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A Mathematical Tool for Predicting Progression of Dementia and Other Neurodegenerative Diseases

Contributing faculty: **Ashish Raj, PhD**

Understanding how neurological diseases interact with the brain's functional and structural connectivity networks has long challenged researchers in the neurosciences. Dementia, epilepsy, Parkinson's disease, autism, and schizophrenia are all examples of network diseases. But now mathematical models developed by Ashish Raj, PhD, an expert in algorithms, computer vision, and graph theory applications in medical imaging, has opened a new door for determining patterns of dementia vulnerability by using mathematical modeling.

"We hope to show that mathematical models operating on brain connectivity networks can explain almost all important macroscopic observations about the brain, whether in health or in disease," says Dr. Raj, Assistant Professor of Computer Science in Radiology and Co-Director of the Image Data Evaluation and Analytics Lab (IDEAL) in the Department of Radiology at Weill Cornell. "We expect that such models can capture how the brain functions as an ensemble of computational nodes connected in a complex but

manageable network. We have a very savvy group of computer scientists and applied mathematicians looking at brain disorders, trying to understand the brain as a network processor and how disease affects this network. There are not many places in the world that do this."

When Dr. Raj came to Weill Cornell in 2008, he put forth a hypothesis that graph theory provides a methodology for representing and analyzing neural networks, and he and his colleagues set about extracting brain networks using neuroimaging data from diffusion tensor imaging, functional MRI, and MRI brain morphometry. Their goal was to find network characteristics that distinguish healthy brains from pathological brains, not only for dementia but for a number of brain disorders. "Neuroscientists have been looking at patterns of dementia in terms of atrophy patterns for a long time but have been unable to identify a unifying model that would basically capture those patterns," notes Dr. Raj.

Mathematical Modeling, continued on page 3

Dr. Jeffrey Lieberman to Begin Role as President of American Psychiatric Association in May 2013

Jeffrey A. Lieberman, MD, the Lawrence C. Kolb Professor and Chairman of Psychiatry at Columbia University College of Physicians and Surgeons and Director of the New York State Psychiatric Institute, will begin his term as the next President of the American Psychiatric Association (APA) in May 2013, having served as President-elect since being chosen by the APA in March 2012.

As president of the APA, Dr. Lieberman plans to actively

address urgent priorities in the field, including influencing healthcare legislation and policies on access to and funding for mental health care, increasing funding for clinically relevant psychiatric research, and supporting graduate medical training in psychiatry.

Throughout his 25-year career as a physician and as a scientist, Dr. Lieberman, who also holds the Lieber Chair for Schizophrenia Research in the Department

Dr. Jeffrey Lieberman, continued on page 2



Dr. Jeffrey A. Lieberman

Investigating a Breakthrough Treatment for Young Patients With Diffuse Intrinsic Pontine Glioma

Contributing faculty: **Mark M. Souweidane, MD**

In May 2012, Mark M. Souweidane, MD, Vice Chair of Neurological Surgery, and Director of Pediatric Neurological Surgery at NewYork-Presbyterian/Weill Cornell, embarked on a Phase I study for diffuse intrinsic pontine glioma (DIPG) – a very rare, incurable brain stem tumor. For Dr. Souweidane and the young patients he seeks to save, the start of the clinical trial is an historic occasion – one that comes after more than a decade of preparation through basic science and pre-clinical investigations.

“We have been paving the path to capitalize on two very basic concepts,” says Dr. Souweidane, who is also Professor of Neurological Surgery at Weill Cornell. “One is direct delivery of an anti-cancer therapeutic agent into the tumor, bypassing the blood-brain barrier. The second is that we are using a targeted molecule which specifically seeks out and looks for tumor cells in a jumble of other important cells in the brain stem itself. This has rarely been done and never in a systematic fashion with this molecule exclusively for this disease.”

There are about 200 new cases of DIPG diagnosed each year, usually in children under the age of 10, with survival time measured in months with no significant increase in survival rates over the past three decades. A pontine glioma occurs in a most delicate area of the brain stem (the “pons”), which controls many critical functions, including breathing. Its location, infiltrating pattern, and ill-defined borders mean a pontine tumor cannot be safely removed through surgery. Chemotherapy is frequently ineffective, since anti-cancer drugs cannot cross the blood-brain barrier and reach the tumor. Radiation is the most common treatment, but unfortunately the benefit is only temporary and does not provide a cure.

In the FDA-approved clinical trial, Dr. Souweidane is using convection-enhanced delivery (CED) to introduce a tumor-fighting agent called 124I-8H9 directly to the site of the glioma through a surgically placed infusion cannula. This enables the therapy to bypass the blood-brain barrier that prevents most drugs from



Dr. Mark M. Souweidane

reaching these deadly brain stem cancers. Injecting a targeted radio-immunotherapeutic drug directly into the tumor avoids intruding on delicate brain stem tissue and eliminates the need for medicine to cross the blood-brain barrier. “Importantly,” says Dr. Souweidane, “by placing the agent outside the blood vessels and directly into the tumor, we can reduce toxicity to the rest of the body while maximizing the attack on the tumor itself.”

The agent consists of the 8H9 antibody, which is produced by mice and has been shown to attack many kinds of tumors, combined with the radioactive substance 124I. In studies on other kinds of cancer, 124I-8H9 has delivered a one-two punch, with 8H9 binding

to the tumor and 124I killing the cancer cells with radiation. The procedure has been tested safely in animals, but this clinical trial is the first time CED has been used to administer 124I-8H9 into a human brain.

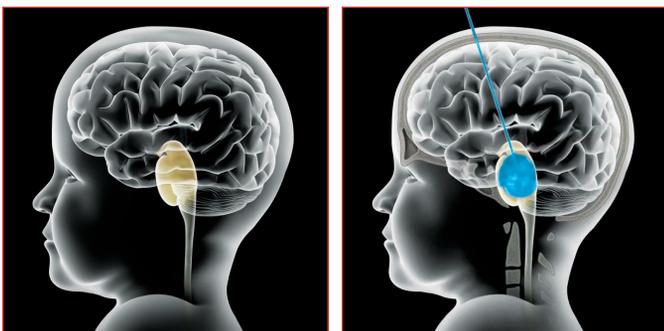
Initial patients have been treated with a small dose of 124I-8H9 and monitored for side effects. New patients are treated with increasing doses as Dr. Souweidane monitors the safety and effectiveness of each dosage. The study will enroll and monitor a minimum of 12 DIPG patients between the ages of three and 21 over the next two years.

The early results of the novel surgical technique are extremely promising from the standpoint of tolerability with the surgical impact of approaching a very complicated and deep-seated tumor. Says Dr. Souweidane, “This trial is about renewed hope and the potential to create a whole new paradigm in brain tumor treatment.”

Dr. Jeffrey Lieberman, continued from cover

of Psychiatry at Columbia, has pursued research on the neurobiology, pharmacology, and treatment of schizophrenia and related psychotic disorders. He has played a pioneering role in demonstrating the importance of early detection and intervention for psychotic disorders, and his work has advanced the understanding of the mechanisms of action and effectiveness of antipsychotic drugs. Dr. Lieberman has also served as principal investigator of the Clinical Antipsychotic Trials of Intervention Effectiveness Research Program (CATIE), the largest study ever sponsored by the National Institute of Mental Health.

Reflecting on his new role, Dr. Lieberman, who is also a Distinguished Life Fellow of the APA, notes, “The scientific foundations and the quality of psychiatric care are better now than at any time in human history and with the potential to improve rapidly. However, unless psychiatric services and mental health care are adequately supported, both the burden of suffering and the costs of untreated mental illness will continue to rise. There is no health without mental health.”



With convection-enhanced delivery, the therapeutic agent 124I-8H9 is delivered via a surgically inserted cannula into the brain stem. *Courtesy Thom Graves Media.*

Mathematical Modeling, continued from cover

The Network Diffusion Model: A New Way of Looking at Neurological Disease Patterns

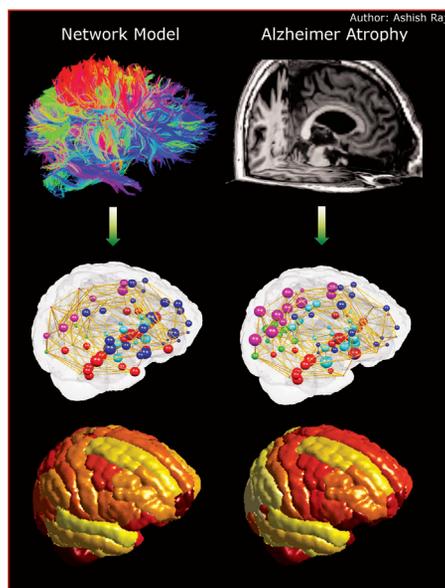
When talking about dementia with Norman Relkin, PhD, MD, Director of the Cornell Memory Disorders Program, and other neurologists, it became clear to Dr. Raj that a network approach was essential in capturing disease patterns. “The focus was on how dementia moves around as a kind of misfolded protein going from neuron to neuron. It struck me that any reasonable model that would predict a disease pattern would have to deal with the connectivity network and that very simple models of the network should give rise to the right patterns.”

This, indeed, turned out to be the case. In his study, funded by the National Institutes of Health and published in the March 22 issue of *Neuron*, Dr. Raj was able to match patterns from the diffusion model, which traced protein dispersal in a healthy brain, to the patterns of brain atrophy observed in patients with either Alzheimer’s disease or fronto-temporal dementia. This degeneration was measured using MRI and other tools that could quantify the amount of brain volume loss experienced in each region of the patient’s brain. “Our study demonstrates that such a spreading

Dr. Raj’s group was one of the first to apply brain-specific and disease-specific mathematical models involving brain connectivity networks and validate the idea that dementia is caused by proteins that spread through the brain along networks of neurons.

mechanism leads directly to the observed patterns of atrophy one sees in various dementias,” says Dr. Raj. “While the classic patterns of dementia are well known, this is the first model to relate brain network properties to the patterns and explain them in a deterministic and predictive manner.”

According to Dr. Raj, the mathematical model could be used to predict where and approximately when an individual patient’s brain will suffer from the spread of “prion-like” toxic proteins – a process that underlies all forms of dementia. Dr. Raj calls his model of transneuronal spread of misfolded proteins simple, mimicking the same process by which any gas diffuses in air, except that in the case of dementias, the



Patterns of dementia are known to fall into dissociated but dispersed brain networks, suggesting that the disease is transmitted along neuronal pathways rather than by proximity. Prevalence rates predicted by the model developed by Dr. Ashish Raj strongly agree with published data. This work has many important implications, including dimensionality reduction, differential diagnosis, and especially prediction of future atrophy using baseline MRI morphometrics.

diffusion process occurs along connected neural fiber tracts in the brain. The model identifies the neural sub-networks into which misfolded proteins will collect

before moving on to other brain areas that are connected by networks of neurons. In the process, the proteins alter normal functioning of all brain areas they visit.

Interestingly, the model makes no prior assumptions about selective neuronal vulnerabilities or protein-specific factors and yet it is able to predict atrophy patterns. “For whatever reason, in certain parts of the brain proteins fail to fold into their normal configuration, but once that occurs, the model we devised suggests that the degenerative process is taken over simply by network dynamics and the future of the atrophy pattern can be completely determined by the connectivity network in the brain,” says Dr. Raj. “Think of it as

a weather radar system, which shows you a video of weather patterns in your area over the next 48 hours. Our model, when applied to the baseline MRI scan of an individual brain, can similarly produce a future map of degeneration in that person over the next few years or decades.”

Dr. Raj’s group was one of the first to apply brain-specific and disease-specific mathematical models involving brain connectivity networks and validate the idea that dementia is caused by proteins that spread through the brain along networks of neurons. The significant finding provides the first independent validation of proteopathy transmission and raises the intriguing possibility that various dementias are different modes of the same proteopathic mechanism. Their work was awarded a EUREKA R01 grant from the National Institutes of Health and was featured in commentaries in *Nature Reviews Neuroscience*, *Nature Reviews Neurology*, *Neurology Today*, and *Science Daily*.

A Tool for Neurologists

Dr. Raj’s findings could help patients and their families confirm a diagnosis of dementia and prepare in advance for cognitive declines over time. He would like to be able to provide neurologists with a video of progression based on their patients’ MRI data. “This could allow neurologists to predict what the patient’s neuroanatomic and associated cognitive state will be at any given point going forward. They could tell whether and when the patient will develop speech impediments, memory loss, behavioral peculiarities, and so on,” says Dr. Raj. “I feel that patients who have incipient Alzheimer’s would probably benefit from knowing exactly what’s in store, enabling them to make informed choices regarding their lifestyle, therapeutic interventions, and plans for the future.”

Because the model is so simple, Dr. Raj believes it could be applicable to any number of neurological disorders. “We also expect to be able to apply this to epilepsy and perhaps autism, but it may also be useful in stroke where you have a focal point of damage,” he says. “For example, in patients who suffer isolated strokes in the cortex, we could obtain brain scans and then use the model to see if we can predict functional recovery.”

Mathematical Modeling, continued on page 4

Meeting the Challenges of Brain Cancer Head-On

Contributing faculty: **Andrew B. Lassman, MD**

“For decades, if not centuries, brain tumors were illnesses with no treatment, devastating neurologic consequences, and rapid mortality,” says Andrew B. Lassman, MD, who joined the Department of Neurology at NewYork-Presbyterian/Columbia a year ago to lead its new Division of Neuro-Oncology. “While it is true that some of these diseases behave aggressively, there are patients who are long-term survivors. Part of our challenge is to understand the disease better in order to make everyone a long-term survivor and to transform these diseases into chronic, manageable conditions, akin to diabetes or hypertension.”

Dr. Lassman has taken on this challenge with considerable expertise, robust plans, and great expectations. “Even a very small tumor that is strategically located can have devastating neurological consequences, as can the treatment,” says Dr. Lassman. “The combined fields of neurology, neurosurgery, and oncology provide a focus for the treatment of these difficult conditions.”

Under Dr. Lassman’s direction, the Neuro-Oncology Division centers on primary brain tumors – gliomas, meningiomas, and primary central nervous system lymphoma – and, just as importantly, on central nervous system metastases (brain and leptomeningeal) from other cancers such as melanoma, lung, breast, and kidney. He and his colleagues interface with laboratory investigators at the Herbert Irving Comprehensive Cancer Center and collaborate on clinical and research activities with many other services, including other divisions in neurology, neurological surgery, radiation oncology, pathology and cell biology, medical oncology, pediatric oncology, and psychiatry.

An internationally recognized expert in translational research on gliomas and central nervous system metastases, Dr. Lassman is applying his expertise in designing and leading clinical trials for new drugs, novel drug combinations, and regimens combining chemotherapy and radiation therapy to developing a major clinical trial program at Columbia. His goal is to have 10 to 15 Phase I through Phase III clinical trials ongoing – both investigator-initiated, single-site studies and participation in multi-institutional studies. Dr. Lassman also serves NewYork-Presbyterian/Columbia as the Medical Director of the Cancer Center’s Clinical Research Management Office, responsible for executing clinical trials



Dr. Andrew B. Lassman

across the spectrum of human malignancies, not exclusive to those of the brain.

Dr. Lassman’s expertise in brain tumors is informed by a longstanding interest in molecular biology and its potential clinical applications. “Brain tumors, such as glioblastomas, are very complex at the molecular level and manifest themselves as at least three distinct diseases,” says Dr. Lassman. “With this understanding, we have created a tumor bank containing the molecular profile of each tumor using cutting-edge biomarkers so that we can develop individualized therapies that target a tumor’s specific molecular signature. The ultimate goal is to extend survival in a dramatic way.”

In addition, plans are underway to establish a neuro-oncology fellowship training program to be accredited by the United Council for Neurologic Subspecialties. As Fellowship Director at Memorial Sloan-Kettering Cancer Center for nearly five years, and twice awarded the annual teaching award there, Dr. Lassman is well aware of the components of a successful education program.

Following undergraduate and graduate work in molecular biology at Yale University, Dr. Lassman received his MD at Columbia University College of Physicians and Surgeons, and completed his residency at the Neurological Institute of NewYork-Presbyterian/Columbia. He then pursued a fellowship in neuro-oncology at Memorial Sloan-Kettering Cancer Center. Before returning to Columbia, he served on the faculty of Memorial for eight years, earning several honors along the way, including the American Academy of Neurology Preuss Award in Neuro-Oncology and the Memorial Sloan-Kettering Cancer Center Boyer Clinical Research Award. He was also a member of the Memorial Sloan-Kettering Cancer Center Clinical Scholars Program. Currently, Dr. Lassman serves on the editorial board of the *Journal of Neuro-Oncology* and is the neuro-oncology representative to the United Council for Neurologic Subspecialties Board.

“As a former trainee at Columbia, I was intrigued by the opportunity to return to build this program,” adds Dr. Lassman. “I have maintained many personal and professional relationships with faculty who I interacted with during my training and shared patients with them in the ensuing years. So to come back to Columbia felt like coming back home.”

Mathematical Modeling continued from page 3

The Next Challenge: Predicting Future Atrophy

Dr. Raj and his colleagues are now focusing on being able to predict future atrophy and cognitive decline – one of the foremost goals of neuroimaging research in dementia. To accomplish this, they are utilizing data compiled by the NIH-supported Alzheimer’s Disease Neuroimaging Initiative – a large ongoing

study that seeks to define changes in brain structure and function as people transition from normal cognitive aging to mild cognitive impairment to Alzheimer’s dementia. “We plan to use their data to corroborate that the atrophy patterns predicted by our methods match their findings to date,” says Dr. Raj. “At some point we will gain the ability to target and improve the health of specific brain

regions and nerve fiber tracts. A good prediction of a subject’s future anatomic state can help identify promising target regions for this intervention.”

Reference Article

Raj A, Kuceyeski A, Weiner M. A network diffusion model of disease progression in dementia. *Neuron*. 2012 Mar 2;73(6):1204-15.

Columbia-Suicide Severity Rating Scale Can Predict Suicide Attempt

Contributing faculty: **Kelly L. Posner, PhD**

A landmark study, published in the December 2011 issue of *The American Journal of Psychiatry*, has shown that the Columbia-Suicide Severity Rating Scale (C-SSRS) is not only important in standardizing the assessment of suicidal behavior, it can also be used to help predict an attempt.

“By using this instrument we actually may be able to make a dent in the rates of suicide that have existed in our population and have remained constant over time. This would be an enormous achievement in terms of public health care and preventing loss of life,” says Jeffrey A. Lieberman, MD, Chairman of Psychiatry at Columbia and Director of the New York State Psychiatric Institute.

“Suicide is one of the world’s great public health epidemics and a leading cause of death across all ages,” notes lead author Kelly L. Posner, PhD, Director of the Center for Suicide Risk Assessment and Associate Clinical Professor of Medical Psychology (in Psychiatry) at Columbia University College of Physicians and Surgeons. “Prevention efforts depend upon appropriate screening and identification.”

The Columbia-Suicide Severity Rating Scale (C-SSRS) was developed in the context of an NIMH trial of adolescent suicide attempters. Subsequently, when the FDA needed a standard tool for classifying adverse events in clinical trials, it approached researchers from Columbia Psychiatry, which led to the development of a retrospective counterpart to the C-SSRS (C-CASA). In 2002, the Institute of Medicine released a consensus report calling for the reduction of suicide as a national imperative, underscoring the lack of uniform definitions in suicide assessment as the major impediment to suicide prevention. In 2011, the Centers for Disease Control and Prevention adopted the Columbia definitions of suicidal behaviors in its publication, *Self-Directed Violence Surveillance: Uniform Definitions and Recommended Data Elements*.

“Before C-SSRS, researchers and clinicians had no diagnostic screening guidelines to define suicide risk,” notes Dr. Posner. “In the past, a patient would only get asked about a suicide attempt – but if you only ask about that you miss the person who bought the gun yesterday or put the noose around their neck and changed their mind.

SUICIDAL IDEATION		Lifetime: Time He/She Felt Most Suicidal		Past 1 month	
Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes”, ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.					
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, describe:					
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one’s life/commit suicide (e.g., “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, describe:					
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, “I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it.” <i>Have you been thinking about how you might do this?</i>		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, describe:					
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to “I have the thoughts but I definitely will not do anything about them.” <i>Have you had these thoughts and had some intention of acting on them?</i>		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, describe:					
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, describe:					
INTENSITY OF IDEATION					

The two types of suicidal ideation on the Columbia-Suicide Severity Rating Scale that indicate one’s intent to act on suicidal thoughts and suggest the need for clinical intervention.

These are things you can’t afford to miss. So asking about preparatory behavior, interrupted suicide attempts, and aborted suicide attempts is critically important in predicting who may go on to end their lives.”

The Columbia-Suicide Severity Rating Scale consists of a series of questions that determine a person’s suicidal thoughts and behavior. It can be administered in minutes by first responders, peer counselors, clergy, and personnel in emergency rooms, prisons, clinical settings, schools, primary care offices, and military departments. A mental health background is not required for administration. If patients reach a certain threshold on the scale they can be referred for further evaluation and possible intervention. The scale, which is available in over 100 languages, has been used extensively in numerous states, across military departments, and worldwide in research and clinical practice. The C-SSRS tracks changes in a person’s suicidal thinking and behavior over time to help determine who is most at risk.

In the recent study, Dr. Posner and her colleagues sought to determine the scale’s validity, reliability, and internal consistency of measures of suicidal ideation and behavior as compared to similar instruments. Funded by the NIH and the American Foundation for Suicide Prevention, the researchers administered the C-SSRS in three sites to teens who had attempted suicide, adults presenting to

emergency rooms with psychiatric problems, and to adolescents in a medication efficacy trial.

They found that their scale could reliably predict potential suicidal behavior in those who had previously attempted suicide. It also was able to determine clinically meaningful points at which a person may be at an even greater risk for subsequent suicidal behavior, something that other scales have been unable to consistently determine. According to the researchers, this type of predictive information can more precisely identify those at imminent risk and avoid unnecessary referrals for those who are not, and opens the door for precision in intervention and prevention of suicide among a wide spectrum of populations. Reduction in unnecessary clinical interventions allows for the redirection of scarce resources in the health care system, enabling improved care delivery and service utilization.

This was the first major study to establish the effectiveness of the C-SSRS in identifying those most at risk for suicidal behavior based on lifetime worst-point suicidal ideation. Subsequent studies have shown that other behaviors in addition to previous suicide attempts – such as interrupted or aborted attempts – may be used as predictors of future suicide attempts. “This tool specifies parameters for triggering referrals to mental health professionals,” says Dr. Posner, “and clinicians now have a real scientific footing on which to base treatment interventions.”

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