# DIAGNOSIS HORACE MANN'S MEDICAL JOURNAL



# Letter from the Editor

Dear Reader,

I am excited to publish this year's first issue of Diagnosis, Horace Mann's premier medical journal! This issue covers a vast array of topics from generative AI in healthcare to the gender gap in medicine and so much more. I hope you enjoy it!

I would like to extend special thanks to everyone who has dedicated their time and effort to make Diagnosis possible: all our writers and editors, for their amazing articles, and our faculty advisor, Mr. Epstein, for his constant support, guidance, and advice.

Best,

Stephanie Lee

Stephanie Lee Editor-in-Chief Volume IV, Issue I

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## The Gender Gap in Medicine: A Historical and Modern Analysis Michelle Grinberg

lthough doctors no longer suggest the surgical removal of a woman's uterus as an appropriate treatment for any slight defiance of their husband, inequities and gender myths are still present within the realm of medicine today. Gender biases are intrinsically woven into society, and socially constructed gender norms have led to the unequal treatment of women within the medical field. As a result, women must recognize the differences in the manifestation of various illnesses in order to advocate for themselves effectively. Since women have historically been excluded from clinical trials, the signs used to diagnose certain illnesses align with the male, not female, symptoms of the illness. This phenomenon is particularly notable when referencing ADHD or heart conditions, which can look vastly different for both men and women.

The differentiation between female and male anatomy and its significance in both social and scientific realms was first studied in Ancient Greece. In the third century BC, Aristotle described female anatomy as the inverse of the male body, with the sexual organs being "turn'd outside in." This anatomical difference reinforced the belief that the sole purpose of women in life is to bear children and evolved into the perception that women are inferior to men. As a result, gendered medical myths surrounding behavior and

roles were constructed and have significantly shaped the medical industry. This phenomenon is evident in understanding women's pain. Women are significantly more likely to be given minor tranquilizers or antidepressants rather than anesthetic or analgesic pain medication. Women are also less likely to be referred to another doctor for further treatment. Additionally, women's pain and other physical symptoms are often viewed as an emotional reaction with a psychological cause, rather than a physical ailment. Therefore, women who suffer from chronic pain illnesses are often not taken seriously.

This disregard for women's pain stems from the historical idea that women's supposedly excessive or unreasonable emotions have a profound influence on their bodies, a theory known as hysteria. While psychological conditions can sometimes manifest as physical ailments, this phenomenon is completely independent of gender. Still, until the 1980s, hysteria was a formal psychological disorder that could be found in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders. Before its categorization as a psychiatric condition, it was considered a physical illness in 1880, and even before that, Ancient Greeks and Egyptians wrote about hysteria. They considered hysteria a sex-selective disorder that could only impact women and stemmed from the uterus. Doctors blamed the uterus for causing almost all health issues in women. In Ancient Greece, it was believed that the uterus migrates around the female body and places pressure on other organs. Physicians called this phenomenon "hysterical suffocation," and used it to explain anything from a fever to depression. While doctors found female reproductive organs detrimental to health, they believed that male semen had healing powers, which is telling of the extent to which gender bias impacted scientific thought.

Hysteria was considered an exclusively female medical condition until the 1880s, when scientist and professor Jean-Martin Charcot redefined it as a neurological disorder rather than a gynecological one. One of his students was Sigmund Freud, a neurologist who published several studies on female hysteria throughout his career. Freud believed that the cause of this illness was not a woman's uterus but rather a psychological scar resulting from women's inability to come to terms with a lack of male genitalia. From then on, scientists used Freud's definition of hysteria to explain absolutely anything that men found mysterious within the female body, from not behaving submissively to any variety of physical sickness.

Historical myths that seem ridiculous to any scientifically educated person today still impact the medical field. For example, it was once believed that women were too

high-strung to become educated and that their ovaries would grow inflamed if they read too much. According to Sex in Education; or, A Fair Chance for the Girls, published by the male scientist Dr. E.H. Clark in 1875, "higher education in women produces monstrous brains and puny bodies, abnormally active cerebration and abnormally weak digestion, flowing thought and constipated bowels." This direct excerpt was subsequently cited in several medical journals. Furthermore, clinical trials have cited women's fluctuating hormones as a reason to exclude them. Since the 1960s, female health advocates have fought against the disparities in the treatment of males compared to females in the healthcare industry, and have made incredible contributions to the field. Notably, they have made contraceptive medication and hormone treatments safer for women.

Women revolutionizing the medical field in terms of accessibility is a relatively new phenomenon. While women have been contributing to the medical field for several millennia, they were barred from entry into medical schools until the late 19th century. Those who could afford medical care were treated by men, but often those who couldn't relied on "wise women" or healers who employed holistic remedies for centuries. However, the church strongly opposed this practice, labeling the women as witches and thus discrediting women in the medical field for centuries to come.

In 1991, Bernadine Healy published an article discussing the differences in heart attack symptoms in women versus men. Her article, "The Yentl Syndrome," showed that women often had worse outcomes after experiencing a heart attack than their male counterparts. Heart attacks manifest differently in women, and the misinterpretation of their symptoms often leads to potentially life-threatening misdiagnoses. A new study highlights that while both men and women tend to experience chest pain before a heart attack, women also face a plethora of other symptoms, including nausea and back pain. The range of in-hospital deaths for heart attacks in women is 2.3%-3.3%, as opposed to 1.2%-2.0% in men. The same study asked patients if they had visited a doctor within the week preceding their heart attack, and found that the doctors failed to identify cardiovascular issues in 53% of women, compared to 37% of men.

Another disparity in diagnosis and symptoms that has recently received recognition is Attention Hyperactivity Deficit Disorder (ADHD). Currently, in the United States, 12.9% of men and boys have been diagnosed with ADHD compared to only 5.6% of women and girls. Many doctors and mental health specialists believe that the disorder is not actually more prevalent among men, but that women are often misdiagnosed. In schools, teachers are much more likely to refer boys for an ADHD evaluation than girls, even when they show the

same symptoms. This is incredibly harmful, as early treatment is essential to prevent the onset of puberty and consequent hormone secretion from exacerbating symptoms of this disorder. Women and men often have similar symptoms of ADHD, but express them differently. Women are less likely to display hyperactivity and impulsive actions but are more likely to be hyperactive internally, in the form of overthinking and negative self-talk. They often experience maladaptive daydreaming, forgetfulness, loss of focus, and anxiety while men are more likely to experience outward hyperactivity and disruptive behavior-more noticeable symptoms.

With the research that has been conducted in the past several decades, women's medicine has improved tremendously. While the healthcare system is not perfect in terms of its treatment of women, it has seen positive change. Doctors are aware of the differences in the manifestation of various illnesses across the gender spectrum and women are advocating for themselves more. Notably, scientists have made contraceptive pills and hormone treatments safer for women and continue to make advancements.



# The Human Connectome: Understanding How We Are Wired

he brain is made of over 100 billion cells called neurons. An axon, which is attached to a neuron, extends from one neuron to another and forms a connection between those neurons. When you observe where these axons begin, where they end, and the trajectory they take, you are essentially studying the human connectome. The connectome is a detailed map which shows how the cells of the brain are connected and how different parts of the brain work with each other. The connectome can be analyzed from an anatomical point of view, where you observe how regions of the brain are connected, and also from a functional point of view, where you observe how these connections are used to process information. Studies of the connectome have occurred at different scales and in different animals. For example, studies have been able to map the connectome of a nematode worm at the nano.

### Ann Karottu

or cellular, level, meaning the study mapped the synapses, or the points of connection between individual neurons in the worm's brain. Due to the amount of connections and neurons in the human brain, it would take thousands of years to map the human connectome at a nano level using current technology. However, studies like the Human Connectome Project (HCP) have been able to create maps of the human connectome on a macro level, meaning the maps demonstrated the connections between different regions of the brain rather than the connections between individual cellular synapses.

Much of the information we have today about the human connectome comes from the HCP. In 2009, researchers were awarded 40 million dollars at two research consortia, the WU-Minn HCP consortium which consists of Washington University in St. Louis, The University of Minnesota and Oxford Uni-

versity as well as the The Harvard/ MGH-UCAL Project which consists of Massachusetts General Hospital, Harvard University and the University of California Los Angeles. These researchers were challenged with mapping the human brain's connections in high resolution. This Project stemmed from the desire to accelerate advances in neuroimaging, especially since many advances in neuroscience were occurring at the time, including the discovery of new types of MRI such as diffusion tensor imaging (DTI). Scientists began to understand that maps of the brain that were previously accepted in the scientific community were outdated. These maps did little to aptly demonstrate the connections between parts of the brain. Scientists' understanding of brain anatomy was very limited at the time and various new regions of the brain were discovered as a result of the HCP.

As part of the project, 1,200 participants including pairs of twins



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and a pair of non-twin siblings were selected for the study. Studying identical twins allowed researchers to look at genetic influences on the brain, as the DNA of identical twins is the same. Studying fraternal twins gave researchers data on environmental influences because although their DNA is different, the environment that they grew up in is the same. Including a pair of nontwin siblings in the study allowed for further analysis on the genetic and environmental influences on brain function and structure. Each participant would undergo a variety of brain scans including different types of MRIs. These scans included DTIs which measure how water molecules behave in the brain. Because water molecules usually move along the length of groups of axons, DTIs allow researchers to see the connections between brain regions. Fiber tractography takes the data from DTIs and assesses the structures of the axons or nerve fibers in a 3D model.

The HCP was successful in not only mapping the human connectome at a macroscale, but also in making improvements to neuroimaging that were necessary for mapping the human connectome. The HCP inspired many other projects such as the Lifespan Connectome and Disease Connectome Project. The Brain Research through Advancing Innovative Neurotechnologies Initiative has funded many studies to further the research started in the HCP. The project also sparked many questions-scientists began to see the possibility mapping the human connectome on a nano level, for example. Scientists began to question how mapping the human connectome at the nano level could contribute to artificial intelligence. They questioned whether, by coding these connections into a program, you could create a program that functions like a human. Studying the human connectome through development can not only help us learn about brain development but also help us recognize the onset of diseases well before the symptoms become obvious. The field of connectomics allows us to visualize the differences in the communications of neurons for people with and without certain neurological disorders. With the help of machine learning technology, the study of connectomics could allow us to gauge the severity of symptoms by inputting patterns of dysfunction in the brain.

Connectomics has endless applications. For example, we could potentially pinpoint where exactly in the brain certain activities occur and stimulate those regions in order to heighten activity. Ultimately, mapping the human connectome will help us understand what makes us human and how we function with a greater depth. It will help us see the fine differences in each one of us, and see what makes each of us unique.

## Lecanemab: Newly Approved Drug for Alzheimer's Gabriela Faybishenko

lzheimer's disease is a devastating neurological disorder which affects over three million people in the US alone and has been known to be extremely intimidating in the world of medicine by medical professionals. When a patient is diagnosed with Alzheimer's, it is usually due to the high buildup of amyloid-beta peptides in their brain, which causes mild to severe memory loss and cognitive impairment. Those who are affected tend to slowly forget simple actions and valuable relationships. Researchers have made numerous hopeful attempts to cure what nobody has yet cured, but in the end, those attempts were unsuccessful. In July 2023, however, a new hope for the future of Alzheimer's therapy emerged. This so-called "hope" is sold under the name Leqembi, or Lecanemab, the first and only anti-amyloid drug approved by the FDA for the purpose of curing Alzheimer's.

In 2014, a Japanese pharmaceutical company, Eisai, strategically partnered with an American biotechnological company, Biogen, to create a drug that would help cure Alzheimer's. After months of work, Eisai and Biogen created a drug which uses monoclonal antibodies consisting of the humanized version of a mouse antibody (mAb158) to remove amyloid-beta peptides from the brain. Amyloid-betas are fragments of larger transmembrane proteins that accumulate to form the amyloid-beta plaques found in Gabriela Faybishenko

the brains of Alzheimer's patients. Lecanemab is an amyloid-directed antibody which is introduced via intravenous infusion (IV). Its purpose is to decelerate memory loss and cognitive function in patients with mild dementia.

By 2020, the IV Lecanemab clinical trials ended with unparalleled success in all three phases. The IV Lecanemab demonstrated impressive success rates, but Eisai and Biogen wanted to take their drug a step further by creating a subcutaneous version of it. The IV version of Lecanemab is more expensive to create and more time-consuming to be infused into a patient's body. The subcutaneous administration of the drug simply consists of a doctor injecting the Lecanemab into the skin of a patient. Subcutaneous administration is simply more efficient in our everyday world. In 2021, the FDA approved the launch of Phase l of subcutaneous Lecanemab. In Phase I, researchers tested the drug in healthy patients in order to understand the side effects of the drug. Over the course of several months, the safety and dosage were established using data collected from about 20-100 volunteers. The subcutaneous Lecanemab appeared to be safe, and in 2022, the FDA approved Phase II of the clinical trial. In Phase II, the researchers administered Lecanemab to 100-300 volunteers with Alzheimer's disease. They found that IV administration of Lecanemab had higher success rates than the subcutaneous version,

so the FDA accepted accelerated approval for IV Lecanemab in January 2023. In July 2023, IV Lecanemab was fully approved by the FDA as a new drug for Alzheimer's treatment. In short, the clinical trials demonstrated an unprecedented success rate in halting or decelerating the progression of Alzheimer's disease in patients. Patients who were unable to remember their loved ones or perform simple tasks were able to regain most of their independence after taking the drug.

Alzheimer's is a disease which affects millions yearly, but not everyone qualifies for a Lecanemab prescription. In order to qualify for Lecanemab, a patient must be experiencing symptoms of mild cognitive impairment due to Alzheimer's disease. In addition, the patient's brain must contain elevated levels of amyloid-beta peptides, detected through a spinal tap or PET scan, as Lecanemab is an amyloid-beta removal drug. Patients with a history of cancer, cardiovascular diseases, brain bleeds, or any neurological deficit unrelated to Alzheimer's that could contribute to cognitive impairment are also not eligible to take the drug. Genetic mutations are the main cause of amyloid-beta accumulation, which means Alzheimer's is mostly a genetic disease, but it is not necessarily limited to people with a family history of the disorder.

According to CBS News, the cost of the Lecanemab drug is about \$26,000 yearly. However, the institute for Clinical and Economic

Review (ICER) concluded that a more cost-effective price of the drug should be in the range of \$8,900 to \$21,500. Nevertheless, Eisai estimated that about 85% of the eligible early onset Alzherimers patients in the US are covered by Medicare. At Lecanemab's current price, about five percent of the 1.4 million US patients eligible for Alzheimer's disease treatment that targets amvloid-beta could be treated within five years without crossing the ICER budget of \$777 million per year. Subsequently, the ICER issued an alert which spread awareness of the high costs of this drug and the rapid increase of insurance costs.

One might wonder whether Lecanemab is too good to be true.

Similarly to most drugs, Lecanemab has several side effects. As an anti-amyloid drug, Lecanemab may cause amyloid-related abnormalities which include temporary swelling or bleeding in the brain. This drug might cause other potentially life-threatening symptoms such as dizziness, confusion, lightheadedness, chest tightness, and weakness. However, Lecanemab currently stands as the safest effective option for Alzheimer's treatment.

Although the creation of Lecanemab and several other drugs to cure Alzheimer's have gone public and have been FDA approved, Alzheimer's remains a mysterious and enigmatic disease that affects millions each year. The Lecanemab

drug is just one of the hundreds of other solutions created to treat Alzheimer's, but like the others, Lecenameb has not been proven to fully cure or undo all the effects of Alzheimer's. Because the causes of Alzheimer's are still unknown, there is not an Alzheimer's drug that completely reverses all the damage caused to everyday people by the disease. Since Lecanemab is one of the most successful Alzheimer's drugs created thus far, many institutions such as the New York Presbyterian, Duke Hospital, and other hospitals in the US have deemed this drug worthy of administering, and are now distributing Lecanemab to patients every day.



# Can Music be the Cure for Alzheimer's Disease?

Aanya Gupta

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**Derived** Very three seconds, someone in the world develops dementia—the loss of memory, language and thinking, and the ability to carry out simple daily tasks. Alzheimer's disease (AD), the most common form of dementia, is a progressive and debilitating neurodegenerative disorder. With the number of people with AD estimated to increase from 55 million in 2019 to 139 million in 2050, AD has been often called the biggest health challenge we face this century.

There is currently no cure for AD, and available treatments attempt to manage symptoms or slow the progression of the disease. Music therapy, such as active participation in music-making, listening to music, or reminiscing with music has been shown to reduce neuropsychiatric symptoms and improve cognitio. However, its use as a non-pharmacological intervention in AD, while popular as there are no side effects and it's cost-effective, is still considered only to be an adjunct to medication.

This may be about to change, as music may be the ingredient that unlocks memories and other cognitive capacities in AD patients.

#### **Musical Memory**

Memory as a cognitive process is generally categorized into episodic/ semantic, short-term/long-term, or implicit/explicit. Episodic memory such as housework, use of transport and management of money is crucial for daily living, and is affected early in AD. Thus, loss of memory in AD is a major contributor to functional disability.

Musical memory is the neural coding of musical experiences. While research has focused on the therapeutic benefits of music therapy, a very limited number of studies over the last 50 years have examined music's conceptual link with cognitive functions, primarily due to the non-availability of noninvasive tools to study the human brain in vivo.

Penfield and Perot (1963) were the first to identify the role of the temporal cortex in encoding musical memory. Subsequent research confirmed that musical memory seems to use multiple brain networks, and different types of musical-related memories appear to involve different brain regions. For example, when one recollects the lyrics of a song, it may involve memory networks which differ from when one recalls historical biographical events associated with a piece of music. Brain processes for semantic and episodic memory aspects of music differ.

We also know that memory for music can be severely damaged

while other memory functions remain mostly unimpaired, and conversely that musical memory can be found preserved in patients with vast lesions. This suggests that the network encoding musical memory is at least partially independent of other memory systems.

## The Anatomy of Alzheimer's Disease Progression

Three biomarkers are often used to track the progression of AD in the human cortex: grey matter atrophy, glucose hypometabolism, and the accumulation of amyloid beta protein in senile plaques. Exhibit B, C, and D display the 3-D renderings of the brain with the pictorial and graphical depiction of the biomarker levels for AD patients. Early degeneration in AD patients is found mainly in the temporal and parietal lobes and precuneus and other large neocortical areas. The primary sensory, motor, visual, and anterior cingulate cortices are spared till late stage.

The development of functional MRI employing pattern classification, provides the ability to investigate memory by determining the coding of information in distributed patterns, rather than analyzing brain activity.

## Connecting Musical Memory and Alzheimer's Disease

Musical memory is known to be well preserved in AD patients, at least until a late stage. Jacobsen et al. (2015) hypothesized that the late-degenerating brain structures in AD, namely the motor cortices, the anterior cingulate gyrus, and the orbitofrontal cortex, may play a crucial role in preserving long-known musical memory in AD patients.

They used different musical stimuli and examined the brain net-

work mediating the effect and coding of each music stimulus using fMRI. Unknown music was used to reflect first time music exposure and recently known music was used to investigate the exposure effect of familiar music. Finally, the effect of long-known music was examined. On examining the brain areas that encode each type of musical experience, they were able to identify the region of the brain where long-known musical memory resides, which was distinct from the other two stimuli. Exhibit A shows this as the region of interest.



(A) Musical memory region of interest (ROI) in red on a 3-D brain render. Alzheimer's biomarker maps and biomarker levels for various regions, with ROI biomarker level shown in red: (B) Cortical atrophy biomarker, (C) Hypometabolism biomarker, (D) Beta-amyloid burden biomarker. (Jacobsen et al., 2015).

Further, they found practically no overlap between the pattern for cortical degeneration and hypometabolism in AD with the region of interest, which evidenced the lowest level of atrophy and hypometabolism in the whole brain. Beta-amyloid deposition was found not to be significantly different in the region of interest compared to the rest of the brain, which is consistent with the fact that this is an early-stage biomarker. This provides the first concrete and objective evidence confirming why musical memory is well preserved in AD patients.

### **Future Possibilities**

If our brain has a mechanism to preserve long-known musical memory, even in the presence of AD, and we know that listening to an old song can bring back memories of historical experiences with people we love, connecting these two opens possibilities for using music to enhance memory in AD patients. Neurodegenerative research continues to search for comprehensive psychopathological models which can help us understand and anticipate the effects of AD. Music as a whole-brain experience, which is intimately linked with our emotional history, may well be that model. The brain mechanisms that support the preservation of long-known music memory may well be the key to understanding and illuminating the specific neural architecture that underlies AD. Music, which has been a language not just for humans, but for all animal species through time, may well transition in our thinking to be not just a therapy for symptomatic relief, but a cure for our most complex neurodegenerative challenges

# The Science Behind Celiac: Will My Gluten-Free Friend Ever Be Able to Enjoy Pizza Again?

Sophie Teitelbaum

hat is celiac disease, you might ask? Affecting one in every hundred people, celiac disease is an autoimmune disorder, meaning one's own immune system attacks their organs and tissues. Contrary to common belief, celiac disease does not just mean gluten-free. A main symptom of celiac is inflammation triggered by eating gluten, which damages the villi or the intestinal lining and, therefore, makes absorbing nutrients difficult. This leads to food intolerance, com-

monly labeled "gluten-free," and a greater chance of acquiring other autoimmune disorders. People with celiac disease are more likely to get gastrointestinal cancers, psoriasis and other skin conditions, iron and other vitamin deficiencies, as well as growth and development delays and insufficiencies. Other neurological problems are also associated with celiac such as migraines and ADHD.

One of the most common attributes of celiac is being gluten-free. Since gluten causes atrophy, or the deterioration of the intestine lining and the damage to the villi, one becomes sensitive to foods such as wheat, barley, oats, rye, and malt, all of which contain gluten. In order for the villi to grow back, one must follow a gluten-free diet as a preventative treatment for flare-ups of celiac. As of now, there is nothing that can strengthen the villi besides omitting glutenous foods from one's diet. However, as the science of medicine and technology changes and advances, so does the chance of there being a possible cure for celiac in the future.





The Future of Celiac: Narrowing Down the Cure

A main reason why finding solutions besides the gluten-free diet is difficult is because scientists struggle to pinpoint specific molecules, tissues, genes, and other specific processes affected by this disease. However, as of August 2023, the Celiac Disease Foundation discovered new genes highly associated with the disease. This trial acquired data by testing both celiac patients and people who did not have celiac. AI was used to analyze the data and found certain genes in celiac patients that could be linked back to their immune system response. These genes were MR1, CCL25, and TNFSF13B. The patients were then tested for how many of these genes were present with an immune genes score (IG), which helps determine how susceptible the patient is to celiac. The trial concluded that those with celiac have a higher immune response and more HIG genes, or "genes highly associated with the

disease." Additionally, the scientists found a new, more efficient way to diagnose celiac by testing for HIG gene levels. From this experiment, further research can be conducted on treatment options.

However, these genes are not the only leads we have on this matter, and scientists continue to take different approaches to treat this autoimmune disease. Preventative drugs, or drugs that limit the risk of gluten contamination, include Latiglutenase, which is consumed with meals and contains enzymes that break down gluten in the stomach and ensure that no gluten enters the digestive system. Similarly, Larazotiden, another preventative drug, protects the lining from any gluten that would enter through the gastrointestinal tract. The PRG-015 drug focuses on regulating the immune system, suppressing the inflammatory response to gluten. Similarly, KAN-10, although still in the early stages of testing, has been shown to teach a celiac patient's body and immune system to tolerate gluten. This would allow those with celiac to enjoy gluten without any harm.

While scientists continue to research, all of the known preventative drugs for celiac are still undergoing testing and will not be available for at least another decade or so. However, the rate at which these drugs are being discovered is rapidly increasing as we now have artificial intelligence and new information regarding gene types that give us more insight into treatment for this disorder. Additionally, the movement toward the cure for celiac heavily relies on patients who are eager to help the science and research of this cause. Foundations such as ICureCealiac hold clinical trials that accelerate the probability of a cure. As celiac disease unfolds before researchers, new information is learned every day that points us towards our goal of finding a treatment that removes the gluten-free diet as a necessity for those with celiac.



# **Generative AI in Healthcare** Sarah Korff

enerative Artificial Intelligence (GAI) has the potential to drastically revolutionize the healthcare industry as we know it. GAI generates new content, such as images, music, and text, through two neural networks: a generator, which creates the content, and a discriminator, which evaluates the quality of the content. GAI is modeled after the human brain, with complex neural networks - a system of interconnected artificial neurons that find hidden patterns and correlations. GAI's neural networks allow it to be capable of machine learning by altering, adding, or losing connections as data is interpreted. Input data passes through several layers of these artificial neurons, called nodes, that process the information before new content is output by the final layer. According to a recent Forbes article, GAI technology has the potential to save the US medical sector as much as \$200 billion in annual expenses. Additionally, Accenture reports that GAI will maximize the working hours of healthcare providers, en-

hancing their efficiency by 40%. By expediting and facilitating processes such as drug development, medical training, documentation, and clinical diagnosis, GAI will ameliorate the world of medicine.

GAI technology is currently being applied in a wide variety of areas. GAI accelerates the speed of drug development and trials, which is otherwise a time-consuming and costly endeavor. Drugs can take decades to develop and approve, and this process costs one to two billion dollars on average, according to the Congressional Budget Office. GAI may be the solution; GAI can create virtual models of compounds to be tested in a computer simulation, saving time, resources, and money. Given a dataset of chemical structures, GAI can generate molecules with the necessary qualities to later be evaluated by researchers in laboratory settings. On the other side of the drug manufacturing process, if a drug has already been designed by humans, GAI also has the ability to predict its qualities, success probability, and potential side effects.

Pre-clinical research can take up to six years, and Insilico Medicine completed the phase in 30 months using GAI for a drug for idiopathic pulmonary fibrosis, a disease that causes scarring of the lungs with no known cause. Drug development also focuses on proteins, macromolecules that play a key role in disease processes. Dr. Michal Levitt, a Stanford professor of Insilico Medicine, won the Nobel Prize in 2013 for his work in protein structure and protein folding using GAI. Similarly, a research team out of the University of Toronto built their own GAI, called ProteinSGM, that generates novel realistic protein sequences that end up folding into real protein structures. This technology will be pivotal for the development of countless drugs.

However, that is not GAI's only benefit in the healthcare industry. GAI can facilitate medical training by creating responsive simulations, allowing medical students to practice procedures in a risk-free environment. Researchers at the University of Michigan designed a GAI



algorithm that can simulate various scenarios for sepsis treatment. Sepsis is a life-threatening medical emergency that occurs when the body's reaction to one infection or trigger results in a chain reaction throughout the body, often leading to the failure of major organs. From the moment symptoms appear, sepsis acts quickly, causing organ failure or death in as few as 12 hours. This creates a chaotic and stressful medical environment in which it is crucial that all medical professionals involved remain focused and collected. This GAI technology provides students with an opportunity to practice their composition and skills with zero lives at stake so that when there are actual lives at stake, medical professionals will be able to give patients their best chance at survival.

While skill is essential for medical professionals, their use of their time is also critical, and all trained medical professionals spend a lot of time on tedious administrative tasks and documentation. Even in the face of a shortage of properly educated physicians, those who are qualified still spend 62% of their time with the EMR (Electrical Medical Record) rather than with the patient. A physician's time is valuable, and handson time with their patients should be maximized, something that GAI cannot imitate. GAI can, though, assist in the administrative aspect of being a physician. Both Stanford and The Masters College (TMC) use DeepScribe, an AI Medical Scribe that generates complete office visit notes by using ambient sound technology, filtering out any small talk and recording all critical medical information. This could save physicians up to three hours a day at a sixth of the price of a real human scribe. In some cases, if a physician wants to administer a certain treatment or issue a certain procedure for a patient, they are required to write a letter to United Healthcare, or an alternate healthcare insurance company to gain approval. Again, this process is often tedious and time-consuming. However, if the necessary data is input into a GAI, it can produce that letter in under three seconds, saving valuable time.

GAI also has the potential to play a major role in clinical diagnosis. The technology takes in a large set of data, such as images or scans, and identifies patterns that are indicative of certain diseases. For example, skin cancer can be diagnosed by GAI algorithms that process images of a patient's skin and search for patterns, cohesively presenting the results to a dermatologist. GAI not only can analyze data but also can enhance the quality and resolution of images and scans. When tested, this approach was proven to lead to a higher accuracy rate in anomaly detection than the scans had before AI enhancement.

Another method of diagnosis comes from doctor's research and search for patients' symptoms. Medical chatbots may remedy this time-consuming process by offering results in mere seconds. Currently, Google has been working on converting a large language model (LLM), into a medical chatbot that high-quality answers, produces called Med-PaLM 2. It is a new variety of GAI technology that may prove useful for both doctors and patients. In fact, Med-PaLM2 was the first GAI to pass the US Medical Licensing Examination with a performance score of 86.5%. For the doctor, Med-PaLM 2 serves as a compressed form of all reference materials, eliminating the search and verification process involved in answering quick questions. For the patient, Med-PaLM 2 can determine the proper course of action regarding at-home complications or questions. While the technology is still in its early stages, all of these different applications of GAI in medicine open the door to a revolutionized healthcare system.

# AlphaMissense: The Future of Genetics

Isha Parekh

https://www.scientificamerican.com/article/ai-tool-pinpoints-genetic-mutations-that-cause-disease/

enes define who every single person is, from their physical traits to their personality. They are sequences of DNA that encode the amino acid sequence of proteins; those proteins then go on to perform important functions within our bodies. Through a process called DNA replication, three billion pairs of nucleotides, the basic structural unit of DNA, have to be copied, and sometimes mistakes are made. While DNA is being replicated, the replacement of a single letter in the nucleotide sequence could change the protein that gene makes, preventing correct functioning. These mistakes are called missense mutations.

A few years ago, Google Deep-Mind, an artificial intelligence program, came out with a new AI, AlphaFold, which could accurately predict the shape of a protein. Each protein has its own unique shape based on its amino acid sequence, encoded by nucleotides, which defines the function of the protein. Any missense mutations would interfere with this shape. With Alpha-Fold technology, these variations would be easier to catch, and their effects would be easier to discern. Earlier this fall, DeepMind released AlphaMissense, a new AI software derived from AlphaFold. This software not only predicts the shape of the protein formed, but also predicts which mutations are safe to ignore and which mutations would cause a drastic and dangerous change in the encoded protein.

AlphaMissense is a machine-learning artificial intelligence, and, as such, allows the software to analyze particular missense variations and determine their pathogenicity—whether and to what extent they cause disease-more accurately and quickly than humans ever could. Before the invention of this AI, experts had only recorded the pathogenicity of 0.1% of all possible missense variations, while AlphaMissense has now categorized 89%. It does so by exploiting patterns in biological data, defining benign variations as variants that are "frequently observed in human or other primate species" and pathogenic variations as variants that are unobserved or rarely observed within the human population. AlphaFold's code and database contain the shapes of different proteins, each having a specific function. By building upon this already existing database, AlphaMissense can calculate the shape of proteins formed by missense variations, thus determining what consequence, if any, these

mutations have. With these tools, the software might even be able to predict the consequences of other variations in nucleotide sequences within DNA (nonsense and frameshift mutations), which still remain a mystery.

DeepMind released a dataset of 71 million different missense variations and the pathogenicity of their relative proteins, including "predictions of all possible 216 million single amino acid sequence substitutions across more than 19,000 human proteins." In an effort to make these predictions a community resource, the missense variation information has been made publicly available for everyone to use in order to improve the fields of healthcare and biology. However, DeepMind has not made the software itself publicly available due to potential biosecurity risks if the software and techniques were

applied on different species.

So, how does this relate to medicine? Before AlphaMissense, it would have been very difficult to understand the purpose of specific sequences of DNA in an individual's genome, and hence it would have been difficult to differentiate between a benign and pathogenic missense variation. This is incredibly important, as sometimes mutations could lead to fatal and harmful diseases like cancer, sickle-cell anemia, and cystic fibrosis. This AI reduces the cost and time of having a gene or a mutation analyzed, increases the accuracy with which the functionality and pathogenicity of the gene is determined, and accelerates research across many medical and scientific fields. AlphaMissense attempts to find the root cause of a particular disease, and has been used by doctors to help understand

the "genetic causes of mysterious syndromes," while also helping molecular biologists and biochemists develop cures for these diseases.

The purpose of AlphaMissense is to diagnose a rare disease, identify its cause, and perhaps develop a treatment. Previously, without this software, many scientists using gene sequencing would often discover a mystery missense variation in an individual's genome, but they lacked the tools to determine its pathogenicity. Therefore, they could not determine whether the mutation needed to be addressed with treatment. AlphaMissense has now been able to help with this. AlphaMissense provides the next stepping-stone in the medical field, and is a software that has the potential to help countless lives.





# Genomic Profiling for Glioma Treatment

Maddie Offit

ne of the most challenging aspects of treating the various types of malignant, or life-threatening, brain cancer is the unique genetic makeup among brain tumors, or gliomas. This heterogeneity means that treatment paths for patients depend on the specific biomarkers and genetic mutations of the patient's tumor. These markers and mutations are then used in tandem with the best-targeted therapies available at the time of treatment.

One of the most lethal and aggressive forms of brain cancer, Glioblastoma (GBM), has an average life expectancy of 12-15 months for patients who undergo treatment, and only four months for patients who choose not to receive treatment. Standard of care treatment for GBM typically involves surgically resecting the tumor, radiation therapy, and chemotherapy. What makes the treatment of GBM so challenging is that once a tumor is resected, and standard-of-care treatment has occurred, the tumor tends to recur, or grow back, and the genetic composition of that new tumor growth varies from the patient's original GBM. This makes the treatment of GBM a dynamic process, where treatment paths can change course based on the various customized therapies needed for each patient as the tumor continues to recur.

Genomic profiling is a critical component in the treatment of GBM and other forms of brain cancer.

Genes, sequences of DNA, are in every cell of the body and act as blueprints for proteins, which form the structure and function of the body. When a gene is damaged, or mutated, the protein that is supposed to be made from that gene might not fold properly, which can affect its ability to function properly, or at all. If a cell has one or more mutated genes, the cell may grow abnormally and become a cancer cell. Genomic profiling looks at the genes in a person's cells to make a list of the ones that have been mutated.

A certain type of genomic profiling software, developed by Memorial Sloan Kettering, called MSK-IMPACT is a targeted tumor sequencing test available to glioma patients. Cerebrospinal fluid (CSF), a clear body fluid that exists within the tissue that surrounds the brain and spinal cord, is what oncologists use to collect information on each patient's tumor. Small fragments of DNA are released from tumor cells into the CSF and can then be extracted by doctors to be used for genomic sequencing. MSK-IMPACT can detect mutations and other critical changes in the genes of rare and common cancers alike. With this technology, doctors can quickly find out whether a tumor has changes that make the cancer particularly vulnerable to certain drugs. This is where the idea of customized therapies comes into play; doctors can design a more apt treatment course for patients with this information

on the DNA of the tumors. Thus, genomic profiling can significantly improve the quality of care a doctor provides to their patient.

With a detailed knowledge of a patient's genetic makeup, certain types of cancer have responded well to immunotherapy, a type of treatment that boosts the body's own immune system to fight cancer. The activity of the immune system in the brain is limited because the brain is separated from the rest of the body by the blood-brain barrier. This means that immune cells cannot freely penetrate the blood vessels into the brain tissue as the purpose of the blood-brain barrier is to protect the brain from viruses, bacteria, and other toxic substances circulating in the bloodstream. An undesirable side effect of the bloodbrain barrier is the protection of the malignant tumor located inside the skull from anticancer immune responses. The blood-brain barrier is largely the reason why treatment for GBM and other malignant forms of brain cancer has seen limited progress over the past 20 years, despite significant research, talent, and money being directed towards this goal.

With strides in genomic profiling for gliomas, comes strides toward better treatment for patients. As this technology becomes more advanced, the lives of patients with glioma, specifically GBM can be prolonged and their quality of life can be improved.

# **ProCAR: Probiotics and CAR T Take on Cancer**

or years, chimeric antigen receptor (CAR) T-cells have been successful in targeting specific markers on cancer cells, called antigens, in order to treat patients with blood cancers such as leukemia and lymphoma. CAR T-cells are T-cells, cells meant to identify and destroy pathogens, that are genetically engineered to recognize cancer cells. CAR T-cell therapy proves remarkably effective for blood cancer. A 2023 study found that 76% of those who received CAR T-cell therapy experienced remission and that CAR T-cell therapy improves the quality of life of patients living with blood cancers. However, until now, this success has been undermined by the fact that CAR T-cell therapy has not been effective in treating solid tumors, such

### Naina Mehrotra

as breast and lung cancer, which are significantly more common in the United States. Recently, researchers at The Danino Lab at Columbia University have found a way to expand the use of CAR T-cells to fight solid tumors as well as liquid tumors, by creating synthetic targets.

The body's immune system is most often ineffective in fighting cancer because cancer cells are not foreign. They are mutated versions of the body's cells. As a result, T-cells do not recognize cancer cells as a threat. The engineering of CAR T-cells transforms the immune system into a weapon to combat cancer. T-cells have receptors that recognize fragments or antigens on cells that indicate that the cell is infected. They then latch onto those antigens and destroy the infected cells. In making CAR T-cells, scientists genetically engineer T-cells to include a special receptor that targets a protein specific to the cancer cells, as well as additional DNA instructions to signal and sustain the killing of the cancer cells. However, concerning solid tumors, scientists have found difficulty in identifying a target for the CAR T-cells as many of the antigens on the cells that make up solid tumors can also be found on healthy cells. Fortunately, the Danino Lab has found that in engineering bacteria to create synthetic targets for the T-cells, there is potential to use CAR T-cell therapy for solid tumors. This marks the first time genetically engineered T-cells have been paired with synthetic antigens in a safe and effective way.

Past research within the field of



tumor-homing bacteria, which explores the use of bacteria to treat cancer, shows that some species of bacteria infiltrate tumor cores that are immune-privileged, meaning that the body's immune system does not regard them as foreign. As a result, these bacterial species are a promising way to form synthetic antigens. To engineer the synthetic antigens and the CAR T-cells to target them, the scientists used a two-step approach. First, they engineered a non-harmful strain of Escherichia coli to deliver synthetic antigens to the tumor microenvironment or the area around the tumor and mark the tumor. Then, they programmed CAR T-cells to recognize the synthetic antigens. To activate the CAR T-cells to kill the cancer cells, they administered a modified Escherichia coli probiotic. They designed the probiotic to release chemokines, proteins that stimulate cell migration, thereby recruiting the CAR T-cells and initiating the therapeutic response. This method proved effective in destroying cancer cells in experimental models of breast

and colon cancer and is the first instance of scientists successfully combining engineered probiotics with CAR-T. Additionally, human and mouse models have shown this therapy to be safe and effective in both immunocompromised and immune-healthy patients. After some refinements, the Danino Lab hopes to begin clinical trials to truly assess the potential of this treatment. They call their discovery probiotic-guided CAR-T-cells (ProCAR) platform.

There are numerous advantages to the use of CAR T-cell therapy over other therapies such as chemotherapy. For example, CAR T-cell therapy is administered through one infusion and therefore only requires two weeks of inpatient care compared to upward of six months for chemotherapy. Furthermore, because CAR T-cells are alive, they remain in the patient's body for many years and continue to recognize and destroy cancer cells in the long term. Most of all, CAR T-cell therapy targets only cancer cells, compared to chemotherapy, which targets all rapidly dividing cells. As a result, with CAR T-cell therapy, patients may not experience some of the negative effects of chemotherapy such as hair loss. The discovery of ProCAR gives all cancer patients an additional, favorable treatment option.

The Danino lab has combined the fields of tumor-homing bacteria and CAR T-cells to overcome each of their limitations in treating cancer, broadening the application of CAR T-cell therapy and finding a new strategy to treat solid tumors. They expect that, eventually, this technology could be used to treat any solid tumor. Additionally, because the CAR T-cells do not need to be designed to recognize an antigen specific to the tumor, scientists will not need to make custom CAR T-cells for each cancer type and patient, making the therapy less expensive and more accessible compared to traditional CAR T-cell therapy. The discovery of bacteria engineered to mark cancer cells for destruction by CAR T-cells signals a new era in cancer treatment and cell therapy.



## Revealing the Truth: Synthetic vs Natural Vitamins Greta Mark

any people opt for easier consumption of nutrients through colorful gummy vitamins, but do these synthetic vitamins truly provide the same benefits as their natural counterparts? What are the possible risk factors in this decision? To fully understand these questions, we can compare natural and synthetic vitamins.

While natural vitamins are micronutrients that occur naturally in foods, synthetic vitamins are artificially produced in labs. Synthetic vitamins are used to replicate the function of natural vitamins, especially in the case of deficiency. Due to their production in a lab, synthetic vitamins generally have greater doses of nutrients than typical natural vitamins, which can pose a threat in some cases. Supplements do not have to be FDA-approved before being sold, which may be a risk factor. More than 70% of Americans consume a multivitamin daily, which is a supplement that contains various nutrients and vitamins.

Different vitamins have different bioavailabilities—the body's absorption response to a vitamin—when consumed in synthetic forms in comparison to its natural forms. Vitamin C is absorbed at a similar rate when consumed naturally through food and when consumed through a synthetic vitamin C supplement.



In contrast, folic acid has a higher bioavailability when consumed as a synthetic vitamin versus as a natural vitamin. Natural folic acid has an absorption rate of 50%, while synthetic folic acid has an absorption rate of 85%, or 100%, when consumed on an empty stomach. Like folic acid, some vitamins have a higher bioavailability when consumed as a supplement on an empty stomach than as a natural vitamin through food. In some cases, vitamins can absorb the nutrients of other foods or meals, which results in a lower bioavailability. For example, a supplement of iron is more bioavailable when consumed on an empty stomach than when taken with food.

Although supplemental vitamins offer many benefits, such as their ability to help with deficiency of certain nutrients, they pose a risk of overconsumption, which can be dangerous. Synthetic vitamins have higher levels of nutrients than natural vitamins found in foods, and the bioavailability of some synthetic vitamins is much higher than their natural alternatives. The National Health and Nutrition Examination Survey (NHANES) determined that children had a higher chance of surpassing the tolerable upper intake level (UL) when they ingested foods with synthetic nutrients, including copper, vitamin A, folic acid, zinc, and selenium. The UL is the greatest level of certain nutrients and vitamins taken daily that does not create a health risk for the majority of the population.

Some vitamins and minerals are proven to have possible negative side effects when taken as a supplement. The Selenium and Vitamin E Cancer Prevention Trial demonstrated that the consumption of synthetic vitamin E led to a 17% increase in prostate cancer in men compared to men taking a placebo. Additionally, 49 different studies have shown that the intake of supplemental vitamin A has led to a 16% increase in the risk of cancer, lower bone mineral density, and an increase in fracture risk for women. The overconsumption of supplemental vitamin A can be toxic and ultimately fatal. Calcium also poses risks when taken in high doses as a supplement. While the consumption of calcium

through natural sources, such as food, does not have negative effects, the consumption of synthetic calcium can increase the chance of coronary heart disease.

Despite all the possible health issues supplemental vitamins may pose, they do prove to be beneficial in many cases. In the United States, approximately 45% of the population is deficient in vitamin A, 46% in vitamin C, 95% in vitamin D, 84% in vitamin E, and 15% in zinc. There are many sources of insufficient levels of vitamins and nutrients, including limited access to, and variety of, food, as well as unhealthy eating patterns; greater vitamin deficiencies are seen in adults with lower socioeconomic status. Supplements of these vitamins can help fight these deficiencies and provide necessary nutrients. Additionally, pregnant women are instructed to consume higher levels of certain nutrients daily, such as B12, choline, folate, iron, calcium, and vitamin D. Supplemental vitamins prove very beneficial in helping these women reach certain levels to maintain their health.

When given the opportunity, naturally occurring nutrients and vitamins found in food are typically the best option to sustain a healthy diet with minimal health risks. Nonetheless, when taken safely and with proper instruction, synthetic vitamins offer a great alternative to reaching the necessary nutrient intake daily. While the taste and appearance of gummy synthetic vitamins may be intriguing, natural vitamins ultimately provide the greatest health benefits.



# Managing Sleep and Assessments: The Necessity of Striking a Balance

t's the night before a big assessment and you are debating whether to sleep or to continue studying. You probably should not debate too long, as recent studies have shown the high value of sleep and the positive effects it has on academic performance.

For teens, the recommended amount of sleep is eight to ten hours per night, but this is not the reality for many students. Around 57% of middle school students and 72% of high school students do not receive the proper amount of sleep per night. Moreover, about 20% of students pull monthly "all nighters." This contributes to insomnia, a sleep disorder that causes daytime drowsiness and prohibits a normal sleep schedule. Sleep consistency is also essential-several nights of good sleep are necessary to improve a sleep schedule. During puberty, many teens are inclined to stay up later, shifting their internal clock with a delayed bedtime. When this cycle starts, it's difficult to reverse the habits of staying up late and the challenges of waking up early for school. From the ages of 13 to 19, teens lose 40 to 50 minutes of sleep in their average schedule within these six years. Poor sleep transfers over into the school day; negative in-school performance is directly related to a lack of sleep.

While there is more research on sleep and performance in adults,

### Ava Parento

studies have found that insufficient sleep can dwindle achievement and attitude in school for teens. Dwindled attention spans, hindered memory, impaired creativity, and slower reaction times are all symptoms of inadequate sleep. A lack of sleep can worsen performance in classes; focus is required throughout the day, and it is imperative to remember lessons learned the night before. Heightened creativity allows one to perceive problems in new ways. Participation is an important part of classes; being ill-prepared, drowsy, or quiet can affect intake of information and grades. A disrupted sleep schedule can also lead to undesirable moods or attitudes during the school day. Exorbitant sleepiness can cause students to fall asleep at their desks, impairing their ability to retain information or pay attention to a lesson. Hostility and poor decision making are also symptoms of insufficient sleep. These not only affect success in school, but also interpersonal relationships with classmates.

Remembering and recalling information is another aspect of schoolwork that can be curbed by a lack of sleep. In recent years, scientists have concluded that sleep can improve information recall by 20% to 40%. Memory and memorization are employed daily in personal relationships and academic contexts; the two are necessary to perform well on assessments and in class, providing sufficient reasoning as to why sleep should be a priority for students.

There are various reasons why teens suffer from a lack of sleep. Conflicting sleep schedules on the weekends, as compared to the weekdays, may affect sleeping habits. This creates difficulty in establishing a healthy and consistent sleep schedule. Excessive use of electronics may also contribute to poor sleep. Using electronic devices late at night often serves as a distraction from sleep and causes adolescents to go to bed at a later time. Also, these devices emit blue light which can disturb a normal sleep schedule. Blue light is emitted on laptops, where most schoolwork is done. When staying up late to cram for a test, the act of staying up late isn't the only harmful consequence; the blue light may also negatively affect sleep. Moreover, school-related stress can promote a sleep deficit by inflicting anxiety onto students. Anxiety, or feelings of uneasiness, have been found to be the cause of several sleep disturbances, such as insomnia. People with anxiety often have their head spinning with concerns at bedtime, leading to a dearth of sleep. Issues with falling asleep could also lead to negative associations with sleep; these negative connotations can cause disturbances in a sleep schedule. However, there are things

to prevent anxiety about sleeping. Creating a comfortable sleeping environment, limiting distractions before bedtime, and avoiding caffeinated beverages help to suppress anxieties around sleeping.

While the effects and reasons for sleep deprivation are apparent, how does this actually affect school performance and learning ability? The hippocampus is the region of the brain where most of the information that we acquire is stored; scientists have concluded that sleep is necessary in refreshing this part of the brain. It is hypothesized that this part of the brain can become full, and with insufficient sleep, the hippocampus is unable to store new information. A study was done by the Sleep and Neuroimaging Laboratory at the University of California, Berkeley, where 44 students attended two difficult lectures, one at 12:00 pm and another at 6:00 pm. One group slept in between the classes, while the other group went on with their day. The study shows that the group that slept in between the lessons was able to grasp information better, and their learning ability was the same in both the afternoon and evening sessions. The group that did not sleep, however, had more difficulty in learning the material during the later lecture. The study concluded that in order to process new information, sleep is necessary to reinvigorate the brain.

In the end, getting one good

night's sleep before a big assessment will not do the trick. Managing sleep throughout the entire learning process is the key to success in school, as proper rest improves several cognitive abilities. Memorization, creativity, and learning ability can all be negatively affected by poor sleeping habits, leading to a lack of understanding throughout the day if healthy sleep patterns are not established.

Next time you're thinking about staying up late to study extra or watch a newly released episode of your favorite TV show, make sure to consider the consequences that staying up may have on your capabilities in school the next day!



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