illumina® News Center



Dr. Matija Snuderl, director of molecular pathology at NYU Langone Health's Perlmutter Cancer Center. Photo by NYU Langone Health

Solving the complexities of brain cancer diagnostics

NYU Langone Director of Molecular Pathology Matija Snuderl explains why every brain cancer journey should begin with DNA methylation profiling

IN THE YEARS SINCE he first came to NYU Langone Health's Perlmutter Cancer Center, Dr. Matija Snuderl can recount a surprising number of scenarios when a patient's cancer diagnosis was reversed or somehow amended, changing their life. "We see these misdiagnoses all the time," he says, having retested patients who came from other hospitals, pulled them from the wrong clinical trial or therapy, and put them on treatments that they actually responded to.

In 2013, Snuderl was NYU Langone's only molecular neuropathologist. Then in 2017 he took over molecular pathology and built a state-of-the-art molecular pathology and diagnostics lab with two units: solid tumors and hematological tumors. The lab processes thousands of samples every year. Although he wears many hats now, Snuderl's specialty and passion is classifying and diagnosing brain and central nervous system (CNS) tumors, which are notoriously complex.

Brain cancer basics

According to a study published in *Nature*,¹ approximately 2% of all cancers arise in the brain, but brain or CNS

cancer is responsible for the fourth highest number of years lost, after testicular, cervical, and Hodgkin lymphoma. It's also expensive to treat, and survivors face years of follow-up appointments.

Until very recently, brain tumors were the leading cause of cancer-related death in the pediatric and young adult population (leukemia has recently pulled ahead). Even a *successful* treatment for a young brain cancer patient can still cause an incredible loss of quality of life, Snuderl explains: "Because a developing brain is very sensitive to radiation and chemotherapy, children suffer for the rest of their lives with the consequences of adjuvant therapy."

Primary CNS tumors have more than 120 molecular subtypes, many of which look similar under the microscope—but should not be treated the same. Because of their sheer number, variety, and diverse set of molecular drivers, many pathologists won't see most of them in their lifetime. "A world expert in brain tumors will still see these incredibly rare ones only occasionally," Snuderl says. "So to get trained and to be able to recognize the subtype is very difficult, and some of them

For Research Use Only. Not for use in diagnostic procedures.

^{© 2025} Illumina, Inc. All rights reserved. All trademarks are the property of Illumina, Inc. or their respective owners. For specific trademark information, see www.illumina.com/company/legal.html.

you cannot tell with your eye. You need an additional tool for that."

Classifying brain tumors based on their methylation profile

DNA, including the DNA of cancerous tumor cells, can chemically modify itself to regulate gene expression. This epigenetic process is called methylation. Each cell has a specific methylation profile that tells a pathologist what kind of cell it is or what tissue or organ it belongs with, and how aggressive the tumor might be. By analyzing a piece of tissue from a tumor biopsy, a lab can determine the cancer's distinct methylation profile, much like a fingerprint.

In early 2014, Snuderl began collaborating with researchers at the German Cancer Research Center (DKFZ)² in Heidelberg to develop an epigenetic map of brain tumors using Illumina methylation arrays.³ To create an extensive database that each new brain tumor could be compared against, the collaborators would need hundreds of thousands of characterized brain cancer samples. The database would be able to confirm each new tumor's classification and support its diagnosis.

Along the way, Snuderl discovered and published numerous brain cancer classifications, which were brought to light through the tumor's novel epigenetic profile. Snuderl and the DKFZ team worked with medical experts around the globe to establish a consensus of how methylation profiling could be used in this way. This led the World Health Organization to incorporate DNA methylation profiling into its guidelines for the classification of CNS tumors, and the National Comprehensive Cancer Network to recommend it in their CNS guidelines.

Snuderl's NYU Langone lab was the first in the US to classify cancers based on DNA methylation. "Wholegenome DNA methylation profiling provides an accurate and robust benchmark that pathologists can use to classify all the cancers and navigate the patient journey," Snuderl says.

A precise molecular diagnosis

Traditionally, CNS tumors are diagnosed by examining an immunohistochemistry stain of the sample under a microscope. But neuropathologists agree that these stains often look similar for different tumor subclasses. An epigenetic approach provides an objective classification based on a reference set, which supports an accurate diagnosis.

In one study published in *Neuro-Oncology Advances*,⁴ Snuderl and his team prospectively profiled nearly 2000 brain tumors over several years. They compared each tumor's original diagnosis, made via traditional visual exam, to what their methylation classification showed. Across all subtypes, the error rate for the original diagnosis was 14%, demonstrating that visual examination can be subjective and misleading. Considering their findings, the 14% of cases with a new diagnosis could be given a more appropriate treatment plan.

To illustrate the impact of misdiagnosis in practice, Snuderl often cites one paper he was not involved in that described how a pediatric clinical trial failed because reanalysis found that 74% of the patients had been misdiagnosed and should not have been enrolled in the trial to begin with.⁵ Misdiagnosis can cause harm and raise costs for members of vulnerable populations seeking life-altering care.

In his practice at NYU Langone, Snuderl recalls numerous cases when his team was able to stop a potentially ineffective or harmful treatment, or put a child on the right clinical trial.

"If you're a cancer patient, you're going to say, 'Okay, who's the best neurosurgeon, who is the best oncologist?"" he says. "Patients don't look for the best pathologist. Most patients assume that their diagnosis is correct. I've seen patients that had a metastatic lung cancer or metastatic melanoma and they thought it was a brain tumor, and vice versa. You name an error, I've seen it."

Clinical pioneers in methylation profiling and classification

When Snuderl became director of the lab in 2017, he was able to design the portfolio of molecular tests that Perlmutter Cancer Center would use. He knew that DNA methylation profiling would have the highest impact for CNS cancer patients. He counts himself lucky to have been able to work with the DKFZ from the early days of the discovery of methylation profiling.

Since Snuderl had so many samples dating back to 2014, and an established relationship with the New York State Department of Health (NYSDOH), NYU Langone Health pursued clinical validation and NYSDOH approval

For Research Use Only. Not for use in diagnostic procedures.

© 2025 Illumina, Inc. All rights reserved. All trademarks are the property of Illumina, Inc. or their respective owners. For specific trademark information, see www.illumina.com/company/legal.html.

^{2.} dkfz.de/en/index.html

^{3.} nature.com/articles/nature26000

^{4.} academic.oup.com/noa/article/5/1/vdad076/7207530

^{5.} ascopubs.org/doi/10.1200/JCO.2017.76.4720

illumina® NEWS CENTER

of this new molecular assay, coupled with an AI algorithm and an extensive database. It was an extremely rigorous process, because it was a new kind of test: Methylation requires working with multidimensional data, the results are not just positive or negative, and the assay uses machine learning to issue a probability score for a diagnosis. In 2019, this was completely new to regulatory authorities, so it was a tremendous achievement for NYU Langone Health to become the first CLIA-certified lab in the US to receive state approval from NYSDOH for whole-genome DNA methylation for the diagnosis and classification of brain tumors.⁶

The Heidelberg Brain Tumour Classifier crossed an even bigger milestone in 2024, when the American Medical Association approved a Current Procedural Terminology (CPT) code for it, enabling any lab in the US to be reimbursed for using the technology. Snuderl believes that this approval is a huge win for patient access, and a recognition that the technology is becoming standard of care for CNS cancer diagnosis.

Before the CPT code was approved, methylation classification was rarely covered by medical insurance and labs had to assume all of the costs. NYU Langone Health relied on funding from the Friedberg Charitable Foundation, Gray Family Foundation, Sohn Conference Foundation, Molly Markoff Foundation, and Making Headway Foundation to develop and administer thousands of tests.

"We never wanted this to be a boutique test that can be only done at NYU Langone Health," Snuderl says. In order to become standard of care, the test had to be analytically and clinically validated and incorporated into medical guidelines. "I'm very passionate about the inequalities in health care, and the worst thing you can do is restrict certain procedures only to the big institutions that have sufficient philanthropic support. Because then everybody else will not have access to the best care, and that's just not fair."

Methylation first

Snuderl admits that for many of these tumor types, it is possible to arrive at the same diagnosis through a combination of other methods—but that takes more tissue, time, and money. "The weeks and dollars add up really quickly. The beauty of DNA methylation profiling is that you can do it as a first test, and it tells you which category this tumor falls in." From there, clinicians can

6. nyulangone.org/news/first-molecular-test-us-better-detect-brain-tumorsnow-available-patients

7. thepathologist.com/subspecialties/im-methylation-man

For Research Use Only. Not for use in diagnostic procedures.

© 2025 Illumina, Inc. All rights reserved. All trademarks are the property of Illumina, Inc. or their respective owners. For specific trademark information, see www.illumina.com/company/legal.html.

select the appropriate treatment, or conduct a followup test for certain mutations to see whether a targeted therapy might be in order. Plus, a handful of tumors in the WHO guidelines can currently be diagnosed using only DNA methylation. "So from that perspective, you could spend a lot of time, money, and tissue doing other multiple tests, and you could still be without the answer."

The assay is one of many tools a pathologist can use to interpret data, and it's highly reproducible. Snuderl says it also enables better prognosis—some tumors are more aggressive than others and require aggressive treatment. He believes we've only just scratched the surface of understanding the implications this technology could hold for prognosis, but he hopes that with time, it could lead to drugs that target specific methylation patterns, and that these patterns will essentially act as predictive biomarkers.

"Despite all the advances in precision medicine, and despite the fact that, for example, the most common brain tumor, glioblastoma, is the most sequenced tumor in the human body, there hasn't been any progress in targeted therapy for brain tumors in almost two decades."

—Dr. Matija Snuderl, NYU Langone Health

Who is Methylation Man?

If brain cancers are challenging for the medical community, they are even more difficult for patients and families to understand. Ever the enthusiast, Snuderl suggested the need for a superhero named Methylation Man. Illumina worked with him to bring the character to life in a series of six educational comics, the first of which was published on The Pathologist.⁷

Today Snuderl's department has successfully incorporated DNA methylation profiling and classification into some of the largest clinical trials in brain tumors. In the future, Snuderl hopes to expand the benefits of the technology to other cancers such as sarcomas, carcinomas, kidney, hematological malignancies, and even the notoriously difficult cancer of unknown primary.

Finally, his ultimate challenge will be incorporating DNA methylation profiling, together with DNA and RNA sequencing and emerging techniques such as 3D genomics to create a multifaceted view of cancer. This looks like a job for Methylation Man. ◆