

# 'Split' decisions in CNS tumor update

## Karen Titus

**October 2017**—Classifying central nervous system tumors has recently become both more complex and easier. Surgical pathologists now have guidance that helps them work through the whys, hows, and what-ifs of using molecular studies when making diagnoses. The 2016 WHO classification for CNS tumors, which has been described as a conceptual and practical advance over the previous incarnation, from 2007, should also help them move closer to precision medicine.



“At the heart of personalized medicine,” says Dr. Eyas Hattab, “is our ability to diagnose each patient’s tumor and categorize it to the narrowest possible classification.” The 2016 WHO classification of CNS tumors is another step on that road.

But the journey will have its challenges, says Eyas Hattab, MD, MBA, the AJ Miller professor and chair of pathology and laboratory medicine, University of Louisville (Ky.) School of Medicine. “What we found is this has been very intimidating to general surgical pathologists, and even to many surgical neuropathologists.” The lack of appropriate resources for molecular assays adds complication.

Advances in the field have improved matters for patients, pathologists, and oncologists, prompting the 2016 classification changes. “We call it an update,” says Dr. Hattab, explaining that the WHO has strict criteria for green-lighting a new, official revision.

Since the 2007 edition, “There has been an explosion of new information,” he says, “mostly in the form of molecular and genetic data on brain tumors that further allows us to subclassify certain entities. In a few cases, molecular testing has become the gold standard for such diagnoses.”

**In a sense, the classification becomes** a rallying cry: Splitters of the (neuropathology) world, unite!

“We are turning into more splitters than lumpers in some cases,” says Arie Perry, MD, professor of pathology and

neurological surgery, and director of neuropathology and the neuropathology fellowship program, Department of Pathology, Division of Neuropathology, University of California, San Francisco.

The reasons for more specific categories are many.

One of the difficulties that emerged from the 2007 scheme, Dr. Perry says, is that in certain glioma types, including oligoastrocytoma, there was insufficient reproducibility among some pathologists, and some of the criteria were too vague. “It made it difficult to treat patients when they would go from one institution to another and get different diagnoses.”

David Louis, MD, pathologist-in-chief, Massachusetts General Hospital, and the Benjamin Castleman professor of pathology, Harvard Medical School, points out that the classification is not aimed strictly at patients and physicians. “Pathologists drive this, but the users are broad,” including researchers, epidemiologists, and payers, says Dr. Louis, lead editor of the 2016 CNS WHO classification. “All these constituencies are dependent on accurate classifications.”

For insurers, Dr. Perry adds, the consensus should make clear the justification for doing molecular testing. “If you’re not doing the testing, you can’t reach that particular diagnosis.”

By introducing molecular parameters into the WHO document for the first time, the authors restructured the classification of diffuse gliomas, medulloblastomas, and other embryonal tumors. This includes subdividing both the gliomas and the embryonal tumors to create cohorts that are as uniform as possible. For example, “Rather than just saying ‘diffuse astrocytoma,’ now you have to know if it’s IDH-mutant astrocytoma or IDH-wildtype,” says Dr. Perry, who helped author, with Dr. Louis, a summary of the classification (Louis DN, et al. *Acta Neuropathol.* 2016;131[6]:803-820). “They have different prognostic implications.”



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Likewise, in the 2007 CNS WHO, Dr. Perry notes, “Medulloblastomas were all just medulloblastomas.” Now they are categorized further into molecular subtypes, including WNT-activated or SHH-activated, with the latter group further refined based on TP53 mutation status (TP53-mutant or TP53-wildtype). Nevertheless, some medulloblastomas remain hard to separate, such as the non-WNT/non-SHH tumors that are either group 3 or group 4.

Embryonal tumors other than medulloblastoma have also undergone major restructuring, incorporating genetically defined entities and removing the term “primitive neuroectodermal tumor,” or PNET. The 2016 classification notes that the amplification of the C19MC region on chromosome 19 leads to a diagnosis of “embryonal tumor with

multilayered rosettes (ETMR), C19MC-altered.” Tumors that lack C19MC amplification and that have histologic features of ETANTR (embryonal tumors with abundant neuropil and true rosettes)/ETMR are diagnosed as “embryonal tumor with multilayered rosettes, NOS,” that is, not otherwise specified.

No matter how complex the material, however, the 2016 classification does simplify matters and should not be intimidating, says Dr. Hattab, chair of the CAP Neuropathology Committee. And ultimately, he says, it is another step on the road to personalized medicine. “It starts with achieving the proper diagnosis. At the heart of personalized medicine is our ability to diagnose each patient’s tumor and categorize it to the narrowest possible classification.”

The simplest example, Dr. Hattab says, is glioblastoma. Under the microscope, it looks similar in adults and children. But genetically speaking, they’re different. “Vastly different,” Dr. Hattab says, “as in completely different tumors.” The 2016 WHO puts more of a separation between adult and pediatric tumors—based on genetic characteristics—than had existed previously.

Dr. Hattab calls this step nothing short of revolutionary. Until now, all WHO classifications for CNS tumors were based on morphology alone. “If we used genetic information, it did not really alter our diagnosis,” Dr. Hattab says. Rather, it was offered as a second layer of information not necessarily employed in classification.

What should not be lost in translation, Dr. Hattab cautions, is that genetic information currently is available for only a small set of CNS tumors, as noted. Other categories have remained largely unchanged. Meningioma, for example, remains a morphologic diagnosis. It is likely that for this, as well as many other CNS tumors, morphology will remain the primary diagnostic approach, at least for the foreseeable future.



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“I think one of the assumptions many clinicians make is that we’re placing more emphasis on genetic information and much less on morphology,” Dr. Hattab says. He suggests another way to think about it: that morphology, used in screening, can drive the appropriate genetic testing.

In some cases, genetic testing borders on breathtaking. The history of glioblastoma was essentially one of death sentences, Dr. Hattab says. Those with the diagnosis lived a year or less, generally. A small (less than 10 percent) subset of patients lived longer, however—from four to six years and sometimes even longer. “We just weren’t able to predict who,” he says.

As it turns out, the patients who did exceptionally well had tumors that almost exclusively belonged to the IDH-mutant class of glioblastoma. Indeed, says Dr. Hattab, the IDH mutation status should take a bow of sorts, since it was the primary driver behind the 2016 update. “This was a major discovery in 2008 and 2009. It was revolutionary. We could not ignore it and wait for a new classification,” he says. With the update, “It now becomes

an expectation.”

Dr. Louis says the four biggest changes are the aforementioned restructuring of diffuse gliomas, medulloblastomas, and embryonal tumors, as well as addressing the overall concept of classifying CNS tumors in the molecular era. The other changes (all are listed in table 2 of the Acta Neuropathologica summary) he categorizes as quite specific additions and subtractions of entities. But this was hardly a simple remodeling project. In the past, says Dr. Louis, WHO updates were generally occasions for adding new entities and deleting older ones. But what many specialties are now discovering—“and what heme-path found out many years ago”—was that incorporating molecular findings into what were histological diagnoses in the past required paying attention to the how as well as the what of adding and subtracting.

The summary’s authors call the update a “conceptual and practical advance.” Or, as Dr. Louis says, “What are the underlying concepts that drive your ability to incorporate molecular into a diagnosis?”

The update’s authors were so concerned about framing this appropriately, in fact, that they held a conference in the Netherlands two years earlier, a sort of medical prenuptial agreement, before tackling the classification itself. “We didn’t want people to show up for the WHO meeting and have the people who deal with, say, the pediatric tumors go off into one room, and the people who deal with adult gliomas going into another room, and they come back with different ways to solve this conceptual challenge,” says Dr. Louis.

**The 2016 classification uses an** integrated diagnosis, which, it is hoped, will add objectivity to diagnoses. As the summary’s authors note, the diagnostic category of oligoastrocytoma, always difficult to define, has long been marked by high interobserver discordance—some centers identify these lesions frequently and others do so only rarely. By using both IDH mutation and 1p/19q codeletion status along with phenotype, however, pathologists can define astrocytomas and oligodendrogliomas with more clarity.

As Dr. Louis explains it, pathologists can use a layered approach to reporting, with the first line being the integrated diagnosis, specifically, the WHO diagnosis that incorporates histology and molecular findings. The second line is strictly the histologic diagnosis. The third line is the WHO grade, and the fourth line contains all the molecular findings.

But if molecular testing has become a standard of practice, at least for certain tumor types, that does not mean all labs are capable or desirous of doing it. While it may be common in most academic centers, the same is not true everywhere. On the other hand, “I do think it’s a bit unrealistic to expect that every brain tumor gets sent out,” says Dr. Hattab. The update should help everyone take steps, little or big, down the molecular path.

The update does not state this next point explicitly, but Dr. Hattab underscores one of its implications: For those who see fewer brain tumors—perhaps one every two months—performing molecular testing in-house may not be a realistic expectation. “But you should at least have basic knowledge of what to ask for. After all, it is the pathologist who is tasked with selecting the appropriate tests in an increasingly complex toolbox,” he says.

One of the difficulties is that molecular pathology is diverse, employing many methodologies, with varying performance characteristics. Down the road, Dr. Louis sees molecular diagnostics evolving in ways similar to shifts in immunohistochemistry. When IHC first became clinically useful, in the 1980s, pathology departments required experts in antibodies and antibody-antigen interactions, he recalls. The 1990s saw the establishment of the immunopathology fellowship. Today, of course, the majority of IHC is done on automated platforms, and “Every pathologist feels comfortable looking at an immunohistochemical slide nowadays.”

Even then, Dr. Perry does not see histology in full retreat. “Every new technique that comes around, you’ll hear some people saying, ‘Well, that’s it—we won’t be using a microscope anymore.’” Electron microscopy, IHC, and molecular pathology—all have been seen, at one time or another, as chauffeurs driving passengers to their doom. “But I don’t think we’re anywhere near that point. I don’t know that we ever will be, because there’s still a tremendous amount of very useful information that you get quickly, very inexpensively, by looking at slides under

the microscope.”

Within the newly created categories, moreover, the mutation information makes sense only once the pathologist looks at the case under the microscope. “If you just take a molecular alteration in a vacuum, without looking at tissue, it may have completely different implications in one type of tumor than in another,” Dr. Perry says.

**In the meantime, those who developed the update** were fully aware that molecular testing throws down two (at least temporary) gloves from the start: availability and cost, which adds to the diagnostic and bureaucratic complexity of classifying cases.

“We knew that would be a problem,” Dr. Louis says. “So we created NOS—not otherwise specified—categories.”

Dr. Louis gives the example of community pathologists who either cannot perform a particular mutational analysis in their lab or do not want their lab to shoulder the financial burden of the test. In the case of a glioblastoma, “They can simply call it ‘glioblastoma NOS.’” When the patient then seeks treatment at a tertiary care center—most patients with brain tumors do, says Dr. Louis—the NOS label serves as a red flag of sorts and should prompt care providers to seek additional IDH analysis.

The WHO classification does not delve into matters of how reports are structured, Dr. Louis says, and thus it doesn’t address precisely how to convey that IDH testing should be done. But, he adds, the International Collaboration on Cancer Reporting process for CNS tumors, which he heads up, is developing a reporting standard, drawing on protocols from groups such as the CAP and the Royal College of Pathologists. The standard will likely address what should be tested for and, in cases when the testing is not done, what should be indicated.

Based on his experiences with referral cases at MGH, Dr. Louis says that general pathologists have caught on fairly quickly to the updated classification. Moreover, “Much of the workup can be done by immunohistochemistry. So we’re not seeing a lot of really inadequately worked-up tumors; we are seeing more partially worked-up tumors. It’s pretty easy for us to add on the additional testing involved.”

Dr. Perry reports mixed reactions to the update at UCSF, “as there always is when a new classification comes out.” Pathologists and oncologists prefer the increased objectivity, he says, but some are anxious about using new assays. “Some of this requires testing that may not have already been in place.”

As much as possible, Dr. Perry says, the authors of the update tried to incorporate surrogate markers for a molecular assay when reliable immunostains were available. “We tried to emphasize that a lot can be done with immunohistochemistry.”

Oncologists, Dr. Perry continues, have been, in his experience at least, “quite happy with the way things have changed.” After all, he points out, “It’s not uncommon that within a week of some publication saying a biomarker is useful, they’re demanding we get it up and running.”

He also echoes Dr. Hattab in reassuring pathologists, saying that the updated classification is “fairly straightforward once you’ve done it. It seems a little overwhelming when you first look at it, because there’s so many new things compared to the 2007 scheme.” But those who have begun using it soon find it improves accuracy and reproducibility. In his practice, “Everyone had their own learning curve, but everybody who’s practiced with it is now happy.”

Despite the many fine-tunings, “quite a few” histologically defined tumors remain, says Dr. Perry, either because pathologists do not yet have a signature molecular alteration or because not enough is known about the genetics involved to use that as part of the definition for the diagnosis. Interestingly, even for entities where a molecular definition has been added, the aforementioned NOS category has been included as well, to reflect when a case lacks molecular information. A tumor that histologically looks like a diffuse astrocytoma on which IDH molecular testing has not been done would be identified as diffuse astrocytoma, NOS. “That tells the oncologist that either molecular testing wasn’t done or it wasn’t definitive for some reason.”

## **What happens when molecular and histology results differ?**

Dr. Louis says pathologists are starting to understand these cases—which he calls “rare situations”—better. “They’re not that common,” he says, “because the combined molecular-histological entities we set up were well established, based on lots of cases and lots of analyses.” The resulting definitions are quite precise.

The layered report also helps with this, he says, offering an example of how this might play out: a tumor that appears to be one type histologically—he calls it type A—but type B based on molecular findings. Each bit of information would appear in the appropriate line. The integrated diagnosis might be a descriptive one or an NOS-type category. Such a report should make a discrepancy quite clear to oncologists and pathologists, says Dr. Louis. “It’s sitting right there in front of you.”

Explaining further, Dr. Louis says, “We’ve seen instances where the oncologists have said, ‘I know the histology says A, but I’m interested in that molecular B. I’m going to treat this patient like a B.’” He and his colleagues have also seen the opposite. “An oncologist says, ‘The B doesn’t make sense in light of what we’re seeing in this patient. I’m going to assume this is a weird A.’” In some cases, oncologists will view the tumor as an A-B, worth following more closely.

With an eye toward the next classification, he notes that while the IDH mutation works well to separate adult diffuse gliomas into different prognostic groups, it has no meaning in pediatric diffuse gliomas that histologically look identical to adult tumors. Instead, a number of different mutations are emerging with more frequency in pediatric cases. “They are now trying to decide which of these are clinically important and belong in the next WHO. Which one of these form tight entities?”

Mismatch cases and other hard-to-pin-down entities, while frustrating, serve an important purpose. They are, says Dr. Louis, “learning experiences for the next time. When you construct these classifications, you’re not constructing them for all eternity,” he says with a laugh.

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*Karen Titus is CAP TODAY contributing editor and co-managing editor.*