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The Role of Biomarkers and Endophenotypes in Prevention and Treatment of Psychopathological Disorders

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The term biomarker is used in numerous scientific disciplines. Accordingly, several different types of biomarkers exist, ranging from biosignatures in geology to surrogate endpoints in medicine. Although any of these types of biomarkers could provide for an interesting discussion, in this editorial I focus on biomarkers as endogenous, measurable characteristics that mark either risk for or manifestation of psychiatric illness. For example, recent proton magnetic resonance spectroscopy (^{1}H MRS) studies indicate that choline concentrations in the cingulate cortex correlate positively with depression ratings among patients with bipolar disorder compared with controls[1]. Thus, choline levels in the cingulate appear to be a state dependent biomarker of the depressive phase of bipolar illness. This state dependence suggests that choline concentrations in the cingulate may serve as an objective biomarker of treatment response.

Biomarkers versus endophenotypes

An important subtype of biomarkers are endophenotypes, which have a more restrictive definition, as outlined by Gould and Gottesman[2]. First, an endophenotype must segregate with illness in the general population. Second, an endophenotype must be heritable. Third, an endophenotype must be state independent, manifesting whether illness is present or in remission. Fourth, an endophenotype must cosegregate with the disorder within families. Fifth, an endophenotype must be present at a higher rate within affected families than in the general population. Finally, an endophenotype should be a characteristic that can be measured reliably, and be specific to the illness of interest[3]. When these six criteria are met, the endophenotype is assumed to mark genetic risk of illness, whether or not illness is expressed phenotypically. Note that by this definition, choline concentrations in the cingulate cortex of bipolar patients do not qualify as an endophenotype because they are dependent on clinical state. Therefore, this marker cannot be used to identify those who are at genetic risk for bipolar disorder yet are not ill.

A good example of an endophenotype in psychiatric research can be found in the literature on schizophrenia. Patients with schizophrenia exhibit irregularities in smooth pursuit eye tracking. These irregularities are measured by eye tracking devices while patients follow a moving stimulus. Although the pathophysiology of eye tracking dysfunction is not fully understood, as many as 80% of schizophrenia patients exhibit this trait, as do up to 45% of their first degree relatives, compared with only 10% of healthy controls[4]. It is noteworthy that this 10% figure is very close to the estimated prevalence rate of schizophrenia liability in the general population[5]. However, because schizophrenia liability is not fully penetrant, the majority of these individuals never develop the disorder.

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Following from the above discussion, eye tracking dysfunction qualifies as an endophenotype of schizophrenia liability because it (a) appears to segregate with risk of illness in the population, (b) is heritable, (c) is state independent, (d) cosegregates with illness within families[6], (e) is present at a higher rate in affected families than in the general population, and (f) can be measured reliably and is specific to schizophrenia liability.

Endophenotypes and prevention

Given their state independence, endophenotypes hold much promise in prevention research because they can be used to identify those who are at high risk of developing psychiatric disorders[7]. Once again, a good example comes from research on schizophrenia. Using a statistical technique called taxometrics, Erlenmeyer-Kimling, Golden, and Cornblatt[8] selected three putative endophenotypes (sustained visual attention, neuoromotor performance, and selected measures of intelligence) to identify a high risk group of 7–12-year-old children of a parent with schizophrenia. Their analysis identified 47% of children as high risk, compared with 4% of controls. Importantly, by age 22–29, 43% of the high risk group had been hospitalized or received significant treatment for a schizophrenia spectrum disorder. Using similar methods, these findings were later replicated by an independent research group[9].

As we have noted elsewhere[10], the implications of these findings are difficult to overstate. Enrolling all children of a parent with schizophrenia in a prevention program is woefully inefficient because only 10%–15% will develop a schizophrenia spectrum disorder. However, analysis of putative endophenotypes can identify a group at nearly 50% risk, making prevention much more efficient. Importantly, prevention programs can be quite effective for those at high risk for schizophrenia. For example, by administering a low dose of risperidone, McGorry et al.[11] substantially reduced the emergence of first episode psychosis in a group of high risk patients. Those who took risperidone and participated in a cognitive behavioral intervention were 95% psychosis free three years later, compared with 30% who received typical needs-based care.

Extending the use of endophenotypes to other psychiatric disorders

In psychiatric research, biomarkers have been identified for many disorders. Yet despite their usefulness for prevention, very few endophenotypes have been discovered. One reason for this is that psychiatric disorders are often etiologically heterogeneous. For example, recent research suggests that there are distinct subtypes of major depression[12]. However, these subtypes are very difficult to distinguish from one another based solely on symptoms. Yet symptoms are usually the only source of information used to diagnose. As a result, etiologically heterogeneous samples are recruited for most research studies, which obfuscates identification of endophenotypes. Thus, until researchers subdivide their samples based on best guesses about alternative etiologies, identification of endophenotypes will remain elusive.

In medicine, it is universally accepted that etiological diagnosis is superior to syndromal (symptom-based) diagnosis. When etiology is understood, prevention and treatment strategies usually improve because mechanisms of illness can be targeted directly. Thus, the search for endophenotypes is an important development in psychiatric research insofar as it brings us closer to etiological mechanisms of psychopathology. Hopefully, future efforts will identify endophenotypes for a host of psychiatric disorders, leading to improved prevention and treatment programs, and legitimizing the current popularity of the term.

References

1. Moore C, Breeze JL, Gruber S, Frederick B, Villafuerte R, et al. Choline, myo-inositol, and mood in bipolar disorder: A proton magnetic spectroscopic imaging study of the anterior cingulated cortex. Bipolar Disord 2000;2:207–216. [PubMed: 11249799]
2. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. Genes, Brain, & Beh 2006;5:113–119.
3. Chan RCK, Gottesman II. Neurological soft signs as candidate endophenotypes in schizophrenia: A shooting star or a northern star? Neuroscience & Biobeh Rev 2008;32:957–971.
4. Gottesman II, Gould. The endophenotype concept in psychiatry: Etymology and strategic intentions. 2003;160:636–645.
5. Korfine L, Lenzenweger MF. The taxonicity of Schizotypy: A replication. J Abn Psychology 1995;104:26–31.
6. Grove WM, Clementz BA, Iacono WG, Katsanis J. Smooth pursuit ocular motor dysfunction in schizophrenia: Evidence for a major gene. Am J Psychiatry 1992;149:1362–1368. [PubMed: 1530073]
7. Beauchaine TP, Neuhaus E, Brenner SL, Gatzke-Kopp L. Ten good reasons to consider biological processes in prevention and intervention research. Dev Psychopath 2008;20:745–774.
8. Erlenmeyer-Kimling L, Golden RR, Cornblatt BA. A taxometric analysis of cognitive and neuromotor variables in children at risk for schizophrenia. J Abn Psychology 1989;98:203–208.
9. Tyrka AR, Cannon TD, Haslam N, Mednick SA, Schulsinger F, Schulsinger H, et al. The latent structure of schizotypy: I. Premorbid indicators of a taxon in individuals at risk for schizophrenia spectrum disorders. J Abn Psychology 1995;104:173–183.
10. Beauchaine, TP.; Marsh, P. Taxometric methods: Enhancing early detection and prevention of psychopathology by identifying latent vulnerability traits. In: Cicchetti, D.; Cohen, DJ., editors. Developmental psychopathology. Vol. 2. Vol. 1: Theory and Method. Wiley; 2000.
11. McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002;59:921–928. [PubMed: 12365879]
12. Beach SRH, Amir N. Is depression taxonic, dimensional, or both? J Abn Psychology 2003;112:228–236.