

BIOGRAPHICAL SKETCH

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NAME: Alexander B. Niculescu III, MD, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): aniculescu

POSITION TITLE: Professor of Psychiatry and Medical Neuroscience; Staff Psychiatrist and Investigator, VA

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
INSTITUTION AND LOCATION University of Bucharest Carol Davila School of Medicine, Bucharest, Romania	M.D.	07/1991	Medicine
University of Geneva Medical School, Geneva, Switzerland	M.Sc.	07/1992	Medical Biology
The Scripps Research Institute Kellog School of Science and Technology, La Jolla, CA,	Ph.D.	07/1997	Molecular Biology
The Scripps Research Institute, La Jolla CA	Postdoctoral	06/1998	Neurobiology
University of California San Diego, La Jolla, CA	Residency	07/2002	Psychiatry
University of California San Diego, La Jolla, CA	Fellowship	07/2003	Biological Psychiatry
American Board of Psychiatry and Neurology	Board Certification	07/2005	Psychiatry
Indiana University Kelly School of Business	Executive MBA	03/2019	Leadership/ Business of Healthcare

A. Personal Statement

The time has come to use broad, empirical, discovery-based approaches to understand and treat psychiatric disorders, as is happening in cancer, the field where I did my PhD. I am fortunate to have a broad background in clinical medicine as well as basic research. I was extensively trained as a researcher at Scripps, and as a clinician at UC San Diego. I am a physician/scientist, who continues to see patients, and run a research operation consisting of two labs (a human research lab, and a basic science/genomics lab). Our work is highly translational, and we have pioneered over the last two decades the development of precision medicine approaches in psychiatry. I have been fortunate to have early on great mentors, and subsequently great collaborators, as well as to receive over the years prestigious and competitive top awards in this field (NIMH Outstanding Resident of the Year, Pfizer Scholar, NARSAD Young Investigator Award (twice), APA/AstraZeneca Young Minds in Psychiatry International Award, Theodore Reich Award from the International Society for Psychiatric Genetics, VA Merit Award, NIH Directors' New Innovator Award), and the funding associated with them, which supported our ground-breaking developments in convergent functional genomics, phenomics, and biomarkers. On the practical side, we have been focused on developing clinically useful apps, blood tests and repurposed drugs to mitigate and prevent in a bio-psycho-social fashion suicidality, pain, stress, as well as mood disorders, anxiety disorders, and cognitive disorders. My life's mission is to help transform mental healthcare and bring psychiatry to the cutting edge of 21st century medical practice.

B. Positions and Honors

Positions and Employment

- 1991-1992 Research Fellow, Department of Pathology, University of Geneva Medical School, Geneva, Switzerland
- 1992-1997 Graduate Student, Program in Macromolecular and Cellular Structure and Chemistry, The Scripps Research Institute Kellogg School of Science and Technology, La Jolla, CA, Laboratory of Dr. Steven I. Reed.
- 1997-1998 Postdoctoral Fellow, Department Of Neurobiology, The Scripps Research Institute, La Jolla, CA, Laboratory of Nobel laureate Dr. Gerald M. Edelman.
- 1998-1999 Internship, UCSD School of Medicine, La Jolla, CA
- 1999-2001 Resident, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA
- 2001-2002 Chief Resident, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA
- 2001-2003 Fellow in Biological Psychiatry and Neuroscience, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA
- 2003-2004 Assistant Clinical Professor, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA
- 2002–2004 Staff Psychiatrist, VA San Diego Healthcare System; Chief, Cognitive Disorders Clinic; Associate Medical Director, Alcohol and Drug Treatment Program; Director, Laboratory of Neurophenomics, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA.
- 2004-2010 Assistant Professor of Psychiatry and Medical Neuroscience, Indiana University School of Medicine, Indianapolis, IN; Director, INBRAIN and Laboratory of Neurophenomics, Institute of Psychiatric Research; Staff Psychiatrist and Investigator, VA Medical Center Indianapolis
- 2010-2015 Associate Professor of Psychiatry and Medical Neuroscience with Tenure; Staff Psychiatrist and Investigator, VA Medical Center Indianapolis
- June 2015- Professor of Psychiatry and Medical Neuroscience; Staff Psychiatrist and Investigator, VA Medical Center Indianapolis

Other Experience and Professional Memberships (selected):

- 1999- Member, International Society for Psychiatric Genetics
- 2005- Reviewer, NIH and VA Extramural Programs. Most recently: NIH-Chair, ZRG1 BBBP S(03) 2010; VA-Member, Mental Health and Behavioral Sciences – B (MHBB) 2010; NIH ZMH1 ERB-S (04) 2012; NIH ZAT1 SRC (99) 2013; NIH ZAT1 PK 29 P 2014; NIH Fogarty International Brain Disorders 2016; ZRG1 IFCN-J (57) R 2017; ZMH1 ERB-B (03) S 2018; BGES 2020-
- 2005- 2011 Member, Institutional Review Board (IRB), Indiana University School of Medicine.
- 2007- Editorial Board, *American Journal of Medical Genetics, Part B:Neuropsychiatric Genetics*
- 2011- Founding Editorial Board member, *Translational Psychiatry*, Nature Publishing Group
- 2014- Founding Associate Editor, *Molecular Neuropsychiatry*, Karger SA
- Reviewer for other leading international journals: *Molecular Psychiatry*, *JAMA Psychiatry*, *American Journal of Psychiatry*, *Biological Psychiatry*, *Neuropsychopharmacology*, *Lancet*, *NEJM*, and others.

Honors (selected):

- 2000 National Institute of Mental Health Outstanding Resident of the Year Award
- 2002 Lewis L. Judd Chairman's Research Award, Department of Psychiatry, UC San Diego
- 2002-2005 Pfizer Fellow in Biological Psychiatry
- 2002-2004 National Alliance for Research in Schizophrenia and Depression (NARSAD) Young Investigator
- 2004 Department of Veterans Affairs Superior Performance Award, July 2004.
- 2005 American Psychiatric Association/ AstraZeneca Young Minds in Psychiatry International Award
- 2005-2007 National Alliance for Research in Schizophrenia and Depression (NARSAD) Mogens Schou Young Investigator
- 2007 Theodore Reich Award from the International Society for Psychiatric Genetics
- 2010 America's Top Psychiatrists, Consumers' Research Council of America
- 2010 NIH Directors' New Innovator Award
- 2012 Indiana University Trailblazer Award
- 2019 Indiana University School of Medicine Trustees Teaching Award

C. Contribution to Science (* corresponding author) (h-index: 36; 12 of the data papers as first or corresponding author cited over 100 times each to date, 5 of them over 200 times, 1 over 400 times and 1 over 900 times)

Convergent Functional Genomics of psychiatric disorders

Combining gene expression and genetic data, from brain and blood, in humans and animal models, has proven to be very useful in terms of prioritizing true, reproducible, signal and minimizing noise inherent in each of the individual approaches. Such a convergent approach is in essence a de facto field-wide integration across silos, relying on our data and all the other published data in the field. I first invented the approach while a resident at UCSD in 1998, and described it in a first author/corresponding author publication in 1999. Since then my lab has developed, amplified, and successfully applied the approach to mapping the genetic landscape of psychiatric disorders (bipolar disorder, schizophrenia, anxiety disorders, alcoholism).

1. ***Niculescu AB**, Segal D, Kuczenski R, Barrett T, Hauger R, Kelsoe JR. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiological Genomics* 2000; 4: 83-91.
2. Ogden CA, Rich ME, Schork NJ, Paulus MP, Geyer MA, Lohr JB, Kuczenski R, ***Niculescu AB**. Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Molecular Psychiatry* 2004; 9(11):1007-1029.
3. Ayalew M, Le-Niculescu H, Levey D, Jain N, Changala B, Patel SD, Winiger E, Breier A, Shekhar A, Amdur R, Koller D, Nurnberger JI, Corvin A, Geyer M, Tsuang MT, Salomon DR, Schork NJ, Fanous A, O'Donovan M, ***Niculescu AB**. Convergent Functional Genomics of Schizophrenia: From Comprehensive Understanding to Genetic Risk Prediction. *Molecular Psychiatry* 2012 Sep; 17(9):887-905. Epub 2012 May 15
4. D.F. Levey, H. Le-Niculescu, J. Frank, M. Ayalew, N. Jain, B. Kirlin, R. Learman, E. Winiger, Z.A. Rodd, A. Shekhar, N. J. Schork, F. Kiefe, N. Wodarz, B. Muller-Myhsok, N. Dahmer, GESGA Consortium, M. Nothen, R. Sherva, L. Farrer, A. H. Smith, H. Kranzler, M. Rietschel, J. Gelernter, **A. B. Niculescu***. Genetic Risk Prediction and Neurobiological Understanding of Alcoholism. *Translational Psychiatry*. 2014 May 20;4:e391. doi: 10.1038/tp.2014.29.

PhenoChipping of psychiatric disorders and mental landscape model (Mindscape)

Studying quantitative phenotypes (phenes) using tools from genomics may be productive in terms of understanding the true structure of psychiatric disorders, as opposed to the ad hoc description in DSM. I invented such an approach in 2004, terming it PhenoChipping, by analogy to GeneChipping, and described it in a first author/corresponding author publication in 2006. Since then, we have used such analyses as part of animal model and human studies. In addition, prior to the current emphasis on dimensional approaches in RDoC, I described a multidimensional mental landscape approach in a first author/corresponding author publication in 2009.

1. ***Niculescu AB**, Lulow L, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ, Caligiuri MP, Lohr JB. PhenoChipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*. 2006. 141(6):653-662.
2. ***Niculescu AB**, Schork NJ, Salomon DR. Mindscape: a convergent perspective on life, mind, consciousness and happiness. *Journal of Affective Disorders* 2010 123(1-3):1-8. Epub 2009 July10.

Blood biomarkers for psychiatric disorders

In our original CFG work in 1999, we conducted a pilot blood gene expression study on one of our candidate genes for bipolar disorder, GRK3 (now called, ADARKB2), which suggested the possibility of a peripheral readout. As the target organ in psychiatry cannot be readily biopsied in live individuals, it is imperative to develop peripheral markers (liquid biopsies, as they are called in cancer). We have pursued this approach years later, using initially case-case and subsequently within-subject designs in high risk psychiatric subjects, with validation in independent cohorts. We have thus demonstrated the identification of biomarkers for mood state, psychosis, and, very recently, for the effects of mood and stress on lifespan.

1. Le-Niculescu H, Kurian SM, Yehyaw N, Dike C, Patel SD, Edenberg HJ, Tsuang MT, Salomon DR, Nurnberger Jr JI, ***Niculescu AB**. Identifying Blood Biomarkers For Mood Disorders Using Convergent Functional Genomics. *Molecular Psychiatry* 2009; 14(2):156-74. Epub 2008 Feb 26.

2. Kurian SM, Le-Niculescu H, Patel S, Bertram D, Davis J, Dike C, Yehyaw N, Lysaker P, Dustin J, Caligiuri M, Lohr J, Lahiri DK, Nurnberger JI, Faraone SV, Geyer MA, Tsuang MT, Schork NJ, Salomon DR, ***Niculescu AB**. Identification of Blood Biomarkers For Psychosis Using Convergent Functional Genomics. *Molecular Psychiatry* 2011 Jan;16(1):37-58. Epub 2009 November 24.
3. Le-Niculescu H, Roseberry K, Levey DF, Rogers J, Kosary K, Prabha S, Jones T, Judd S, McCormick MA, Wessel AR, Williams A, Phalen PL, Mamdani F, Sequeira A, Kurian SM, *** Niculescu AB**, . Towards Precision Medicine for Stress Disorders: Diagnostic Biomarkers and Targeted Drugs. *Molecular Psychiatry* 2019 March 12. doi: 10.1038/s41380-019-0370-z. [Epub ahead of print].
4. Le-Niculescu H, Roseberry K, Gill SS, Levey DF, Phalen PL, Mullen J, Williams A, Bhairo S, Voegtline T, Davis H, Shekhar A, Kurian SM, **Niculescu AB**. Precision medicine for mood disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. *Molecular Psychiatry*; 2021 Apr 8; doi: 10.1038/s41380-021-01061-w. [Epub ahead of print] PMID: 33828235.

Precision Medicine for Suicide

Following our ground-breaking biomarkers in psychiatry studies, we focused on discovering blood biomarkers for suicide, and then on combined approaches using apps along with biomarkers.

1. H. Le-Niculescu, D. F. Levey, M. Ayalew, L. Palmer, L. M. Gavrin, N. Jain, S. Bhosrekar, G. Shankar, E. Belanger, K. Olesek, H. Duckworth, J. Vergo, R. Schweitzer, M. Radel, M. Yard, A. Ballew, A. Shekhar, G. Sandusky, N. J. Schork, S. M. Kurian, D. R. Salomon, **A. B. Niculescu***. Discovery and Validation of Blood Biomarkers for Suicidality. *Molecular Psychiatry* 2013 Dec;18(12):1249-64. doi: 10.1038/mp.2013.95. Epub 2013 Aug 20.
2. ***Niculescu AB**, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, Belanger E, James A, George S, Weber H, Graham DL, Schweitzer R, Ladd TB, Learman R, Niculescu EM, Vanipenta NP, Khan FN, Mullen J, Shankar G, Cook S, Humbert C, Ballew A, Yard M, Gelbart T, Shekhar A, Schork NJ, Kurian SM, Sandusky GE, Salomon DR. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular Psychiatry* 2015 Nov;20(11):1266-85. doi: 10.1038/mp.2015.112.
3. Levey DF, Niculescu EM, Le-Niculescu H, Dainton HD, Phalen PL, Ladd TB, Weber H, Belanger E, Graham DL, Khan FN, Vanipenta NP, Stage EC, Ballew A, Yard M, Gelbart T, Shekhar A, Schork NJ, Kurian SM, Sandusky GE, Salomon DR, ***Niculescu AB**. Towards understanding and predicting suicidality in women: biomarkers and clinical risk assessment. *Molecular Psychiatry* 2016 Jun;21(6):768-85. Epub 2016 Apr 5.
4. **Niculescu AB**, Le-Niculescu H, Levey DF, Phalen PL, Dainton HL, Roseberry K, Niculescu EM, Niezer JO, Williams A, Graham DL, Jones TJ, Venugopal V, Ballew A, Yard M, Gelbart T, Kurian SM, Shekhar A, Schork NJ, Sandusky GE, Salomon DR. Precision Medicine for Suicidality: from universality to subtypes and personalization. *Molecular Psychiatry* 2017. Sep;22(9):1250-1273. doi: 10.1038/mp.2017.128. Epub 2017 Aug 151 PMID: 28809398

Clinical trials and practical applications

I have been a site PI for a large trial comparing augmentation of treatments for depression published in JAMA, and am currently a site PI for a large trial examining lithium augmentation for suicide prevention. Have proposed streamlined trial designs using precision medicine approaches. Our work on biomarkers is being extended into new indications (pain, Alzheimer), new drug discovery and repurposing drugs, and we are stratifying risk in various populations.

1. Mohamed S, Johnson GR, Chen P, Hicks PB, Davis LL, Yoon J, Gleason TC, Vertrees JE, Weingart K, Tal I, Scrymgeour A, Lawrence DD, Planeta B, Thase ME, Huang GD, Zisook S; and the VAST-D Investigators, Rao SD, Pilkinton PD, Wilcox JA, Iranmanesh A, Sapra M, Jurjus G, Michalets JP, Aslam M, Beresford T, Anderson KD, Fernando R, Ramaswamy S, Kasckow J, Westermeyer J, Yoon G, D'Souza DC, Larson G, Anderson WG, Klatt M, Fareed A, Thompson SI, Carrera CJ, Williams SS, Juergens TM, Albers LJ, Nasdahl CS, Villarreal G, Winston JL, Nogues CA, Connolly KR, Tapp A, Jones KA, Khatkhate G, Marri S, Suppes T, LaMotte J, Hurley R, Mayeda AR, **Niculescu AB** 3rd, Fischer BA, Loreck DJ, Rosenlicht N, Lieske S, Finkel MS, Little JT. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *JAMA*. 2017 Jul 11;318(2):132-145. doi: 10.1001/jama.2017.8036.

2. Brucker KM, Duggan C, Roseberry K, Le-Niculescu H, ***Niculescu AB**, *Kline JA. Assessing Risk of Future Suicidality in Emergency Department Patients, *Academic Emergency Medicine*, 2018 Oct 30. doi: 10.1111/acem.13562. [Epub ahead of print] PMID: 30375082
3. * **Niculescu AB**, Le-Niculescu H, Levey DF, Roseberry K, Soe KC, Rogers J, Khan F, Jones T, Judd S, McCormick MA, Wessel AR, Williams A, Kurian SM, White F. Towards Precision Medicine for Pain: Diagnostic Biomarkers and Repurposed Drugs. *Molecular Psychiatry* 2019 Apr;24(4):501-522. doi: 10.1038/s41380-018-0345-5. Epub 2019 Feb 12. PMID:30755720.
4. ***Niculescu AB**, Le-Niculescu H, Roseberry K, Wang S, Hart J, Kaur A, Robertson H, Jones T, Strasburger A, Williams A, Kurian SM, Lamb B, Shekhar A, Lahiri DK, Saykin AJ. Blood biomarkers for memory: toward early detection of risk for Alzheimer disease, pharmacogenomics, and repurposed drugs. *Molecular Psychiatry* 2019 Dec 2. doi: 10.1038/s41380-019-0602-2. [Epub ahead of print] PMID: 31792364.

Complete List of Published Work:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=Niculescu+AB>

D. Research Support

Active

Indiana University – tenured academic appointment

R01MH117431 (Niculescu)

08/02/19-05/31/24

NIH-NIMH

Biomarkers for Suicidality

We propose to conduct studies as a way of accelerating the discovery of clinical useful biomarkers for suicidality, as well as to use biomarkers information as a way of understanding biology and developing treatments. Role: PI

Richard L. Roudebush Veterans Affairs Medical Center – part-time appointment

Department of Veterans Affairs, BLR&D

01/01/20-12/31/23

Collaborative Merit Review Award for Traumatic Brain Injury (Niculescu)

“CTBI: Traumatic brain injury-induced inflammation effects on cognitive evaluations and response inhibition: Mechanisms of increased risk for suicidality.” Role: PI

Completed (in the last 5 years)

1 K12 HL133310 (Kline)

08/15/16-06/30/21

NIH-NHLBI

The Indiana EMERGENCY Care REsearch (Indiana EMCARE) training program at Indiana University School of Medicine (IUSM)

Major Goals: To address the critical need for researchers who can design and execute investigator-initiated clinical trials in the emergency care setting, the Indiana EMCARE interdisciplinary program will recruit and train scholars to have the basis to become independent, R01-funded clinical trials.

Role: Co-I, Psychiatry Program Director

VA CSP 590

08/30/13-09/30/19

VA Cooperative Studies Program

“A Randomized Double-Blind Placebo-Controlled Trial of Lithium Augmentation and Enhanced Suicide Prevention Management”. Role: Indianapolis Site PI.

VA 2I01CX000139 (Niculescu)

2009-2018

VA Merit Award

“Blood Biomarkers for Mood and Related Disorders”

Goals: To discover biomarkers for mood and related disorders. Role: PI