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Biomark Med. Author manuscript; available in PMC 2020 January 27.

Published in final edited form as:

Biomark Med. 2014 ; 8(1): 51–57. doi:10.2217/bmm.13.134.

Biomarkers in psychosis: an approach to early identification and individualized treatment

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Abstract

Numerous biomarkers for somatic disorders are used in routine medical practice. Yet, despite remarkable advances in mental health research, we are not able to identify biomarkers with established clinical utility for mental disorders such as schizophrenia. While identification and characterization of biomarkers are crucial first steps in this process, their predictive diagnostic and treatment utility need to be better developed for clinical practice. The heterogeneity of psychotic disorders etiologically, pathologically and symptomatically presents both a challenge and an opportunity for the use of biomarkers in clinical practice. Simply said, a single biomarker might not exist that necessitates the search for a biomarker profile. In this review we discuss research findings in light of such an approach. We summarize some examples of emerging biomarkers in early psychosis research and delineate how these can be applied to a clinical setting to inform treatment on an individual basis fostering a personalized treatment approach.

Keywords

algorithm; biomarkers; prodrome; psychosis; schizophrenia; treatment

The term biological marker or biomarker has been defined in many different ways in the literature. For instance, the NIH Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” In practical terms, a biomarker refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly [1]. In the case of nonpsychiatric illness, such as HIV, the observation of certain clinical manifestations (Kaposi’s sarcoma) and blood tests (HIV ELISA and viral count) can provide both an accurate and reproducible measure of the presence of illness. These markers can be used in a clinical setting to not only accurately diagnose but also generate an appropriate treatment plan for patients. In the case of

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No writing assistance was utilized in the production of this manuscript.

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neuropsychiatric disorders, however, the task has been much more difficult. For instance, in schizophrenia (SCZ), no single symptom is unique to the disorder. Positive symptoms can be seen in virtually all mood and anxiety disorders; negative symptoms are common in depression; and cognitive impairments are not necessarily unique to SCZ. The prodrome of psychosis is marked by attenuated psychotic symptoms. These are symptoms that deviate from normal behavior but are not frankly psychotic, as described by Yung and colleagues [2,3]. At present, diagnosis is based largely on patient reports of symptoms and/or collateral reporting, but remains relatively devoid of objective, brain-based biological markers. Beyond diagnosis, the disorder is characterized by marked heterogeneity and impressive individual level variability. Thus, the search for biomarkers in neuropsychiatric disorders to date has taken into account the fact that psychotic disorders are neurodevelopmental disorders with genetic and environmental contributions to disease.

Promising research has identified candidate biomarkers in multiple domains (genetic, electrophysiological, neuroimaging, neurocognitive, inflammatory and neuroendocrine) in SCZ patients [4–7], unaffected first-degree relatives [8,9] and in the prodrome of the disorder as predictors of later psychosis (for a comprehensive review, see [1]) (Figure 1). The question that arises is how one can bridge the gap between research and practice; that is, implement and utilize this multitude of biomarkers to identify individuals at greatest risk for psychosis and individualize treatment.

Thus far, most research in psychiatry has focused on identifying single biomarkers that are evident at the group level but are not sufficiently sophisticated to identify individual differences. Currently, research consortia such as the North American Prodromal Longitudinal Studies are in the process of developing Psychosis Risk Algorithms that combine clinical, demographic and biomarker data to inform risk and perhaps treatment. The development of a reliable algorithm that can be used clinically to inform the degree of risk and specify treatment is essential. Further research is needed to generate a biomarker-defined risk profile that can inform interventions in a more targeted and individualized fashion, matching treatment to the individual patient’s risk domain(s) of dysfunction [10–12].

The practical application of an at-risk algorithm that includes a battery of biomarkers for psychosis will in part depend on the development of reliable measures that can easily be administered in the laboratory or office, and ideally used as part of the evaluation process for each patient. Many biomarkers are linked to dysfunctional neural systems and can also be used as surrogate end points to predict and monitor clinical benefit in specific domains [13]. A number of psychosocial and pharmacologic interventions have great potential as neuroprotective, diseasemodifying or procognitive interventions in early psychosis [14], and have been shown to modify specific biomarker-defined deficits.

It is well conceivable for clinical settings to start expanding diagnosis and treatment planning by incorporating biomarkers in the evaluation process of patients in the early stages of psychosis. In the Cognitive Assessment and Risk Evaluation Program at the University of California San Diego (CA, USA), for example, patients undergo a comprehensive evaluation including clinical, functional, laboratory, neuropsychological and neuroimaging assessment

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– all domains that are associated with risk for psychosis. Based on the initial evaluation, a profile is generated for each individual, highlighting areas of weakness that can benefit from intervention and areas of strength that can be drawn upon. In addition, comorbid symptoms such as anxiety and depression can be immediately therapeutically addressed. Treatment of these symptoms facilitates diagnosis and at the same time decreases the illness burden for patients. Similarly, if deficits in social skills are present, these can also be addressed through social skills training. Patients can acquire more adaptive ways of communication and emotion regulation when interacting with family or healthcare providers. This, in turn, can help patients create or foster their support network, as well as potentially create a therapeutic atmosphere more conducive to success.

In terms of promising biomarkers, neurocognitive deficits are prominent across the SCZ spectrum [15–18], are known to predict functional outcomes [19,20], as well as explain 20–60% of the variance in community functioning, social problem solving and acquisition of psychosocial skills [21]. It is well documented that substantial cognitive deficits predate the onset of psychosis, and these tend to exacerbate before the onset of psychotic symptoms and may worsen after the initial episode of the illness [22]. Neurocognitive deficits across multiple domains have been documented in individuals at high clinical risk for psychosis, with more significant impairments in those individuals who later convert to psychosis [23–31]. A recent longitudinal study in individuals at risk for psychosis identified that processing speed, verbal learning and memory had highest sensitivity in discriminating between at-risk and healthy individuals, and that worse verbal memory predicted more rapid conversion [26].

Consequently, through comprehensive neuropsychological testing, individuals who demonstrate weakness in the cognitive domain can be offered cognitive training and remediation, which have shown promise in patients early in the course of illness [32–35], when intervention is likely to make the greatest impact on the developing brain. Cognitive remediation or training interventions have included restorative (e.g., computer-based approaches [36]), compensatory (e.g., strategy-based approaches [37,38]) or environmental adaptation [39]. It appears that patients with SCZ benefit most from compensatory strategy-based approaches in the context of psychiatric rehabilitation [40]. These strategies, also known as cognitive prosthetics, teach patients to use their cognitive strengths to work around their deficits within a real-world context. Improvements in memory and attention also help with concomitant treatments such as medication adherence. Although a number of cognition-enhancing medications [41,42] have been tested in psychotic patients with some evidence of success, there are no reported trials in the prodromal phase of illness. Clinical trials are needed with agents known to have a safe side-effect profile with evidence of efficacy in SCZ. Interesting candidate procognitive interventions include those that target the NMDA system (benzoate, glycine, *N*-acetyl-cysteine, D-cylcloserine, as well as minocycline) [41,43–45]. A double-blind, randomized study by Levkovitz and colleagues reported improvements in negative symptoms as well as executive functioning in early psychotic patients treated with minocycline versus placebo [45]. Most recently, a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor demonstrated significant improvements in a variety of symptom domains, including neurocognition, in patients with chronic SCZ, highlighting the promise for D-amino acid

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oxidase inhibition as a novel approach for new drug development for SCZ [43]. The potential for cognitive enhancement in the early phases is intriguing and may have even more positive and longer lasting results than those seen in SCZ.

In the not too distant future, patients may undergo electrophysiological testing in an initial evaluation. For instance, some of the electrophysiological paradigms currently under development as potential biological markers with treatment implications include mismatch negativity (MMN), P300, γ-band synchrony [46–49] and markers derived from neural targets in the mirror neuron system. In the case of MMN, duration of MMN predicts conversion to psychosis, and could therefore be used at initial testing to identify patients at the highest risk of psychotic transition. Furthermore, the fact that treatment of SCZ subjects with *N*-acetyl-cysteine, a glutathione precursor, increases MMN makes it an especially useful biomarker [50]. In this way, MMN could be used to identify patients at high risk for psychosis and to match them with a treatment that specifically modifies MMN. Another application of this concept utilizes μ rhythm suppression, an EEG marker derived from mirror neuron function. Mounting evidence indicates that μ rhythm suppression is impaired in patients with SCZ, and that the neural impairment is correlated with loss of social functioning. This finding, combined with early indications that μ suppression is improved with oxytocin treatment, provides a practical avenue to identify patients with neural evidence of poor social information processing and treating those patients with prosocial treatments such as oxytocin or social skills training. Similarly, in a recent review of the literature, Lewis *et al.* showed evidence for impaired γ synchrony in SCZ [51]. In addition, based on preclinical and clinical data, they hypothesize that compounds that impact GABA-ergic and cholinergic signaling are likely to improve γ synchrony in SCZ.

Similarly, neuroimaging methods show promise and can be utilized to facilitate diagnosis and treatment planning. Structural and functional MRI, PET and proton spectroscopy have been implemented in finding biomarkers in SCZ, as well as in the prodrome and early psychosis, all with reasonable success [52–55]. In general, differential prefrontal cortical functioning along the SCZ spectrum has been repeatedly reported [56], with recent studies showing hyperactivity in multiple brain regions in prodromal subjects, specifically the ones who later converted to psychosis [57,58]. Similarly, changes in cortical gray matter and aberrant neurochemical levels have been linked to SCZ and psychosis [56,59]. Identification of the latter two biomarkers is less invasive, more accessible and reliably assessed. MRI scans are easily administered and should become a regular assessment tool for individuals who show early signs of psychosis, not only because they may pick up rare neurological causes of psychosis (e.g., brain tumors), but because of the potential importance as a biomarker for psychosis. Although as previously mentioned we are still unable to predict conversion or identify the emergence of psychosis at an individual level using MRI scans, longitudinal MRIs at the individual level can be helpful in treatment planning. Progressive neuroanatomical changes that are greater than those seen in normal development have been repeatedly reported in SCZ [60–63]. As reviewed by Pantelis *et al.* [64], extant neuroimaging data provide evidence of pre- and/or peri-natal neurodevelopmental changes in SCZ that may lead to a vulnerability to postpubertal insults that contribute to the accelerated loss of gray matter and aberrant connectivity in the prefrontal regions. These, in conjunction with substance abuse, stress and hypothalamic–pituitary–adrenal axis

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dysregulation, may lead to neurodevelopmental abnormalities that may be neurodegenerative, involving medial temporal and orbital prefrontal regions. Thus, while disturbances of brain structure early in life may be necessary for the future emergence of SCZ [65], neurodevelopmental events during the late adolescent period may participate in psychotic symptom formation via a range of possible mechanisms including inflammation, glutamatergic or dopaminergic transmission [63,65,66]. Pharmacological agents show promise. For example, neuroprotective properties of serotonin reuptake inhibitors are documented in animal models, showing increased neurogenesis, dendritic arborization and synaptogenesis [67]. A preliminary study by Berger *et al.* showed a reduction in neuropathological change in the hippocampus of putatively prodromal subjects treated with low doses of lithium in comparison with untreated prodromal subjects [68].

In addition to pharmacologic interventions, there is research on nonpharmacologic treatments that indicate slowing of gray matter loss in SCZ. A recent study by Falkai and colleagues reported an increase in gray matter density after 3 months of aerobic exercise training in healthy individuals [69], while another group demonstrated hippocampal changes associated with improvements in memory performance in SCZ [70]. While the authors were unable to find exercise effects in chronic SCZ, aerobic exercise in at-risk and early psychotic patients may show results similar to healthy individuals. Thus, as part of treatment planning for individuals who present to the clinic, a moderate level exercise regimen can be suggested. Other interventions can include computer-based cognitive enhancement therapy. Eack *et al.* demonstrated greater perseveration of gray matter in early psychotic patients who were involved in computer-based cognitive enhancement therapy compared with those who received supportive psychotherapy over 2 years [33].

Finally, SCZ is associated with increased inflammation, including abnormal blood levels of the acute-phase reactant C-reactive protein (CRP) [71,72]. Testing for inflammatory biomarkers in the early phases of disease may be useful and inform treatment. Recent data suggest that baseline elevated plasma CRP is predictive of increased risk of developing late-onset SCZ [73]. While studies are necessary to replicate risk prediction in the early phases, assessment of CRP in the early phases may prove to be beneficial.

Conclusion

Psychiatric disorders are complex and necessitate a multidimensional approach for diagnosis and to inform treatment planning. In the SCZ spectrum, advances in research have identified promising biomarkers, although more research is needed to fortify current research findings and refine diagnostic accuracy. At the same time it would be futile for patient care not to incorporate existent knowledge into treatment planning. While caution is warranted, a more tailored treatment approach guided by comprehensive evaluation is preferable to a one-fits-all approach.

Future perspective

Further research in biomarkers, especially to aid in generating biomarker profiles addressing relevant domains of dysfunction or deficits, is exigent. Such an approach has been

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successfully used in the Framingham studies introducing the risk score calculator for coronary heart disease. It may be necessary to shift focus away from a one-size-fits-all approach and instead generate a profile for each patient highlighting his/her strengths or deficiencies. For research purposes it may be helpful to use stratification and investigate groups of patients with shared or similar characteristics or profiles to study the optimal management for the patients and achieve the best possible treatment outcome. For example, in clinical settings patients may test positive for neurochemical biomarkers and cognitive deficits, indicating risk for psychosis, but test negative when it comes to social functioning biomarkers. This profile suggests a different treatment approach compared with a profile that is positive for only some mild prodromal symptoms and social functioning problems. In the case of the former example, in addition to cognitive-enhancing medication, the particular patient's treatment could be augmented by cognitive remediation therapy. On the other hand, the latter patient may benefit from social skills training and other interventions addressing social functioning, which may be sufficient to prevent exacerbation of symptoms [74].

Several robust biomarkers for conversion to psychosis have already been established [59,75–84] and many putative biomarkers show promising results but need to be further investigated. Ideally, longitudinal studies in large samples could demonstrate linkage between putative biomarkers and clinical end points. To further advance research it may be necessary to create shared datasets as well as draw on successful models outside of psychiatry, such as lessons learned from the Framingham studies or the Alzheimer's Disease Neuroimaging Initiative [85,86].

Acknowledgments

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- Despite remarkable advances in mental health research, there is a lack of biomarkers with clinical utility.
- Promising candidates include genetic, electrophysiological, neuroimaging, neurocognitive and inflammatory biomarkers.
- All these biomarkers have potential implications for treatment and personalized mental healthcare.
- Research in schizophrenia thus far has focused on single biomarkers.
- A shift towards a biomarker profile may be necessary to identify individuals at greatest risk for psychosis and individualize treatment.
- Future directions may draw on successful models outside of psychiatry such as Framingham studies or the Alzheimer's Disease Neuro-Imaging Initiative.

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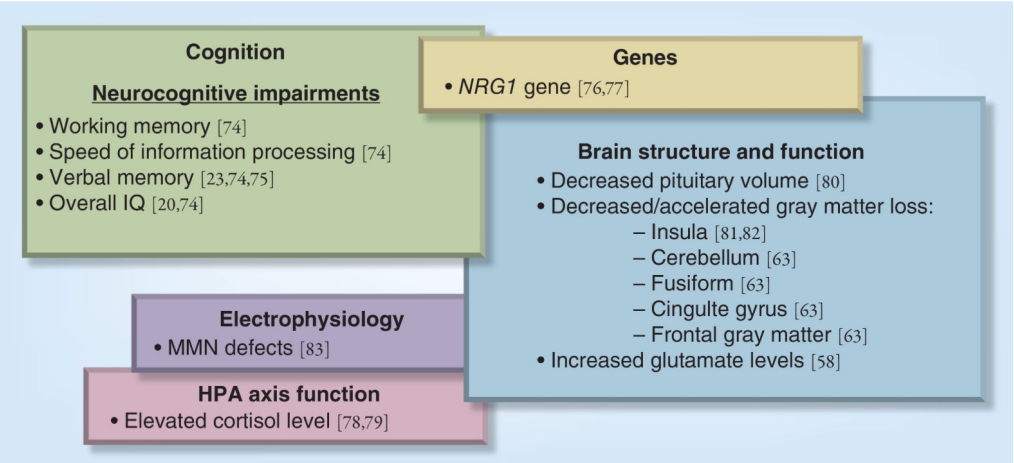

Figure 1. Model of biomarkers in the prodrome predicting conversion to psychosis.
HPA: Hypothalamic–pituitary–adrenal; MMN: Mismatch negativity.