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INVITED COMMENTARY

Predicting Suicidal Behavior: Are We Really that Far Along? Comment on "Discovery and Validation of Blood Biomarkers for Suicidality"

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Abstract A recent publication focused on biomarkers of future suicidal behaviors identifies several genes expressed in high-risk states among four samples. We discuss the implications of this study as well as the current state of research regarding biomarkers of suicidal behavior.

Keywords Suicidal behavior · Prediction · Biomarkers

> *Mr. Marks, by mandate of the District of Columbia Precrime Division, I'm placing you under arrest for the future murder of Sarah Marks and Donald Dubin that was to take place today, April 22 at 0800 hours and four minutes.*
>
> "Minority Report", Steven Spielberg (2002)

Predicting future behavior is a long-standing goal and a matter of particular interest for behavioral scientists. The prediction of suicidal behavior, from minimally harmful to lethal suicide attempts, is particularly challenging because, thus far, it depends on the subjective reports of the individual at risk. However, the elevated expression of certain RNA biomarkers might help to predict future suicidal behavior according to a recent paper published in *Molecular Psychiatry* by Le-Niculescu and colleagues [1]. Their findings aim to take us closer to an objective measure of suicide risk. The relevance of such studies is sustained by other reports showing that suicidal subjects often do not disclose their suicidal thoughts [2, 3], with myriad underlying reasons –i.e., hospitalization, fear of stigma, thwarted plans– for hiding this information [1].

The low base rate of attempted and completed suicide [4], and the relatively poor performance of models based on a restricted number of variables [5] are major difficulties in the prediction of suicidal behavior. To date, clinical factors (notably depression and alcoholism), previous suicide attempts, and life events are among the best predictive factors for suicidal behavior [6–8]. Some biological factors have also been closely associated with suicide risk, particularly reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) and abnormal results in the dexamethasone suppression test (DST) [9]. Given that biomarkers should be simple to obtain, non-invasive, and inexpensive, recent research has focused on other putative biomarkers of suicidal behavior such as reduced cholesterol, omega 3 fatty acids [10], or brain-derived neurotrophic factor (BDNF) in serum or plasma [11].

An essential issue is that biomarker studies must use not only excellent biological approaches but robust phenotypes. Indeed, given that for complex behaviors such as suicidal behavior, it is anticipated that only biomarkers of small effect sizes will be in play, identification is likely to only be attained when reliable, valid clinical characterization is used. This is a high bar and one of the reasons why identification of biomarkers, thus far, has been disappointing.

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Le-Niculescu and colleagues explored blood gene expression biomarkers for suicidality in four small male cohorts: i) one discovery cohort of live bipolar subjects (n=9); ii) one age-matched cohort of suicides from the coroner's office (n=9); and iii) two prospective follow-up cohorts with subjects affected by bipolar disorder (n=42) and psychosis (n=46) [1]. Suicidal behavior in the live subjects was identified using the suicide-related item of the Hamilton Depression Rating Scale (HDRS). Suicide was determined by the coroner. Hospitalization for suicidal behavior was determined through chart review. Although the higher scores on the HDRS suicide-related item confound different suicidal behaviors (a score of 3 can mean "gesture" or pronounced suicidal ideation), the scores were used to classify individuals as having no suicidal ideation (SI) or high SI. Those with low and high scores were compared to identify potential biomarkers in the discovery cohort. Putative relevant biomarkers related to suicidality were then validated in the cohort of suicides. After correction for multiple comparisons, four biomarkers differentiated future and past hospitalizations with suicidality in the prospective cohorts of individuals with either bipolar disorder or psychosis. SAT1 (spermidine/spermine N1–acetyltransferase 1) was identified as the top biomarker comporting with alterations of the polyamine system in brains of suicides described by Turecki and colleagues [12]. In fact, several genes implicated in polyamine biosynthesis seem to be up-regulated in the brains of suicides. On the other hand, SAT1 and another "top" biomarker (CD24 molecule/small cell lung carcinoma cluster 4 antigen) are related with apoptosis, or *programmed cell death*.

Le-Niculescu and colleagues are to be commended for the use of multi-dimensional approaches in the prediction of suicidal behavior. The authors sequentially added data about mood, anxiety and psychosis to the expression levels of the biomarkers. They generated a series of receiver-operating characteristic (ROC) curves together with the average area under the curves (AUC) for increasingly complex models (SAT1; SAT1+anxiety; SAT1+anxiety+mood; SAT1+anxiety+mood+psychosis) of future hospitalizations due to suicidal behavior. In this way, they found that the AUC for future hospitalizations with suicidality increased progressively from 0.640 (with SAT1 alone) to 0.835 (with SAT1, anxiety, mood, and psychosis). In other words, they enhanced their capability to predict hospitalizations with suicidality by combining genetic and clinical factors.

Previous models have achieved better results in classifying suicide attempters just using the most discriminant items from four assessment scales and socio-demographic factors (AUC=0.92) [5]. For a biomarker to be clinically useful, it must have high sensitivity (>90 %) and specificity (>90 %) [13]. They should also show strong predictive value [14]. Unfortunately, ROC curves with an AUC<0.75 are not clinically useful [15]. However, the combination of biological factors with other variables (clinical, psychological) associated with suicidal behavior may be a good strategy to improve the predictive capacity of explanatory models.

While acknowledging the value of the study by Le-Niculescu and colleagues, a number of limitations should be noted. The most relevant one is the construction of a "predictive" model of suicidal behavior from a small sample of nine male bipolar individuals with/without suicidal ideation, and the use of human postmortem brain evidence, a completely different suicidal endophenotype, to test the model. Even suicide attempters, a more proximate population than suicide ideators, share only some of the characteristics of suicide completers [16]. Before any generalization can be made, their results need to be replicated in larger, more clearly characterized samples. Moreover, the suicidal behavior of live participants was not well-characterized. The concept of 'suicidality', widely used by the authors, lacks precision and decreases the validity of their findings [17].

The study by Le-Niculescu and colleagues [1] exemplarizes a potential strategy to identify routine blood tests in the prediction and prevention of suicidal impulses. Unfortunately, we are still far from this point. Among other pending tasks in suicidal research, clinicians can refine known endophenotypes for suicidal behavior, such as impulsive aggression traits or psychological pain, to facilitate the identification of expressed genes that are associated with them. Predicting suicidal behavior can also be enhanced by selecting the most discriminant variables [5], using predictors from different domains (clinical, neurobiological and cognitive) [18], and by applying novel methodological instruments such as data mining [19]. For the time being, we should remember that several strategies, such as assuring aggressive treatment for depression [20] and continuity of care to prevent relapses [21] may successfully reduce suicide rates, until such time as we reach the goal of predicting future suicide events.

Compliance with Ethics Guidelines

Conflict of Interest Hilario Blasco-Fontecilla has received lecture fees from Eli Lilly, AB-Biotics, and Shire.

Jorge Lopez-Castroman, Lucas Giner, Enrique Baca-Garcia declare that they have no conflict of interest. Maria A. Oquendo has received unrestricted educational grants and/or lecture fees form AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire. She receives royalties from the commercial use of the C-SSRS, and her family owns stock in Bristol-Myers Squibb.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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