American College of Neuropsychopharmacology

HOT TOPICS

Precision medicine in psychiatry: biomarkers to the forefront

Alexander B. Niculescu[1,2,3]✉ and Helen Le-Niculescu[1,2]

Neuropsychopharmacology (2022) 47:422–423; https://doi.org/10.1038/s41386-021-01183-3

We have initiated and developed over the last two decades a translational methodology for identifying clinically informative and actionable biomarkers, from bench to bedside. This was made possible by our long-term longitudinal studies combining deep phenotyping, genomics, and clinical outcomes. Biomarkers, as their name implies, are biological measures that serve as objective quantitative markers of the function of an organ or system. In the case of the brain, they can be molecular, electrophysiological, or imaging. Each has advantages and limitations, and synergy may be obtained by their integration. One useful analogy is with cardiology, where cardiac enzymes, EKG, and cardiac imaging may be useful in terms of assessing function and risk. For the brain, surrogate molecular markers can be found in peripheral tissues and fluids. In particular blood, containing secretion products of various tissues, and cells of the immune system, has become a useful accessible source of biomarkers. In cancer, the comparable term of the art for this is "liquid biopsy".

Why would markers in the blood correlate with brain function and with behavior? First, there are in some instances leakage, direct secretions and exosomes from the nervous system into the blood and other fluids. Second, and more importantly, the vagus nerve directly connects the nervous system with the rest of the body, influencing multiple physiological systems. Third, and most importantly, next to the nervous system, the immune system is the most reactive, active and complex system in the body. It has some developmental commonalities with the nervous system, and has bi-directional interactions during all of life. Moreover, common internal milieu (hormones, al.) and external environmental factors (medications, al.) lead to some common gene expression patterns in brain and white blood cells. Our approach has focused on whole-blood gene expression (RNA) biomarkers. These can be identified using a careful and systematic four-step approach: discovery, prioritization, validation, and testing for clinical utility, in independent cohorts. RNA can be more easily assessed in a comprehensive fashion (whole genome) than the proteome, or metabolome. This is important for unbiased discovery. These type of RNA biomarkers vary over time, unlike DNA, i.e. they have a state severity component. They also have some integration of past events, and predictive ability for future events, i.e. have a trait component as well.

In addition, each biomarker can be tied to multiple existing psychiatric medications that can influence its levels of expression (pharmacogenomics), in a direction opposite to the one in disease, i.e. normalize its expression. Thus, existing psychiatric drugs can be ranked for potential ability to treat/normalize the biomarkers of that particular patient, and their effect monitored with biomarkers.

Finally, panels of biomarkers can also be used to match patients with non-psychiatric medications or nutraceuticals. This may provide new avenues for treatment with repurposed drugs.

We have demonstrated the above series of steps and approaches, in published studies to date for six indications: suicidality [1], longevity [2], pain [3], PTSD [4], memory/Alzheimer [5], and most recently mood disorders (depression/bipolar) [6]. Such approaches can help psychiatry become a 21st century, cutting-edge, biomedical specialty.

REFERENCES

1. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, et al. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. Mol Psychiatry. 2015;20:1266–85.
2. Rangaraju S, Levey DF, Nho K, Jain N, Andrews KD, Le-Niculescu H, et al. Mood, stress and longevity: convergence on ANK3. Mol Psychiatry. 2016;21:1037–49.
3. Niculescu AB, Le-Niculescu H, Levey DF, Roseberry K, Soe KC, Rogers J, et al. Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs. Mol Psychiatry. 2019;24:501–22.
4. Le-Niculescu H, Roseberry K, Levey DF, Rogers J, Kosary K, Prabha S, et al. Towards precision medicine for stress disorders: diagnostic biomarkers and targeted drugs. Mol Psychiatry. 2020;25:918–38.
5. Niculescu AB, Le-Niculescu H, Roseberry K, Wang S, Hart J, Kaur A, et al. Blood biomarkers for memory: toward early detection of risk for Alzheimer disease, pharmacogenomics, and repurposed drugs. Mol Psychiatry. 2020;25:1651–72.
6. Le-Niculescu H, Roseberry K, Gill SS, Levey DF, Phalen PL, Mullen J, et al. Precision medicine for mood disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. Mol Psychiatry. 2021. https://doi.org/10.1038/s41380-021-01061-w.

ACKNOWLEDGEMENTS

We would like to acknowledge our gratitude for the work and results of the many other groups, cited in our papers, who have conducted and published studies (clinical, genetic, and biological) in psychiatry. Combining their work with ours makes a convergent approach possible. We would like to thank members of the Niculescu Lab for the excellent work over the years. We also would particularly like to thank the subjects in our studies and their families. Without their contribution, such work to advance the objective understanding and treatment of psychiatric disorders would not be possible.

AUTHOR CONTRIBUTIONS

ABN conceived and wrote the manuscript. HLN provided comments and suggestions.

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. [2]Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA. [3]Indianapolis VA Medical Center, Indianapolis, IN, USA. ✉email: anicules@iupui.edu

Published online: 28 September 2021

FUNDING INFORMATION
This work was supported by NIH grants (1DP2OD007363 and R01MH117431) and a VA Merit Award (2I01CX000139) to ABN. ABN is listed as inventor on patent applications filed by Indiana University, and is a co-founder of MindX Sciences. HLN has no disclosures

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Alexander B. Niculescu.