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Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

Bruce M. Cohen: An eclectic life and a multidisciplinary approach to the complex determinants and diverse presentations of psychiatric disorders

Genomic Psychiatry; https://doi.org/10.61373/gp025k.0104

Keywords: Schizophrenias, bipolar disorders, late-onset dementias, complex causes, diagnostic models

Bruce M. Cohen, MD, PhD, stands as one of psychiatry's most innovative research leaders, transforming our understanding of neuropsychiatric disorders through groundbreaking multidisciplinary approaches at McLean Hospital and Harvard Medical School. As Robertson-Steele Professor of Psychiatry at Harvard and Director of the Program for Neuropsychiatric Research at McLean Hospital, Dr. Cohen has pioneered revolutionary techniques combining brain imaging, genomics, and induced pluripotent stem cell models to unlock the complex biological mechanisms underlying schizophrenia, bipolar disorder, and Alzheimer's disease. With over 400 peer-reviewed publications and five awarded patents spanning nearly five decades at McLean, his discoveries in mitochondrial dysfunction and energy metabolism abnormalities have opened unprecedented therapeutic pathways. His laboratory's cutting-edge ability to grow brain cells from patient samples represents what he describes as technology "giving us leads we did not have forty years ago." Named Psychiatrist of the Year twice by the National Alliance on Mental Illness of Massachusetts, Dr. Cohen's impact extends beyond research to institutional transformation. As McLean's President from 1997 to 2005, he reversed the hospital's financial decline, establishing over 30 new programs while achieving record levels of patient care, research funding, and educational training. His current work challenges century-old psychiatric diagnostic models with evidence-based dimensional approaches that better capture the complexity of mental illness. In this comprehensive Genomic Press Interview, Dr. Cohen shares insights from his remarkable journey from molecular genetics at MIT and Case Western to becoming a leading voice advocating for the replacement of stigmatizing terms like "schizophrenia" with scientifically accurate alternatives, while revealing the personal experiences and intellectual curiosity that have driven his dedication to understanding and treating the most challenging neuropsychiatric conditions.

Figure 1. Bruce M. Cohen, MD, PhD, McLean Hospital/Mass General Brigham, Harvard Medical School, USA.

Part 1: Bruce M. Cohen – Life and Career Bruce M. Cohen

Where were you born, and where do you live now?

I was born in Cleveland, Ohio, and grew up in Shaker Heights, Ohio, just East of Cleveland. Currently, I live in Lexington, Massachusetts, USA, just West of Cambridge/Boston, where I have lived for the last 50 years.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

As early as I can recall, I was able to read, and I liked to read 'non-fiction'. My family, friends, and teachers saw me as quiet and thoughtful. (I did play sports, was strong, and was good at throwing and catching balls, as well as hitting balls, with a bat or racquet.) Science, especially physics, has fascinated me since elementary school, and I have developed a passion for mathematics. I wanted to understand the basic principles of how the world worked. I thought I would have a career in basic science. By my teenage years, I was reading non-specialist pieces on special and general relativity, as well as quantum mechanics. The core concepts and the unresolved issues in the relationship between those models were fascinating and frustrating.

Throughout public schooling, I had great teachers and opportunities, and I entered MIT, younger, shorter, and even more awkward than the average student, but with a lot of advanced placement credits, which allowed me to explore various new topics. These topics included biology, which I had never studied in public school, and philosophy, which I had never read. I began to think of a career studying the brain and how it worked. My father was a prominent internist, beloved by his patients, as well as by family and friends. His subspecialty was cardiology, and he published research with collaborators on the relationship between diet and heart health. He had considered other careers, and we had conversations about various callings. I realized that among many choices, medicine was unusual in the options it offered. One could treat patients, study diseases, teach, or pursue any combination of those possibilities. In addition, what one chooses to do can yield rewards, including helping others, such as loved ones, and even taking care of oneself. I chose that career and its commitments. My father warned that medicine would be hard to learn and hard to practice well.

Received: 24 September 2025. Accepted: 3 October 2025.
Published online: 14 October 2025.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

Exposure to molecular biology at MIT, including a lecture and lab course with Nobel Laureate Salvador Luria and lab experience with David Botstein and Elizabeth Jones, opened my mind to a more physics-like side of biology, which greatly interested me. Philosophy courses on our abilities to assess reality, and reading Einstein's ideas, helped me understand that all knowledge is contextual. That is, all models of reality are approximations and can be replaced by more accurate, more complete, and better approximations. Conversations with the philosopher Bert Dreyfus, who published on models of the brain and its simulations, along with a mathematics course on the same topic, drew my interests toward aspects of typical and atypical brain function.

Entering medical school, I thought I would be a neurologist. After taking a few courses, I realized that to explore illnesses, including those of the brain, thoroughly, I would need more specialized scientific training. For that, I entered a PhD program, in addition to the MD program. Molecular genetics seemed particularly relevant to the future of medicine, and I completed training and a doctoral thesis in that area with Elizabeth Jones. The organism was E. coli, and we may have revealed the first operon containing genes for a biosynthetic pathway. When I graduated, I had to chuckle when the dean misread the genetic descriptor in my thesis title.

During my clerkship years, I still intended to pursue a career in neurology. Then, I had my psychiatry clerkship. I was the only clerk among five assigned to the locked inpatient unit. My first patient was a young woman who was agitated, delusional, and talking rapidly and rather incomprehensibly. A few weeks later, on antipsychotic medication, she was among the most rational and delightful people I have known. That change was remarkable. The disorder and the success of treatment impressed and fascinated me, and I considered a new career choice. Three additional patients, with different psychiatric disorders, seen on the inpatient unit and in the clinic, all improved dramatically with treatment. And I provided that treatment. This was rewarding. Psychiatry focuses on thinking and feeling, the traits that are most refined in humans and that most define our lives. Furthermore, when thinking and feeling are off, treatments can provide significant help.

These realizations, that psychiatrists could study what is most human and help those whose lives were in disarray, changed my career choice. I decided to become a psychiatrist, with a focus on mood and psychotic disorders. It helped that my closest friend and medical school colleague, Peter Harris, was also pursuing a career in psychiatry. Going back to my first patient, I presented her case to our consulting psychiatrist, with the other students present. I noted the symptoms of psychosis and mania. He recommended a diagnosis of schizoaffective disorder. We, the five students, found that to be a somewhat odd descriptor. We had been taught categorical diagnoses, and this seemed to be a 'mash-up' of categories, rather than a true category itself. My concern about the categories and terms used in psychiatric diagnosis began then and became a recurring theme in my career.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My career has been non-traditional, more characterized by intertwined paths than a single trajectory. While I have never given up research and continue to provide clinical consultations, I have also held a series of administrative and major teaching roles. In a way, this validates my original view of medicine as offering many career opportunities, but it sacrifices focus for breadth. My most prominent administrative role was as President and Psychiatrist-in-Chief at McLean Hospital. I came to McLean as a psychiatry resident to work in the research group established by Seymour Kety, who was moving his program from the MGH to McLean. Seymour was the first to measure energy use in the living human brain. He won the Lasker Prize for that foundational work. He had switched to psychiatric genetics, with later colleagues, and had a diverse group of investigators in his research program. A large addition to the existing research building at McLean was added to accommodate his laboratories. Some investigators in his program and some faculty at McLean were welcoming to a young MD, PhD; others were not. Steve Matthysse, a brilliant psychologist and mathematician working with Seymour, was very supportive. Among other novel contributions, Steve had clearly presented the problems underlying the dopamine hypothesis of antipsychotic drug action and schizophrenia. He encouraged me to follow my own directions, but I was too insecure to stray too far from the norm until I was much older.

Jonathan Cole, who had come to McLean after founding the Psychopharmacology Service Center at the NIMH, was an invaluable clinical mentor. Moreover, the training director, Phil Isenberg, was a staunch protector of his wards, including the outlier, who was then at McLean and aspired to a career in biological psychiatry. He chose himself as my residency mentor, and we became good friends. My entry into hospital administration came in 1986 when Sherv Frazier returned from his role as Director of the NIMH to become the head of McLean. He sought help, and the director of research, Joe Davis, a splendid and thoughtful person who could handle any dispute and resolve most issues, recommended that Sherv choose me as his assistant. I accepted, both out of interest and to protect myself in a highly competitive environment. (One senior colleague told me that there was no room at McLean or in town for the two of us, even though we were both in productive careers. Those words made it sound like we were in an old Western.) Not long into his tenure, Sherv resigned due to a disputed plagiarism charge.

Until the next leadership change, I oversaw research, which we doubled in size, as well as training and some clinical services. During those years, primarily due to 'managed care', which drastically reduced reimbursements for psychiatry, McLean began running a large deficit. Its parent organization, Partners HealthCare (now Mass General Brigham), was considering closing the hospital and relocating its research to a site in Charlestown, where the MGH had laboratories. Working with the Chairman of the McLean Board of Trustees, Charles Baker, Sr, I presented the case for maintaining McLean to the McLean and Partners trustees. I ended up being offered the Presidency of McLean. I valued McLean and took the job. We led the hospital to solvency and substantial surpluses by cutting bureaucracy and establishing over 30 new programs across clinical care and research. Research added a new wing to its core labs and doubled its funding for basic and clinical investigations.

Both my clinical and research experiences were highly relevant to working with others and making decisions as President, and I remained grounded by continuing to see patients and conduct research. Meanwhile, I learned a lot about finance, facilities, personnel, and legal issues. Charlie Baker must be acknowledged for being so competent and helpful. A figure in two US Presidential administrations and a professor of business administration, he is one of those unsung heroes who advance society and its institutions behind the scenes. Some trustees thought I could not be tough enough to save McLean; he said I was the guy for the job. Sam Their, an exceptional clinician and the head of Partners, when I was appointed President of McLean, agreed to let me run McLean my way. After he retired, Partners moved towards more control from above. McLean was stable and productive, and in 2006, I moved back to research. Though I miss the breadth and pace of being a hospital chief, I enjoy directing a research program. Progress is slow, but the findings are rewarding and the leads the findings suggest are promising.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

There were so many embarrassing mistakes to choose from, but most had clear, undesirable outcomes. None killed a patient, but some sent me down difficult personal and career paths. Each taught me something, and each lesson was a valuable outcome.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

Medical training helped me appreciate the great diversity of factors that determine biological outcomes, including health or illness. In medicine, these factors encompass social, cultural, and environmental aspects, in addition to genetic and stochastic components of development and response. With experience, it became increasingly clear to me that the

classical medical models for categorizing illnesses, based on single external causes such as an infection or a nutritional deficit, often did not apply to other common illnesses. As examples, cardiovascular disorders or metabolic disorders, such as type 2 diabetes mellitus, are complexly determined by the interactions of numerous inherent and environmental factors and are expressed in a variety of individual ways.

Graduate education and research experience exposed me to the fundamentals of study design and analysis, including statistical methods beyond those commonly used and sometimes misapplied in medicine. This includes the misinterpretation of medical tests, which often assume a 'bell-curve', even when the underlying distribution of results in a healthy population does not fit that model. As an example of the problems that can arise, we published a paper noting how TSH levels are often misinterpreted in patients with treatment-resistant depression. Research training and experience have helped me become more comfortable with interpreting hard-to-understand or unexpected results and more attuned to considering alternative and complex explanations, rather than settling on a simple conclusion or description. Notably, in medicine, assigning a definitive diagnosis often results in categorizing a patient with a single descriptive name, thereby losing important details specific to the individual being assessed and treated. Addressing that problem, I have published on alternative, evidence-based, non-categorical models of psychiatric disorders.

Please tell us more about your current scholarly focal points within your chosen field of science.

I continue to pursue multiple interests. Currently, I directly oversee three laboratories documenting inherent factors that determine the risk for psychotic and mood disorders and late-onset Alzheimer's disease. We study brain cells and organoids derived from induced pluripotent stem cells (iPSCs) that are reprogrammed from fibroblasts or blood cells. Each disorder studied is complexly determined, but we have identified some key abnormalities related to the disorder. We collaborate with geneticists and brain imagers, seeking convergent evidence on the role of the abnormalities we see as markers of risk and mechanisms underlying illness. More than any organ, the brain depends on high-energy production and precise connectivity. It is no surprise that we observe inherent abnormalities in energy metabolism as well as in processes supporting accurate cellular interactions in our cell lines from people with neuropsychiatric disorders. Some of these abnormalities may be modifiable before illness develops.

Concurrently, I retain an interest in clinical care and psychiatric diagnosis. My clinical colleagues, our statistician, and I have published on issues associated with DSM and ICD diagnostic models for the psychotic disorders. Our studies, as well as those of others, strongly suggest that these largely categorical models, proposed a century ago, do not adequately describe clinical presentations or fit the underlying biology of these disorders. Rather, the evidence suggests that psychotic and mood disorders are best modelled by dimensions such as positive or negative symptoms of psychosis, mood dysregulations, and a few other descriptors, including the course of illness. Such descriptions are practical, as they are similar to how clinicians evaluate patients. They provide richer descriptions of individual patients than diagnostic categories do. The descriptions can also be used to create more homogeneous patient groups for research purposes.

What impact do you hope to achieve in your field by focusing on specific research topics?

In our biological research, we aim to uncover the mechanisms that determine substantial proportions of the risk of illness. Further, we hope that these mechanisms will be targetable for the treatment and even prevention of illness. As psychotic disorders rarely appear before adolescence and dementias rarely appear until older age, prevention should be possible. We are among many pursuing these goals. Regarding modeling psychiatric disorders, we hope that our work and that of others will lead to a new evidence-based nosological system. Updated terminology, based on input from clinicians and consumers, should be a part of that progress. Archaic, confusing, and pejorative terms, such as 'schizophrenia', should be replaced with better alternatives.

What do you most enjoy in your capacity as an academic or research leader?

There are many ways to collaborate with others on issues and projects. I enjoy the process of deciding among possibilities and seeing the results of our efforts. In research, especially, I have enjoyed the interplay of ideas and the pleasure of discovering new findings, whether they confirmed our hypotheses or not.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?

Medicine has long been based on established authority and controlled by networks of individuals with the power to determine practices and allocate resources for clinical work and research. During my career, psychiatry has been somewhat rigid in its adherence to standard diagnostic models and not very open to the full breadth of research possibilities. Regarding nosology, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) remain based on expert consensus, rather than the growing body of evidence that clearly shows their largely categorical systems, which still mimic century-old models, are incorrect.

Regarding research, funding too often goes to what a friend of mine, who also led a major department of psychiatry, called 'next least step' research. New investigators, without established connections, and scientists with innovative approaches that deviate from the norm have low chances of obtaining attention or support. Let us take more chances on new people and novel ideas. The psychiatric press is a part of this rigid system. Reviewers are often highly critical of ideas or approaches that are unconventional or do not align with their views. There could be more consideration of alternative ways of looking at the state of our knowledge and our field.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I enjoy strolling through towns and cities with my wife, visiting shops and museums, and having a good meal. At home, I enjoy reading books and journals on scientific topics, as well as history and biography.

Part 2: Bruce M. Cohen – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?

Broad interests and curiosity; a need to understand. Skepticism of accepted practice, primarily if it is just based on tradition, and discomfort with authority, especially if it is misused.

[1]In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

Among your talents, which one(s) give(s) you a competitive edge?
Having known so many talented and successful colleagues, I did not have any special competitive edge. Rather, I found my 'ecological niche'. I was blessed from birth by having a wonderful mother and father who made me feel valued. My wife doubled that. My interests being spread across clinical and research domains, including multiple research approaches, diluted my expertise but strengthened my knowledge of the multiple interactive factors underlying psychiatric disorders. Traits that helped me in my professional life included perseverance, a tendency to think about alternatives and contingencies, and open-mindedness. I am highly opinionated, but I recognize my opinions as just that, beliefs that should be challenged. I listen to others and welcome results different from what I expected.

If you could change one thing about yourself, what would it be?
Anxieties. Great shyness has limited my connections and experiences. Professionally, those anxieties, along with discomfort with travelling, have prevented me from participating in academic societies and their meetings or pursuing collaborative opportunities as much as I would have liked.

What is your current state of mind?
Optimism about the continuing value of science. Pessimism about the direction of society.

What is your idea of perfect happiness?
No such possibility. Just thinking has often been a happy place for me. I enjoy the companionship of those I love.

When and where were you happiest? And why were so happy then?
Undergraduate years at MIT. They were rich and intellectually rewarding, and I can proudly boast that I achieved exceptional grades at a time when high grades were still rare. In addition to learning, I experienced significant social growth and had numerous positive interactions, including meeting and eventually dating my future wife. We have now been married for over 55 years.

What is your greatest fear?
Anything that would hurt the family. Personal aging brings declines and fears of illness. Eventual demise is not a cheery prospect.

What is your greatest regret?
Early in my career, I focused on what others suggested, and I did not publish some results and ideas that ran against accepted models. In one case, a senior mentor commented that pursuing publication of a critique of standard practices and models would end my career. It took me decades to revisit and publish on that subject.

What are you most proud of?
I am proud of my parents, though I can take no credit for them. I am proud of my wife, my children, and my grandchildren. I am proud that I cared for patients, supported individuals in their careers, conducted valuable research, and contributed to the improvement of McLean Hospital.

What do you consider your greatest achievement?
As an institutional leader, I guided McLean Hospital to health by supporting front-line staff, decreasing bureaucracy, and establishing numerous new clinical and research programs. Most new programs helped the 'bottom line', along with advancing care and knowledge. Some, including Waverley Place, our peer-run center supporting people with mental illnesses living in the community, advances our mission of serving others without also generating income for the hospital.

As a clinician, at times, I had a large practice, and there were patients I had treated and whole families I had advised for decades. Despite not being cures, psychiatric treatments are among the most effective interventions in all of medicine. Clinical care is a rewarding and important achievement. I treasure the experience of knowing and helping others.

As an investigator, documenting the complexity of psychiatric disorders and their treatment, early on, this effort involved observing the multiple targets and sites of action of antipsychotic drugs. I led the team that discovered and reported that the relative distribution of a drug to the brain correlated strongly with its clinical dose potency. In fact, distribution explained potency as well or better than affinity for any particular receptor target. At the levels achieved, all antipsychotic drugs, including those called receptor-specific, interact with multiple receptors. Our findings, along with those of many others, clearly showed that antipsychotic drug effects were not simply due to the consequences of dopamine D2 receptor antagonism; their therapeutic mechanisms were far more complex than that.

Figure 2. In mid-September, a view from our house down to East Boston and the harbor. Gazing out from the hill, our grandson says he is looking into the universe. Our granddaughter calls the house her happy place. It is our happy place, too.

Similarly, our work has helped reveal the numerous interacting inherent determinants underlying risk for psychotic and mood disorders and, in more recent studies, late-onset Alzheimer's disease. Developmental abnormalities occur in both glial and neuronal cell types. Multiple inherent metabolic abnormalities are seen. These occur in addition to synaptic and neurotransmitter abnormalities. All the factors interact to determine the overall risk of illness. Lastly, resulting from my earliest experiences in psychiatry, we have developed and presented evidence suggesting that a specific dimension-based approach to the diagnosis of psychotic disorders fits clinical presentations and biological findings better than the standard DSM or ICD diagnostic models.

What or who is your greatest passion?
Wife, kids, and grandkids. In research, pondering evidence, considering current and alternative models, and examining new findings.

What is your favorite occupation (or activity)?
I greatly enjoy many aspects of work. Privately, I enjoy reading, good food, good company, and some travel, now local.

What is your greatest extravagance?
Expensive food and wine, on some occasions.

What is your most treasured possession?
Mementos of my parents and my wife's parents. They were wonderful people. Children's and grandchildren's drawings and letters.

Where would you most like to live?
I would not change where I grew up, nor would I change where I live now (see Figure 2). From Lexington, we have access to outstanding universities, medical centers, and museums, as well as great food and entertainment. The area is surrounded by nearby hills, shores, and rivers of exceptional beauty, as well as interesting towns to explore. Many of these places, such as Lexington itself, hold historical significance.

What is the quality you most admire in people?
Integrity, compassion, commitment, a sense of humor about life and self.

What is the trait you most dislike in people?
Meanness, manipulativeness, dishonesty, selfishness.

What do you consider the most overrated virtue?
Loyalty. Too often, allegiance clouds sound judgment and leads to misguided actions. Trustworthiness is better.

What do you most value in your friends?
Love, kindness, tolerance, intelligence, open-mindedness, appreciation of humor, and a variety of interests and experiences.

Who are your heroes in real life?
My father. He was a talented, dedicated, and caring man. Up at 5 am every morning, he visited his patients in the hospital, followed by his office practice, and then returned to the hospital to check on his patients. We had dinner with him every night, at 7 pm, upon his return home. After dinner, we read together or listened to music. He studied medicine later in the evening. There were trips, theater, and concerts, as well as golf, a favorite relaxation for him. He had a delightful sense of humor that was charming and never deprecating. Life with him felt safe. Time with him was precious and rewarding.

If you could have dinner with any historical figure, who would it be and why?
Two very interesting people, who should be faulted for the treatment of their wives, but who mostly tried to do what was right in their lives: Albert Einstein. Brilliant, creative, with broad interests, including revolutionary accomplishments in physics, but also insights into social issues. Benjamin Franklin. Brilliant, creative, a highly accomplished investigator, not just a kite-flyer, some of whose physics is still used, and broadly interested in science and social issues.

Who are your favorite writers?
My reading for pleasure tended towards comedy when I was younger. James Thurber has been a favorite since late childhood. I have always appreciated political and social cartoons. Some of my favorite authors and works include Walt Kelly's *Pogo*, Bill Watterson's *Calvin and Hobbes*, Berke Breathed's *Bloom County,* and, for science, Gary Larson's *The Far Side.* Scott Adams' *Dilbert* helped me get through the stresses of corporate management. Gary Trudeau's *Doonesbury* is often excellent.

In high school and college, I enjoyed Shakespeare and Chaucer, and even learned to read Middle English and pronounce it properly at MIT. Arthur Miller's plays. Orwell and Vonnegut, for novels. Robert Frost and Dylan Thomas for poetry. For the most part, in recent decades, I have read science, history, and biography. For serious science outside my field, I read articles in *Nature* and *Science.* For popular mathematics and science books, some favorite authors are Douglas Hofstadter, Susan Hossenfelder, and Sean Carroll—Richard Feynman, of course, both texts and popular books. For history, none better than Barbara Tuchman, and for biography, I have enjoyed H.W. Brands.

Who are your heroes of fiction?
From my youth: Odysseus, who was small but strong, clever, and persistent. Cyrano de Bergerac (only partly fictional), an outsider with a large nose who was smart, intense, and persistent. Superman, who was strong, intelligent, and good, and who arose from a near East Cleveland suburb, the one where my parents met in High School.

What aphorism or motto best encapsulates your life philosophy?
My perspective on life evolves with age and experience. I struggle to keep learning and exploring. I try to understand. I try to do good.

Lexington, Massachusetts, USA
24 September 2025

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