

Mirko Manchia: Exploring the biological landscape of psychiatric disorders to innovate clinical management with precision medicine approaches

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Dr. Mirko Manchia is an Associate Professor of Psychiatry at the Department of Medical Sciences and Public Health of the University of Cagliari, Cagliari, Italy, and holds an adjunct appointment in Pharmacology at Dalhousie University, Halifax, Nova Scotia, Canada. Dr. Manchia's research examines the genetic basis of bipolar disorder and other related complex traits such as response to long-term treatment with lithium and suicidal behavior. His work is not only of theoretical interest but also clinically relevant. One such example was the publication in the *Lancet* of genome-wide significant association signals for lithium response in a large cohort of bipolar patients (Hou et al. 2016) performed in the context of the international consortium on pharmacogenetics of lithium response (ConLiGen) of which Dr. Manchia is a co-investigator and founding member. In addition, he was responsible for the phenotypic analysis of the sample (Manchia et al., 2013). During his career, Dr. Manchia has established an excellent track record, having published 230 papers to date in international peer-reviewed journals on molecular genetics and the clinical aspects of bipolar disorder. He is an active Principal Investigator (PI) of research projects funded by EU and national agencies, and he is also involved in several other international consortia, including PGC-BD. He is the chair of the European College of Neuropsychopharmacology (ECNP) Bipolar Disorders Network. Furthermore, he serves as the Senior Editor for *Neuroscience Letters* and is an associate editor for several international Journals. Dr. Manchia has successfully combined molecular-genetic and statistical methods with a clinical understanding of research problems in psychopharmacology and pharmacogenomics. In this Genomic Press Interview, Dr. Manchia is delighted to provide our readers with reflections on his life and career.

Part 1: Mirko Manchia – Life and Career

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

I was born in Sassari, a city in northern Sardinia, but I have spent most of my life, except for a hiatus in Canada, in Cagliari, the capital of the island.

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

I come from a family with no medical or scientific background. However, I have always had a profound interest in biology that, during my adolescence, connected profoundly with mental health in the context of some familial events. When I started the medical faculty at 19 years old, I wanted to study a discipline that could connect basic and clinical research. This seemed an impossible task in some areas of medicine, but not for disciplines like psychiatry within clinical neuroscience. I was fortunate to study at the University of Cagliari, which had been for decades



Figure 1. Mirko Manchia, MD, PhD, University of Cagliari, Italy.

the cradle of a prominent school of neuroscience led by Prof. Gianluigi Gessa, a pupil of Bernard B. Brodie, who followed the steps of Prof. Erminio Costa (another prominent Sardinian neuroscientist) in the US to perform the seminal studies on the dopaminergic system. The encounter with Prof. Maria Del Zompo, a disciple of Prof. Gessa, significantly shaped my career, as she was an exemplary researcher who was both clinically committed and research-oriented in the fields of pharmacogenetics and psychiatric genetics. With her, I trained in clinical pharmacology and neuroscience.

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

I was interested in understanding why the effect of drugs varied substantially from person to person, from patient to patient. I saw patients who had severe illness trajectories and who had remained well after several years of treatment with mood stabilizers (especially lithium), while others experienced continuous recurrences with dire consequences on their lives. This led me to explore those biological phenomena that could underlie this apparent difference in response to treatment, including also suicidality.





Figure 2. Mirko Manchia at a recent national conference on neuropsychopharmacology in Rome discussing precision medicine approaches in psychiatry.

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

Three moments shaped my career fundamentally. First, I spent time as a student intern in the Laboratory of Human Physiology at the University of Cagliari, led by the late Prof. Rino Mancinelli, where I learned about the strengths and limitations of animal models. Second, the training in clinical pharmacology and genetics with Prof. Maria Del Zompo, and third, the clinical fellowship with Prof. Martin Alda at the Mood Disorders Unit of the Department of Psychiatry at Dalhousie University in Halifax. The latter experience shaped me as a clinical researcher in psychiatry and taught me how to conduct and coordinate research at the highest level.

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?

Training in psychiatry as a second specialty after my experience abroad was not an easy choice at the time. However, after completing this second residency training, I was able to combine knowledge in pharmacology, pharmacogenetics, and psychiatry, developing a clearer perspective "from a gene to behavior."

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

Being perseverant, patient and calm in facing challenges and difficulties, as well as never neglecting the quality of interpersonal relationships.

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

I am currently focused on developing healthcare pathways in mental health where the implementation of precision medicine tools can be tested and verified. One such example would be the application of phar-

macogenetic testing in depressed patients with treatment resistance, as well as the implementation of AI-based predictive tools.

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

We are at a point in psychiatric genetics where clinical utility is emerging. We are not there yet, but in 20 years, I foresee a significant change in how mental health is managed and delivered.

Digital monitoring, psychometric assessment, omics, and brain imaging are being integrated into predictive models that will have an impact on the trajectories of these severe mental disorders.

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

Teaching medical students and residents is not only a duty but a commitment with profound implications for the future of our communities. Secondly, I enjoyed tremendously when our research produced results that could tangibly modify clinical practice in a meliorative way.

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?

We need to take a stand on issues such as public underfunding of psychiatric research at the global level. Other areas of medicine (oncology) have seen profound changes following massive investments in research. This could also be achieved in psychiatry, but we need to act in a harmonized way, involving all stakeholders, particularly patient and family associations, in the development and dissemination of our research findings.



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 spend as much time as possible with my family and in the rare spare moments I read and listen to classical music.

Part 2: Mirko Manchia – Selected questions from the Proust Questionnaire¹

What is your most marked characteristic?

I am patient but tenacious, and this has helped me in my career since the early years of my medical training.

Among your talents, which one(s) give(s) you a competitive edge?

It is determination and a bit of chutzpah in trying to achieve results in contexts that are not necessarily favorable.

If you could change one thing about yourself, what would it be?

At times, I tend to be too perfectionist.

What is your current state of mind?

Calmness.

What is your idea of perfect happiness?

Mental and physical health, and the freedom to develop one's ambitions and talents.

What is your greatest fear?

Spreading of ignorance.

What are you most proud of?

My family.

What do you consider your greatest achievement?

Professionally, having been able to pursue a career in research and academia.

What or who is your greatest passion?

Roman and modern history, movies, playing guitar.

Where would you most like to live?

The beautiful island of Sardinia.

What is the quality you most admire in people?

Honesty.

What is the trait you most dislike in people?

Lack of passion.

What do you most value in your friends?

Sincerity.

Who are your heroes in real life?

Mental health operators.

If you could have dinner with any historical figure, who would it be and why?

Louis II of Bourbon, Duke d'Enghien, and Prince of Condé, to know if he had really slept well the night before the Battle of Rocroi.

Who are your favorite writers?

Umberto Eco and Willem L. Shirer.

Who are your heroes of fiction?

Those who impersonate roles of explorers and pathfinders.

What aphorism or motto best encapsulates your life philosophy?

*Carpe diem.*²

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¹In 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.

²*Carpe diem*, Latin for "seize the day," originates from the Roman poet Horace's *Odes* (Book 1, Ode 11), written around 23 BCE. The complete phrase—"Carpe diem, quam minimum credula postero"—translates to "Seize the day, trusting as little as possible in tomorrow." Horace was advising his friend Leuconoe to savor the present moment rather than anxiously trying to predict the future, reflecting the Epicurean philosophy popular in ancient Rome that emphasized finding joy in life's immediate pleasures given our uncertain and brief existence. While the phrase gained renewed popularity through works like the 1989 film *Dead Poets Society*, its modern interpretation as simply "live life to the fullest" somewhat simplifies Horace's original message about accepting life's inherent uncertainty and making the most of the time we have.

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