INTRODUCTION/BACKGROUND

After a mass is first identified in a patient’s brain, one of the usual first steps is a near-immediate surgery to remove as much of the mass as possible. During this operation, the neurosurgeon will typically take a sample of tissue from the mass – or biopsy – and send it to the hospital’s “pathology” department, which is in charge of analyzing the sample of tissue/cells and determining the exact diagnosis. Pathology answers questions such as: is the mass really a tumor or something else, like an infection or cyst? If it is a tumor, is the tumor benign or malignant? Is it an oligodendroglioma, meningioma, astrocytoma, or another tumor type? What grade is the tumor?

These answers will then play a critical role in determining a patient’s subsequent treatment plan. Will the patient need radiation? Will they need chemotherapy? Both? Will doctors take a “wait-and-watch” approach?

Historically, pathologists analyze biopsy samples by examining the tissue under microscopes and produce a report (pathology report or surgical pathology report) on the tumors’ grade and diagnosis from an observable set of standard characteristics that define the different “classifications” of brain tumors. This microscope-based approach is called “histopathology.”

However, because of biological diversity of tumors, there can be some uncertainty and variability in obtaining an accurate diagnosis. New studies over recent years demonstrate that molecular alterations in tumor cells define different groups of brain tumor types (including gliomas) that have distinctive characteristics. These studies also suggest that analyzing a tumor for mutations or deletions in certain genes or regions of chromosomes can provide a deeper level of understanding of each tumor’s make-up. By using molecular markers, doctors can more accurately define and classify brain tumors compared to current pathology methods. These findings have begun to move the neuro-oncology field toward a more informed and precise classification for the many different types, and subtypes, of brain tumors, which may better inform how patients should be treated.

“Unfortunately, classifying a tumor only by [microscopic] appearance and grade has not provided sufficient information about the way the tumor is likely to behave, how it will respond to treatment, or the patients likely survival time,” said Dr. Margaret Wrensch of UCSF. “These markers will potentially allow us to predict the course of gliomas more accurately, treat them more effectively, and identify more clearly what causes them in the first place.”

Thus, in mid-2014 a group of top neuropathologists – who specialize in the pathology of brain tumors – began discussing how to integrate the latest science and the most accurate techniques into the current classification system of brain tumors, which was last updated in 2007. And after two years of work, the group – in conjunction with the World Health Organization, the international organization charged with setting standard grades and categories for tumors – has published a new standard classification system for brain tumors that incorporates molecular information alongside traditional histopathology, establishing “integrated diagnoses” that should lead to improvements in diagnostic consistency, prognostic estimation, and therapeutic prediction.
The 2016 World Health Organization Classification of Tumours of the Central Nervous System (the “Blue Book”) is based on years of research and culminated with a consensus meeting of top international neuropathologists in 2015.

OVERVIEW – TUMOR CLASSIFICATIONS*

Periodic revisions of tumor classifications have important effects on many aspects of individual and population health.

Based on the latest knowledge from molecular characterization studies, researchers have come to better understand how brain tumors are a heterogeneous group of molecularly distinct entities, with some tumors sharing common characteristics and others based on very different sets of alterations and mutations. As such, the groups charged with producing the new 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 CNS WHO) sought to answer the following questions:

- Can an entity (brain tumor type) be defined on the basis of histology and genetics?
  - If so, what should a histologically similar tumor without the corresponding genetic findings be called?
- Are there “new” entities to add?
- Are there “old” entities to delete?

After reviewing all the latest scientific information on brain tumors, the consensus was that:

- Molecular information should be incorporated into the definitions of some tumor types
- For some of these tumor types, molecular information will be necessary to provide an “integrated” diagnosis and a traditional histological diagnosis will only be used if no molecular diagnostic testing is available
- To do the above, some disease entities need to be redefined and some new disease entities need to be defined/added
- Some pediatric tumor types will require the creation of entities independent of their adult histological “look-alikes”
- Other tumor type “look-alikes” that are actually molecularly the same will also be merged

Major Changes from 2007’s CNS WHO classifications to the 2016 CNS WHO will include:

- Major restructuring of diffuse gliomas, with incorporation of genetically defined entities
- Major restructuring of medulloblastomas, with incorporation of genetically defined entities
- Major restructuring of other embryonal tumors, with incorporation of genetically defined entities and removal of the term “primitive neuroectodermal tumor”
- Incorporation of a genetically defined ependymoma variant
- Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity
- Addition of newly recognized entities, variants and patterns
  - Glioblastoma, IDH-wildtype and Glioblastoma, IDH-mutant (entities)
  - Diffuse midline glioma, H3 K27M–mutant (entity)
  - Embryonal tumor with multilayered rosettes, C19MC-altered (entity)
  - Ependymoma, RELA fusion–positive (entity)
  - Diffuse leptomeningeal glioneuronal tumor (entity)
  - Anaplastic PXA (entity)
  - Epithelioid glioblastoma (variant)
  - Glioblastoma with primitive neuronal component (pattern)
- Multinodular and vacuolated pattern of ganglion cell tumor (pattern)
- Deletion of former entities and variants
  - Gliomatosis cerebri
  - Protoplasmic and fibrillary astrocytoma variants
  - Cellular ependymoma variant

(*The above descriptions and tables are taken from lectures by Dr. David N. Louis, the lead editor of the 2016 CNS WHO classification.)

**OVERVIEW – DIAGNOSIS/PROGNOSIS/TREATMENT**

Based on the new edition of WHO brain tumor classifications, a percentage of brain tumor diagnoses will now be based on **BOTH** microscopic analysis **AND** molecular analysis. Previously, diagnosis and classification was based on **just** microscopy.

This means diagnoses for many brain tumors will be much more precise and give the treating physician a better idea of what treatment course to take.

However, not every tumor in the new classification will have molecular information included; sometimes the traditional microscopic analyses (which is based on what’s called “phenotype,” or the observable traits of a cell) will remain the most important information for classification.

In instances where **genotype** (the tumor’s collection of genes) trumps phenotype, or both molecular and histological information is needed, diagnoses for brain tumors will take on an “integrated” and “layered diagnosis.” With the new integrated and layered diagnoses, diagnostic pathology reports will now have four lines of information based on the integration of molecular analysis:

1. Integrated diagnosis
2. Histological (microscopic) diagnosis
3. WHO (histological) grade
4. Molecular information

Patients will still receive their traditional microscope-based diagnosis within a week, but it may take 3-4 weeks for the full, integrated diagnosis with the molecular information to come in.

The 2016 World Health Organization Classification of Tumours of the Central Nervous System will have a significant impact in terms of how physicians both diagnose and plan therapies by providing more accurate information on an individual patient’s tumor characteristics.
Frequently Asked Questions (FAQ)

1. Why are these changes happening now?

The World Health Organization sets international standards for how tumors are classified, and in conjunction with leaders in each field, periodically review their classifications to ensure that the latest science is guiding how tumors are defined. Recent findings from brain tumor research studies in the past few years have provided new information on the distinct molecular make-up of many brain tumor types, as well as how some types that look different under a microscope may actually be driven by the same mutations, and thus behave the same way...or, conversely, that two current types look the same under a microscope, but have very different genetic alterations, and thus should be treated differently.

2. Why does it matter how tumors are defined? Why does re-classification matter?

How tumors are classified – or defined, or characterized – has an impact on many different and important aspects of individual, as well as population, health in any given disease area. This includes (according to Dr. Louis’s lecture notes):

- **Care of individual patients** – more accurate diagnosis, estimating prognosis, guiding therapy
- **Conduct and interpretation of clinical trials** – ensure that patients participating in clinical trials are comparable within and across trials
- **Stratification for future clinical trials** – matching patients by their molecular signatures with target therapies most likely to benefit them
- **Getting the right results from scientific experiments** – more accurate analysis and understanding of experimental studies in the lab
- **Disease epidemiology** - better interpretation of population-based disease trends that may help identify causes and risk factors
- **Research funding** - allocation of resources by governments and health insurers to support health care based on areas of greatest need

3. What does this mean for my (or my loved-one’s) brain tumor?

It means that their medical team will better understand the specific molecular and genetic alterations that are driving the tumor, and will allow them to better plan and identify treatment courses.

4. What if I’ve already been diagnosed, though?

NBTS recommends that if patients are concerned about their current diagnosis, or believe they could now benefit from an updated diagnosis, that they should first discuss the possible need for an updated diagnostic interpretation with their treating oncologists. If it is decided by the medical team that additional testing may provide useful information in that particular tumor type and that particular treatment situation, then it may be possible for the patient to request his or her tissue from the medical center that originally diagnosed them. Patients can ask their medical teams if there is still tissue available from their biopsy. If their tissue has been preserved, and the medical center has the appropriate technology for testing, that center can perform the molecular analysis.
5. **What if my medical center doesn’t have the technology to do the molecular analysis needed for the integrated diagnosis?**

The first option would be to try to see a brain tumor specialist at a large academic medical center, or a cancer center of excellence (listed on the website of the National Cancer Institute – cancer.gov). Additionally, there are a number of companies that perform comprehensive molecular profiling, to which tumor specimens could be sent for analysis.

6. **What does this mean for the future of brain tumor research and treatment?**

This is really a big step in moving brain tumor research and treatment development further into the 'precision medicine' paradigm that is dominating the field of biomedical research this decade. As Dr. Louis said to us recently: "The evolution from histopathology (just classifying/diagnosing a tumor based on what it looks like under a microscope) to where we are now (incorporating molecular characteristics), really coincides with the dawn of precision medicine."

This doesn't mean that precision medicine will now be fully realized in neuro-oncology – we still need to develop better drugs. But having more accurate and precise diagnoses and classifications is the foundation on which better clinical care and precision drug development can advance.

Bottom line - the field is moving forward in a positive way.

7. **Will these classifications change again in the future?**

As we continue to learn and understand brain tumors more, there will likely be further updates to the WHO classification of tumors of the CNS. It will likely be a number of years down the road, however.
**DEFINITIONS/GLOSSARY**

**Disease/Molecular Entity(ies):** A subtype of a condition, which is defined by a distinct functional or pathobiological mechanism. In more common terms: tumor type.

**DNA Sequencing:** A laboratory process used to learn the exact sequence (order) of the four building blocks, or bases, that make up DNA. Information is stored in DNA in a code made by arranging the four bases (identified by the letters A, C, G, and T) in different orders. DNA sequencing can be used to find DNA mutations (changes) that may cause diseases, such as cancer.

**Genomic Sequencing:** A laboratory method that is used to determine the entire genetic makeup of a specific organism or cell type. This method can be used to find changes in areas of the genome that may be important in the development of specific diseases, such as cancer.

**Genomic Characterization:** A laboratory method that is used to learn about all the genes in a person or in a specific cell type, and the way those genes interact with each other and with the environment. Genomic characterization may be used to find out why some people get certain diseases while others do not, or why people react in different ways to the same drug. It may also be used to help develop new ways to diagnose, treat, and prevent diseases, such as cancer. Also called genomic profiling.

**Genotype:** A genotype is an individual's or a tumor's collection of genes. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of a person's genotype contributes to the individual's observable traits, called the phenotype; in a tumor, the expression of the tumor genotype contributes to the tumor's traits.

**Histology/Histopathology/Histologic examination:** The study of diseased cells and tissues using a microscope.

**Molecular analysis:** In medicine, a laboratory test that checks for certain genes, proteins, or other molecules in a sample of tissue, blood, or other body fluid. Molecular tests also check for certain changes in a gene or chromosome that may cause or affect the chance of developing a specific disease or disorder, such as cancer. A molecular test may be done with other procedures, such as biopsies, to help diagnose some types of cancer. It may also be used to help plan treatment, find out how well treatment is working, or make a prognosis. Some molecular analyses use microscopes but others use liquid-based specimens.

**Molecular diagnosis:** The process of identifying a disease by studying molecules, such as proteins, DNA, and RNA, in a tissue or fluid.

**Molecular marker/signature/characteristic:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A molecular marker may be used to see how well the body responds to a treatment for a disease or condition. Also called biomarker and signature molecule.

**Pathology:** A branch of medical science and clinical care primarily concerning the examination of tissues and bodily fluids in order to understand diseases, make medical diagnoses and guide clinical care.

**Pathologist:** A doctor who identifies diseases by studying cells and tissues under a microscope and through analysis of liquid-based specimens (e.g., blood).
**Pathology Report:** The description of cells and tissues made by a pathologist based on microscopic evidence, and sometimes used to make a diagnosis of a disease. If the report is based on material from surgery, it is sometimes referred to as a “surgical pathology report.”