## Use of Gene Expression Biomarkers to Predict Suicidality

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Since the tragic accident of Germanwings flight 4U9525, there has been discussion about methods to identify and prevent suicidality in pilots. Neurogenetic scientists claim that biomarker tests for suicidality as part of healthcare assessments may lead to early identification of suicidal behavior. In this commentary the value of these gene expression biomarkers for aeromedical purposes is evaluated based on relevant literature. It is concluded that the currently identified biomarkers for suicidality need thorough validation before they can be used. The aeromedical examiner's most important tool is still an anamnesis, in which warning signs of suicidal behavior can be picked up.

**KEYWORDS:** pilots, identification of suicidality, prevention, biomarkers.

Simons R. Use of gene expression biomarkers to predict suicidality. Aerosp Med Hum Perform. 2016; 87(7):659-660.

Since the tragic accident of Germanwings flight 4U9525 in 2015, when it appeared that the aircraft was deliberately flown by a pilot into a mountain side, there has been speculation and discussion about methods to predict and prevent suicide of pilots. Some discussants hope, or think, that there is a simple test or biomarker to identify high risk cases. There have been many studies which have emphasized the importance of various factors in leading to suicide. These factors are considered to be the expression of suicidal ideation, the presence of bipolar depressive disorder, depression, and schizophrenia, alcohol and drug dependence, increasing age, chronic physical illness, longer-term disturbed sleep, social isolation, availability of self-destructive means, and increasing publicity about suicide.<sup>1,4</sup>

Current theories of suicide suggest individuals end their own lives in order to escape intolerable circumstances, whether or not due to adverse life circumstances or psychiatric disorders. Most people in such circumstances, however, use another escape than suicide and find ways to cope with adversity. What is the mechanism by which some will sacrifice their life to suicide, while others in a like-environment would not even consider the thought? Suicide prevention thus needs markers that predict suicidal behavior and serve as a substrate for treatment.<sup>10</sup> In the quest for predictive markers, neurogenetic scientists have considered the use of blood gene expression biomarkers for suicidality.<sup>6</sup>

The aim of this commentary is to discuss literature on these biomarkers in order to consider their usefulness in the aeromedical context and to emphasize the value of psychological warning signs that can help us to identify high risk cases. Developing biomarkers for quantitative and objective ways to predict and track suicidal states would have immediate practical applications and positive societal implications. Individuals who are truly suicidal often do not share their thoughts with clinicians<sup>3</sup> and, therefore, assessment of blood gene expression biomarkers for suicidality would be advantageous to identify high risk cases.

Le-Nicolescu et al.<sup>5</sup> have published a study detailing the identification of blood gene expression biomarkers for suicidality. The study used a longitudinal within-subjects design in male bipolar subjects, a high-risk group for suicide, identifying a subgroup of subjects who exhibited major switches in suicidal ideation during different testing visits. Differential gene expression studies within each subject were carried out and changes in expression across the different subjects were analyzed. A convergent functional genomics (CFG) approach was used to prioritize the differentially expressed gene list, using independent lines of evidence for suicide (human

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This manuscript was received for review in February 2016. It was accepted for publication in March 2016.

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genetic studies, human postmortem brain studies). The genes prioritized by CFG were validated by testing for changes in expression in the blood of a cohort of male violent suicide completers, matched for gender and age. Six genes (SAT1, MARCKS, UBA6, PTEN, MAP3K, and MT-ND6) showed a statistically significant, Bonferroni corrected, stepwise change in expression from not-suicidal bipolar subjects to high suicidal subjects to suicide completers. In a larger bipolar cohort, it was also found that biomarker levels can predict psychiatric hospitalizations for suicidality.<sup>6</sup> The area under the curve (AUC) that was created by plotting the sensitivity against the false positive rate (1-specifity) of the combination of the above six markers was 0.73, which is considered as fair.<sup>9</sup> This result is promising, but the AUC of 0.73 also indicates that the predictive value should improve before this test is ready to implement as part of routine assessments. Further validation studies covering different groups of male and female nonbipolar individuals are needed. Although there is still a long way to go, blood gene expression biomarkers for suicidality have potential to become useful diagnostic aids in combination with clinical observations. In the future, biomarkers may even enable differentiation between violent vs. nonviolent and impulsive vs. planned suicide completers using different sets of markers.<sup>6</sup> Punzi et al.<sup>7</sup> have replicated the marker MARCKS in the brains of male violent suicide completers with schizophrenia, but not in those with depression or with nonviolent suicide.

This work has raised hopes for progress, but for aeromedical assessments the tests are still futuristic and attention should currently be focused on picking up warning signs of suicidal behavior. In a study of aircraft-assisted pilot suicide, Vuorio et al.<sup>11</sup> found that in five out of the eight completed suicides, someone knew of a victim's suicidal ideation. They conclude that it is important that indications and warnings for suicides be taken seriously so that effective interventions can be implemented.

Analyzing 237 suicide death investigation files of U.S. Air Force airmen, Cox et al.<sup>2</sup> found that the most frequent factors that were communicated before and at death (via suicide notes) were hopelessness (35.7%), perceived burden-someness (31.6%), and thwarted belongingness (29.6%). These factors are also considered warning signs of suicidal behavior by the Suicide Prevention Resource Center of the Substance Abuse and Mental Health Services Administration (SAMHSA)<sup>8</sup> mentioned below:

- Talking about wanting to die or kill oneself;
- · Looking for a way to kill oneself;
- · Talking about feeling hopeless or having no reason to live;
- · Talking about feeling trapped or being in unbearable pain;
- Talking about being a burden to others;
- Increasing the use of alcohol or drugs;
- Acting anxious or agitated; behaving recklessly;
- Sleeping too little or too much;

- Withdrawing or feeling isolated;
- Showing rage or talking about seeking revenge;
- Displaying extreme mood swings.

It is concluded that the currently identified biomarkers for suicidality need thorough validation before they can be used in an aeromedical context. There is currently no simple test to identify the risk of suicidal behavior. The aeromedical examiner's most important tool is still an anamnesis, in which warning signs of suicidal behavior can be picked up. This is most likely to succeed when aeromedical examiners develop a trustful and understanding relationship with their pilots. In such a relationship, early signs of an adverse professional and/or social development of the pilot can be identified and guidance can be given concerning coping strategies and preventive measures.

## ACKNOWLEDGMENTS

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