and development of the upper bound has been observed where species have evolved reinforced barriers to mating in some areas of sympatry and not others (17). Only in clonal species would these bounds not apply and entities can be subdivided *ad infinitum*. In

**TABLE 1** Some examples of medically important fungi that have undergone recent multiple changes, with year of publication and reasons for rearrangement

Original name in medicine	Transitional name(s)	Current name
<i>Hendersonula toruloidea</i> 1933	<i>Scytalidium hyalinum</i> 1977 (supposed synonymy) <i>Scytalidium dimidiatum</i> 1989 (earlier synonym <i>Torula dimidiata</i> 1887) <i>Nattrassia mangiferae</i> 1989 (supposed identity of coelomycete anamorph) <i>Fusicoccum dimidiatum</i> (2005) (phylogenetic rearrangement) <i>Neofusicoccum mangiferae</i> 2006 (phylogenetic rearrangement) <i>Neoscytalidium hyalinum</i> 2013 (phylogenetic rearrangement)	<i>Neoscytalidium dimidiatum</i> 2006 (phylogenetic rearrangement)
<i>Trichosporon capitatum</i> 1942	<i>Geotrichum capitatum</i> 1977 (phylogenetic rearrangement) <i>Blastoschizomyces capitatus</i> 1985 (synanamorph genus) <i>Blastoschizomyces pseudotrichosporon</i> 1982 (synonymy) <i>Dipodascus capitatum</i> 1996 (description of teleomorph)	<i>Saprochaete capitata</i> 2004 (phylogenetic rearrangement of anamorph) <i>Magnusiomyces capitatus</i> 2004 (phylogenetic rearrangement of teleomorph; priority of either genus name still to be established)
<i>Candida utilis</i> 1952	<i>Hansenula jadinii</i> 1979 (conspecificity with <i>Candida utilis</i> , description of teleomorph) <i>Pichia jadinii</i> 1984 (phylogenetic rearrangement) <i>Lindnera jadinii</i> 2008 (phylogenetic rearrangement)	<i>Cyberlindnera jadinii</i> 2009 (nomenclatural correction)
<i>Allescheria boydii</i> 1922	<i>Pseudallescheria boydii</i> (teleomorph)	<i>Scedosporium boydii</i> (consensus chosen by <i>Scedosporium</i> community, but <i>Pseudallescheria</i> teleomorph genus name has been prioritized by nomenclatural community)
<i>Cephalosporium boydii</i> 1922 <i>Dendrostilbella boydii</i> 1922 (anatomic names for a trimorphic fungus)	<i>Scedosporium boydii</i> (prevalent anamorph; name for third morph neglected)	

practice, many, perhaps most, fungal lineages combine enough recombination with clonal behavior to be constrained by both upper and lower species boundaries. There is no gold standard as a measure of taxonomic diversity at the species level, and thus optimal barcoding genes are differentially effective between different groups.

Differences between molecular siblings may not always have clinical relevance. Distinction of cryptic species may then be taxonomically valid and scientifically meaningful but remain undetectable in routine laboratory analyses. On a global scale of daily

clinical diagnostics, attempting to detect these species would require an investment that would not contribute to patient care and is therefore not recommended until further research provides justification of these additional efforts. For example, *Aspergillus niger* was recently found (18) to contain a molecular sibling, *Aspergillus awamori*. Varga et al. (19) explicitly mention that there are no differences in phenotypic characteristics, such as metabolite profiles between the two, and clinical differences between the two species have yet to be discovered. As difficult as it might be to distinguish two species, imagine the case of the ubiquitous con-

**TABLE 2** Some taxonomic definitions appropriate for medical mycology that are used in the present paper

Term	Taxonomic definition
Species complex	A monophyletic clade of species with equivalent clinical relevance
Sibling species	Species that share the same, most recent common ancestor
Cryptic species	Species recognized by nucleic acid variation that had not been recognized as distinct by morphological phenotypes. Once recognized, phenotypic characters useful for identification may be discovered in the future.
(Sub)clade/monophyletic group	Phylogenetic group consisting of an ancestral species and all its descendants. Clades and subclades can be recognized at any given taxonomic level. Statistical tests are used to gauge the support for these groups.
Lineage	Series of species connected by evolutionary descent, not necessarily representing all known descendants
Cluster/group	Terminal series of phylogenetically related species, used when precise relationships are uncertain.
Type	Entity defining a taxonomic name and indicated as such in the protologue. Species and below are defined by a specimen, whereas higher taxonomic entities are defined by the first lower category.
Neotype	New specimen in accordance with the protologue in case the original type material is lost.
Epitype	Reference specimen accordance with the protologue when the original material is not interpretable.
Protologue	Original description and any other representation of a taxonomic entity.

taminant *Cladosporium cladosporioides*, which today contains 39 cryptic species (20), 38 of which have never been proven as agents of human infection.

Neighboring siblings that are identical in patient management and normally characterized phenotype might in routine diagnostics better be taken together as “complexes.” A “species complex” of medically important fungi would be considered a cluster of cryptic species that are clinically identical. This is the current indication of series of closely related *Fusarium* species (21), and similar approaches have been adopted for *Cladosporium* (20) and elsewhere. The word “complex” has no nomenclatural status and does not require any name change. Species complexes can nevertheless be sharply delimited and validated by molecular data. Diagnostic markers can be developed for the molecular siblings and for the species complex. If an author wishes to describe other, less clearly defined species diversities, terms like “group,” “cluster,” “lineage,” and “clade” are available (Table 2).

In summary, a major source of name changes at the species level is increased precision of molecular techniques; this nomenclatural instability is thus largely method driven. The distinguished entities, even when scientifically correct and meaningful, may not always have clinical relevance, although this significance may perhaps be discovered in the future.

## CONCLUSIONS AND PROPOSALS

During the process of naming each fungus, teleomorph and anamorph names as well as their synonyms are being considered in a way that would increase acceptance and stability. Even strict nomenclatural rules provide a certain degree of liberty. Many of the classical medical fungi and many of their synonyms were described a long time ago, and type material is often lacking or uninterpretable. The present paper does not argue for one solution or the other in any of the examples above but simply notes that there is more than one way to apply one name for one fungus. Nomenclatural changes of medically important fungi usually take decades to gain wide acceptance. Any change may be viewed as a process taking place in the community, rather than as a singular result of a phylogenetic study. Taxonomy is a dynamic science, which cannot be muzzled by nomenclatural protocols. Reallocations, rank changes, and generic disarticulations or reunifications will remain common practice. Theoretically, the taxonomic system should reflect the true phylogeny of the fungal kingdom, but obviously we have not yet reached that stage. Additional data and techniques improving the system are continually generated and published. Therefore, it may be more prudent to wait until a larger degree of stability and consensus is achieved. Many names of opportunistic fungi are published as part of studies on environmental fungi, where genera might comprise dozens or hundreds of species. The genus name is linked to its type species, and if this species appears to be different from all the others, all remaining names need to be recategorized in another genus. The result is that the number of name changes can be tremendous—a compelling reason to be careful with reallocations where scientific support is still fragmentary.

How should the field of medical mycology treat the new diversity seen in the taxonomy of medically important fungi? At the genus level, these are reallocations, rank changes, and generic disarticulations or reunifications that stem from studies of more materials and from having to choose one name from two or more current names. Where examination of new materials suggests new

names, we urge taxonomists to delay introduction of new names until they have sampled sufficient material. Where name change results from having to choose one of several names, maintaining taxa that have similar medical attributes would serve medical mycology; such taxa should neither be so big as to hide medically important phenotypic variation nor so small to lessen the distinction between genera and species. Where the names of medically important fungi do change—and many will change as the new code is applied—it may reflect the fact that medical mycology is just one of many socially important activities that focus on fungi. Good taxonomic studies do not always need new names immediately. For clinical routine, it is advocated to follow changes with some delay, after validation by a convincing body of data, until a sufficient degree of stability and consensus is reached.

At the species level, most changes concern subdivisions of classical phenotypic species, as new methods allow mycologists to examine more and more of the genetic variation, including the entire genomes of populations of fungi. As new research techniques become widespread in clinics, clinicians also will be able to recognize more species. Until, after clinical evaluation, newly discovered species prove to be different in terms of patient management, in daily clinical routine, it might be better to unite such siblings as “species complexes.”

Researchers and clinicians should work together to achieve a reasonable degree of nomenclatural stability during the decades when large changes are unavoidable. Even when a disease caused by two or more closely related species is treated by the same therapy, insights into diversity of the species may advance medicine by allowing clinicians to use this knowledge to discover previously overlooked and consistent differences. Specialized websites are available where diagnostic materials are provided as an aid for identification and the best current taxonomy is available as matters change.

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