Looking for a “biological test” to diagnose “schizophrenia”: are we chasing red herrings?

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The developments in the rest of medicine have shown us that the ability of a diagnosis to predict treatment and prognosis is usually improved once one has a firm biological test. General treatment of “heart failure” was rather poor when the same treatment was used for all forms of heart failure, while the precise diagnosis of valvular dysfunction, myocarditis and ischaemic heart disease led to more precise treatments, better outcomes and better ability to predict outcome. That has been the fond hope in biological psychiatry, and Lawrie et al carefully and systematically analyze how far we have come to realizing it in schizophrenia.

Their article carefully reviews data from risk factors, clinical signs and symptoms, genetics, blood-based markers and imaging “markers” with respect to their sensitivity, specificity and predictive value. The paper achieves two important goals. It is a thoughtful synthesis of such evidence, presented from the perspective of sensitivity, specificity and likelihood ratios. Furthermore, by drawing attention to the lack of useful clinical biological tests, it reminds us of the journey ahead. While I laud the authors’ effort, I question whether it is even feasible, at present, to look for a biological “test” in psychiatry just as they do in the rest of medicine.

The way “tests” are evaluated in the rest of medicine is versus a “gold standard”. A simple blood test often is used to substitute for a definitive pathological diagnosis. A simple ECG recording is used to substitute a complex invasive angiogram. Thus, in medicine, indices of sensitivity, specificity, likelihood ratio etc. are all premised on measuring a new test against the definitive “gold standard”. No test can better the “gold standard”. But, what today would be the “gold standard” for the diagnosis

of schizophrenia? It would have to be DSM (or the ICD) (1). There is no other option. Given that our current and foreseeable DSM/ICD labels are empirical and pragmatic collections of clinical symptoms, the looking for a biological finding to predict this heterogeneous collection of symptoms is shaky.

The second major problem at present is the “artificiality” of the current data from a clinical perspective. The extant data in genetics, imaging and biological markers of schizophrenia has been collected in individuals who fully and unambiguously meet the classical DSM criteria and are usually contrasted to perfectly healthy, one might say “hyper-normal”, normal volunteers (2). Where is the problem in distinguishing two such people? Classical schizophrenia is easily distinguished from perfect normalcy by even an untrained observer. The real challenge in the clinic is to distinguish the nearly-psychotic depressed-looking individual from the nearly-depressed psychotic-behaving individual and firmly classifying one into major depression and the other into schizophrenia (if either of these have a deeper meaning – see the gold standard problem above). Very few studies have attempted this at present. And therefore any predictive value derived from current data separating classical illness from perfect normalcy is artificially inflated.

So, we are in a Catch-22. Until we have a gold standard we are unlikely to find meaningful biological tests. And until we have a better biological understanding we cannot redefine the illness to make it more valid. What’s the way out?

A solution lies in the pursuit of biologically defined “subtypes”. There is little hope of, or purpose in, replacing the well-established and relatively standardized method of diagnosing schizophrenia clinically (which has taken a 100 years to get to) with an *ad hoc* biological test of limited clinical value. It would be

too disruptive and would yield little benefit. Thus, the DSM-5 and ICD-11 carry on the tradition of their ancestors (1). In the meantime, what biological psychiatry should seek are biological tests that can either improve treatment choice or predict differential prognosis. This requires a shift in the research we do. The emphasis is not anymore in finding biological differences versus supernormal controls. The focus is on prediction within the phenomenologically defined diagnosis. Thus, I can foresee meeting a new patient, diagnosing his/her to have a DSM-6/ICD-12 schizophrenia, and then telling him/her “you have a schizophrenia of the ‘hypofrontal’ subtype, and this means that you will not respond well to standard antipsychotics and therefore let’s start with clozapine instead”; or meeting another young man and saying “you have a schizophrenia with ‘conserved executive function’; in this subtype we find that antipsychotics can be stopped after two years, provided there is active involvement in cognitive-behavioural therapy”.

What fish you catch, is largely a function of where you fish. Rather than focussing on schizophrenia versus normal controls with biological tests – something fraught with several taxonomic (dimensional vs. categorical) and practical challenges – let’s use the umbrella diagnosis and “subtype” it. And let’s judge the game empirically – let the test that best improves or best predicts real-life outcome of patients win the prize.

References

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2. Kruesi MJP, Lenane MC, Hibbs ED et al. Normal controls and biological reference values in child psychiatry: defining normal. *J Am Acad Child Adolesc Psychiatry* 1990;29:449-52.