



REVIEW ARTICLE

Diagnostic profiling in clinical translational research — a European perspective



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Abstract

Background: Personalisation of treatment is a development in general medicine that may be of relevance for psychosomatic psychiatry as well.

Objectives: Discuss how diagnostic profiling can contribute to clinical translational research in psychosomatic psychiatry.

Methods: Critical review of current shortcomings and required strategies in clinical translational research.

Results: Current shortcomings in clinical mental health research concern 1) the validity and applicability of biological tests as biomarkers; 2) the diagnostic classifications and 3) the conceptualisation of mental disorder. Clinical psychosomatic research should broaden the current search for etiological mechanisms from the biological domain to include physical symptoms, cognitive function, psychological symptoms, their subjective appraisal by the patient, social factors such as experienced trauma, and resilience factors. The methodology of a profiling study is introduced, that would be particularly useful to describe profiles of patients associated with favourable or less favourable treatment outcome and to develop personalised treatments based upon that. These can then be evaluated in Randomised Clinical Trials (RCTs).

Conclusions: Development of new treatment strategies for mental disorders requires diagnostic procedures to provide clinicians and patients with tools, validated in humans, for tailoring treatment as much as possible to the particular problem, preference and profile of the patient, as a way of developing personalized treatment in psychiatry. Patients with Somatic Symptom Disorders (SSD) might be a group of particular interest to perform profiling studies, as they present the highest phenomenological variety alongside the different domains. In this manner, innovative clinical translational research can pave the way with a contribution from psychosomatic psychiatry.

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Introduction

Since the second world war, psychiatric research has used diagnostic classifications that used criteria for classification as a categorical approach without etiological considerations. This is still the case for the American Psychiatry Association (APA) DSM-IV and DSM-5^{1,2} as well as for the World Health Organisation (WHO) ICD-10 and the recently released ICD-11.^{3–5} The use of these classification systems has been of great value for worldwide psychiatric epidemiological research. However, in the current timeframe a new avenue of psychiatric research is developing, that tries to establish new treatments that may focus upon certain core symptoms and that may be fed by new knowledge about the etiology of psychiatric conditions, a development for which DSM-5 or ICD-11 are less useful.⁶ Although this research is mostly biologically driven, it has been suggested that psychiatry should follow the lead of other medical sciences, that would be much farther in developing such precision medicine. It seems that the suggestion to develop precision medicine inspires mental health researchers and clinicians, and that it is highly relevant for clinical research in mental disorders. This article will address what is needed for such research and how we can be successful in it.

What does clinical research need?

Clinical research needs studies that are relevant for patients, in the sense that they should evaluate patient related outcomes such as signs and symptoms, as well as the subjective appraisal of these symptoms by the patient. The studies should focus on diagnosis and interventions in patients with clearly described disorders of a certain level of severity. Intervention studies in less severe disorders often do not yield clear results, as those 'disorders' overlap with normality and thus may be subject to a normal course of improvement; and in case of research, this would dilute the effect of the interventions under study. Also, intervention studies that do not clearly delineate the subjects before inclusion often do not show clear results. However, in the context of innovative research, DSM and ICD classifications may not be useful for the development of precision medicine, and for the inclusion in studies; inclusion may preferably be based on a core symptom such as, for example, anhedonia. Or on a combination of symptoms of a certain severity that are associated with disability, such as for example depression and pain.^{7,8} In other words, we do need a clearly delineated and validated description of phenomenology that includes not only biological parameters and behavioral observations, but also patient related signs and symptoms as well as their subjective appraisal. And whilst focusing on core symptoms, inclusion should be based on clear descriptions of such symptoms and on standardized symptom severity assessments. From this it follows that for clinical research, especially if we want to explore the avenue of precision medicine, we need something different than classification. We need a diagnosis.

The clinical relevance of diagnosis is associated with its consequence, namely the indication for treatment. Diagnosis requires clear delineation of symptoms and severity required for level of disorder, suffering, and disability of

the patient. It also requires knowledge regarding the course, and knowledge of treatment possibilities. If such treatment possibilities are not yet available or insufficiently effective, they should be further developed by clinical research. Decisions regarding treatment should take the preference of the patient into account and should establish a hierarchy of treatment steps as well as an appropriate treatment setting for addressing danger, containment of behavior, addressing comorbidity, treatment of symptoms and improvement of function. Furthermore, ethical procedures following the requirements laid out in the declaration of Helsinki are of utmost importance for clinical research and should be the least interfering on the patient as possible.

However, so far, there is a relative gap between research in the field of mental health, and actual clinical work with patients, as a lot of research has been done with animal models that is not validated for humans. As a consequence, in a survey regarding the clinical research agenda for mental health research, a subjectivity gap was described by experts in clinical research: imaging and other preclinical studies do not provide input regarding what happens in our mind. So far, no biological test exists that can confirm a diagnosis of a specific mental disorder in humans. And there is a discrepancy between the level of suffering that is experienced subjectively in mental disorder, and the lack of biological data that can confirm this.⁹

Possible causes of the subjectivity gap

Since Kraepelin,¹⁰ attempts have been made to understand the mechanisms of disease and to bridge this subjectivity gap. The wish to find a pathophysiological substrate, a mechanism of disease, and a test to establish a diagnosis according to the Trias of Koch however has so far almost never been fulfilled in psychiatry. There are the exceptions of states such as psychotic mania in neurosyphilis caused by *Treponema Pallidum*,¹¹ or mania, psychosis, personality changes and dementia in HIV infected patients;¹² but they are rare. This relative shortcoming in comparison to general medicine may be due to a shortcoming in the tests, a shortcoming in our diagnostic classifications, or a shortcoming in our concept of mental disorder. They are discussed below.

Shortcomings in the tests

So far, for a clinical diagnosis and effective treatment, knowledge of the underlying mechanism often was not available. However, in clinical practice it was feasible to establish a diagnosis and to provide effective treatment without knowledge regarding the specific underlying mechanism. Apparently, such knowledge is not necessary for provision of effective treatment in many cases; and this is not unique for psychiatry but applies to medicine in general. For example, validated questionnaires would be used with validated cut points such as the PHQ9¹³ and CESD¹⁴ for depressive disorder, the GAD7¹⁵ or BAI^{16,17} for anxiety disorder, and the PHQ15 for somatoform disorder.¹⁸ Apart from such questionnaires,¹⁹ semi structured and validated interviews such as the SCID²⁰ or the MINI²¹ would also be used. It should be kept in mind, however, that the expanding number of categories in DSM-5 has not been helpful for clinical research. The number of

classifications is growing, but they are not precise. Clinical research should therefore result in more specific diagnostic criteria. So far, indications are that biomarkers can only explain up to 10% of the variance of mechanisms of disease, which is disappointingly low and has prompted a call for research efforts to improve this.²²

Shortcomings in our diagnostic classifications

How should we interpret the fact that, so far, biomarker findings do not provide a diagnosis? It can be a construct issue. Many biomarkers that were explored so far, such as the dexamethasone suppression test, are related to our stress systems. Mental disorders are stress-related too, and hence such biomarkers are non-specific and cannot be an indicator of outcome.^{23–25} In an attempt to introduce a research classification system that tries to establish an etiological basis for mental disorders, the USA National Institute of Mental Health (NIMH) instituted the Research Domain Criteria (RDoC) project in 2009.²⁶ Originally mostly biological and molecular of nature, its aims and structure have been debated in an exchange between USA and European researchers as well as WHO representatives involved in the development of ICD-11 in a meeting in 2014, and has been adapted since to include social and patient self-report dimensions in the context of ongoing discussions.²⁷ It currently encompasses six pillars or boxes: Negative valence systems, positive valence systems, cognitive systems, social processes, arousal and regulatory systems, and sensorimotor systems. The aim of RDoC is to reach an understanding of the mechanism of disease that might lead to biologically optimized treatment or so-called precision medicine.^{27,28} It is an etiological, dimensional approach that would involve validating cut points for interventions. This seems to be a worthwhile endeavor, however, there are some problems with RDoC. There are no gold standards for the six constructs mentioned above. Subjective appraisals cannot be included. Valences cannot be studied without studying interactions between people. Also, the brain does not survive without body and environment, yet they are not in RDoC. And how can you study cognitive systems without considering motivational aspects? Finally, there is overlap between constructs and domains. Hence, on an operational level, in clinical research using the RDoC approach, patients may be classified in several boxes or systems at a time, and crowding of the boxes may lead to diagnostic confusion. Thus the caveat of nonspecific biomarkers remains despite this well intended attempt for a new research classification in mental health research.

Shortcomings in our conceptualization of mental disorder

An explanation of the problem related to concept may be that mental disorder can be a state with *parallel, reciprocal* processes instead of *causal* processes in the brain. For example, PET scans show that the head of the caudate nucleus and the pathway that connects the caudate with the prefrontal (orbitofrontal) cortex and cingulate gyrus seem to be hyperactive in OCD. Kandel writes: “after SSRI or Cognitive Behavioral Treatment (CBT), hyperactivity of the caudate

nucleus and the orbitofrontal cortex decreases significantly. This suggests that psychotherapy and pharmacologic therapy lead to a similar biological change. Maybe central serotonergic transmission is abnormal in OCD, and psychotherapy can reverse this effect as well as specific serotonin reuptake inhibitors.”²⁹ However, we might put this more precisely, namely that as both after SSRI or CBT, hyperactivity of the caudate nucleus and the orbitofrontal cortex decreases significantly, and symptoms decrease, this suggests that psychotherapy and pharmacologic therapy lead to a similar change in *activity* in the caudate nucleus. Psychotherapy as well as antidepressant treatment thus both produce symptom reduction and change of metabolism at the same time in the brain. And this might indicate that dysregulation of central serotonergic transmission is the *cause* of OCD, but it might indicate just as well that it is a *parallel phenomenon* in the brain that disappears as soon as the symptoms disappear. Probably, there is no certain way to find out which of both is the case, and thus we should take into account that a purely causal conceptualisation of mental disorder may be too limited.

What to do about heterogeneity in the design of clinical research?

Research aiming to acquire knowledge regarding underlying mechanisms and identifying and validating biomarkers for mental disorder in general is considered to try to avoid biological heterogeneity in research patients, as such heterogeneity would preclude proper identification or validation of biomarkers. For example, in RDoC, diagnosis is envisioned “by analysis of genetic variants that should predict exactly what treatment will be optimal, as in cancer or cystic fibrosis.”²⁶ Diagnosis by analysis of genetic variants predicting what treatment will be optimal may be possible in some cases. It is, on a small scale, already being done in medication treatment for some mental disorders in the clinical setting. However, research shows that there is only a limited number of randomized clinical trials performed in this domain, with ambiguous results, and indications were that the tests used were of limited validity.³⁰ Another study showed that a model derived from 20 genetic variables predicted remission after treatment with an antidepressant explaining only approximately 36% of the variance in which patients achieved remission.³¹ Indications are that in psychiatry, as in many other medical specialisms, genetic variation at the origin of mental disorder is mostly of a multifactorial and epigenetic nature, and resilience in individuals with high risk for such mental disorders is polygenic as well and interacts with this predisposition.³² Such findings compel us to take other factors than genetic factors into account as well. Thus, this genetic approach avoiding heterogeneity may be of limited relevance for clinical mental health research.

Introduction of the methodology of a profiling study

Now to avoid heterogeneity is certainly an understandable wish for biological research. However, there is no indication that *heterogeneity* was the cause of lack of identification

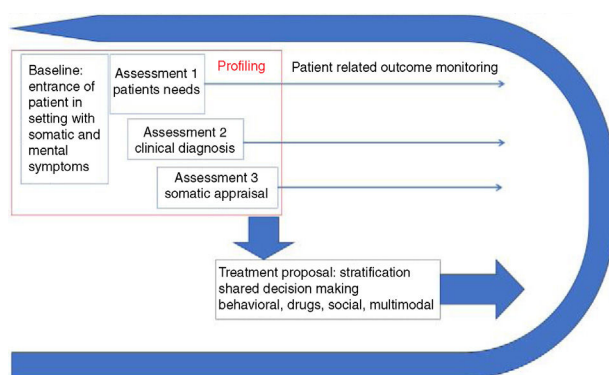


Figure 1 Profiling study: backwards exploration of patient profile related with patient related outcome (PROM).

of validation of biomarkers in psychiatry, or that avoiding it will be practical, or a solution of that problem, in clinical research.²⁹ From a clinical research perspective, it may be better to *explore* the heterogeneity, and to describe it fully, than to try to avoid it, in order to explore the phenomenology of mental disorders in patients. This should not only be attempted in biological factors but also in *contextual* factors, and their *appraisal* by the patient, as both are of great importance in the development of mental disorders. It would be good to start with such an exploration of phenomenology, devoid of preconceived classifications, and to explore how core symptoms hang together with each other and with contextual factors. Part of this is already being done in the context of a network approach to mental disorders.³³

For the sake of the subjectivity gap, it would be important to explore this phenomenology not only in terms of mental health symptoms, but also in terms of the meaning of the symptoms, and the diagnosis that is provided to patients. For the sake of clinical psychosomatic research, also physical symptoms and their meaning to the patient should be explored. And all of this should be taken together in order to describe a patient profile that would allow for personalization of treatment. This might produce profiles with etiological and prognostic value. In order to explore this, we introduce a new methodology: a so-called profiling study design. In such a design, one would look backwards, to explore which treatment works in which patient group, and then try to find out what the pathogenic mechanism would be. The design of a profiling study is shown in the Figure below (Fig. 1).

This method can be used in both an observational design and in a Randomised Clinical Trial (RCT) design. In the clinical situation, the patient related outcome (PROM) scores on validated questionnaires can be used to determine treatment success; and this may be extended to certain indicators of biological, psychological, or social nature. Using the method of a profiling study design, one could include all kinds of variables deemed possibly relevant at the start of treatment, to analyze later which patients profited most. A study with such a design found, for example, that childhood sexual abuse had a negative effect on treatment outcome in conversion disorder.³⁴ So, profiles may provide answers.

Instead of symptom counting, as in DSM-5 or ICD-11; and instead of genetic biomarkers.

Individualized treatment and personalised medicine would be a longterm potential of clinical translational research. Such research would endeavour to describe heterogeneity in research patient groups, to use this to make profiles of patients, based on biological, dimensional symptom description, and contextual factors, to bridge this to validated questionnaires' symptom scores, to the *meaning* of symptoms for patients, and to patient preferences. This aligns perfectly with the research priorities defined by a group of 73 experts in the Research agenda for Somatic Symptom Disorders, Bodily Distress Disorders and Functional Disorders, published on behalf of the European Association for Psychosomatic Medicine (EAPM) in 2018.³⁵ The first priority was to perform research into assessment of diagnostic profiles relevant to course and treatment outcome. This is exactly what would be endeavoured in a profiling study. Another research priority is the development of new methodologic designs to identify and explore mediators and moderators of clinical course and treatment outcomes. This is why we propose the new methodological design of a profiling study. And this would lead to working on two other named research priorities, namely translational research exploring how psychological and somatic symptoms develop from somatic conditions and biological and behavioral pathogenic factors, and, as final goal, the development of new, effective interventions to personalize treatment. Patients with Somatic Symptom Disorders might be a group of particular interest to perform such studies, as they present the highest phenomenological variety alongside the different domains, and thus the largest potential to develop personalised treatment, as well as the largest potential for the patients to benefit from this approach.

Conclusion

Development of new treatment strategies for mental disorders requires diagnostic procedures to provide clinicians and patients with tools, validated in humans, for tailoring treatment as much as possible to the particular problem, preference and profile of the patient, as a way of developing personalized treatment in psychiatry. Etiological exploration should include the possibility of parallel processes instead of causal thinking, include the body, that is, somatic comorbidity, the mind, and context. Profiling studies would be a method of choice, exploring treatments that work and trying to find the pathogenic mechanism underlying the symptoms. They should use patient profiles to do so and incorporate the patient perspective. In such profiling studies, heterogeneity should not be avoided, but explored and described. Patients with a combination of somatic and psychological symptoms, such as for example somatic symptom disorders, would be a good candidate for such studies, as they show a plethora of somatic and psychological symptoms and social contextual factors that may be used for profiling, and as they may benefit specifically from such new methodologies in view of the current paucity of effective treatments for some of these conditions. This way, innovative clinical trans-

lational research can pave the way with a contribution from psychosomatic psychiatry.

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Conflict of interest

The author has no conflict of interest to declare.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-5. 4th ed. Washington, DC; 2001.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
3. World Health Organization. The ICD-10 classification of mental health and behavioural disorders: clinical descriptions and diagnostic guidelines. second edition Geneva: World Health Organization; 1993.
4. World Health Organisation. International Classification of Diseases -11 (ICD-11), 2019.
5. World Health Organisation. WHO releases new international classification of diseases (ICD-11): WHO; 2018 [updated 18/06/2018].
6. National Academy of Sciences. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC; 2011.
7. de Heer EW, Gerrits M, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, Spinhoven P, Penninx BW, van der Feltz-Cornelis CM. The association of depression and anxiety with pain: a study from NESDA. *PLoS One*. 2014;9(10):e106907.
8. de Heer EW, Ten Have M, van Marwijk HWJ, Dekker J, de Graaf R, Beekman ATF, van der Feltz-Cornelis CM. Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: a longitudinal, population-based study. *Pain*. 2018;159(4):712–8.
9. Van der Feltz-Cornelis CM, van Os J, Knappe S, Schumann G, Vieta E, Wittchen HU, et al. Towards Horizon 2020: challenges and advances for clinical mental health research - outcome of an expert survey. *Neuropsychiatr Dis Treat*. 2014;10:1057–68.
10. Kraepelin E. Lectures on Clinical Psychiatry Franklin Classics 1909/2018.
11. Seo EH, Yang H, Kim SH, Park JH, Yoon H. Psychotic mania as the solitary manifestation of neurosyphilis. *Ann Gen Psychiatry*. 2018;17(24).
12. Perry SW. Organic mental disorders caused by HIV: update on early diagnosis and treatment. *Am J Psychiatry*. 1990;147(6):696–710.
13. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282(18):1737–44.
14. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Appl Psychol Measure*. 1977;1(3):385–401.
15. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–7.
16. Borden JW, Peterson DR, Jackson EA. The Beck Anxiety Inventory in nonclinical samples: Initial psychometric properties. *J Psychopathol Behav Assess*. 1991;345–56.
17. Beck AT, Steer RA, Ball R, Ciervo CA, Kabat M. Use of the Beck Anxiety and Depression Inventories for primary care with medical outpatients. *Assessment*. 1997;(3):211–9.
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med*. 2002;64(2):258–66.
19. Kroenke K, Spitzer RL, Williams JBW, Löwe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: A systematic review. *Gen Hospital Psychiatry*. 2010;32: 345–59.
20. First MB, Williams JBW, Karg RS, Spitzer RL. Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV. Arlington, VA: American Psychiatric Association; 2015.
21. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20: 22–33.
22. Quinlan EB, Banaschewski T, Barker GJ, Bokde ALW, Bromberg U, Büchel C, Desrivieres S, Flor H, Frouin V, Garavan H, Heinz A, Brühl R, Martinot JL, Paillère Martinot ML, Nees F, Orfanos DP, Paus T, Poustka L, Hohmann S, Smolka MN, Fröhner JH, Walter H, Whelan R, Schumann G; IMAGEN Consortium. Identifying biological markers for improved precision medicine in psychiatry. *Review. Mol Psychiatry*. 2019, <https://doi.org/10.1038/s41380-019-0555-5>.
23. Nierenberg AA, Feinstein AR. How to evaluate a diagnostic marker test. Lessons from the rise and fall of dexamethasone suppression test. *JAMA*. 1988;259(11):1699–702.
24. Ribeiro SC, Tandon R, Grunhaus L, Greden JF. The DST as a predictor of outcome in depression: a meta-analysis. *Am J Psychiatry*. 1993;150(11):1618–29.
25. Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. *Am J Psychiatry*. 1997;154(11):1497–503.
26. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013;11(126).
27. NIMH. RDoc 2009.
28. Cuthbert B. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry*. 2014;13(1):28–35.
29. Kandel E, Schwartz JH, Jessel TM. Principles of Neural Science. 4th edition New York: McGraw-Hill; 2000.
30. Fabbri CZJ, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: Comparison of the available testing kits and clinical trials. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;(86):36–44.
31. Iniesta R, Hodgson K, Stahl D, Malki K, Maier W, Rietschel M, Mors O, Hauser J, Henigsberg N, Dernovsek MZ, Souery D, Dobson R, Aitchison KJ, Farmer A, McGuffin P, Lewis CM, Uher R. Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. *Sci Rep*. 2018;8(1):5530.
32. Hess JL, Tylee D, Mattheisen M; Schizophrenia Working Group of the Psychiatric Genomics Consortium; Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Børglum AD, Als TD, Grove J, Werge T, Mortensen PB, Mors O, Nordentoft M, Hougaard DM, Byberg-Grauholm J, Bækvad-Hansen M, Greenwood TA TM, Curtis D, Steinberg S, Sigurdsson

- E, Stefánsson H, Stefánsson K, Edenberg HJ, Holmans P, Faraone SV, Glatt SJ. A polygenic resilience score moderates the genetic risk for schizophrenia. *Mol Psychiatry*. 2019. <https://doi.org/10.1038/s41380-019-0463-8>.
33. Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017;16(1):5–13.
 34. Van der Feltz-Cornelis CM, Allen SF, van Eck van der Sluijs JF, Submitted for publication Childhood sexual abuse predicts treatment outcome in conversion disorder. An observational longitudinal study; 2019.
 35. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Van den Bergh O, Schaefer R, Kop WJ, Lobo A, Sharpe M, Söllner W, Löwe B. A European Research Agenda for Somatic Symptom Disorders, Bodily Distress Disorders, and Functional Disorders: Results of an Estimate-Talk-Estimate Delphi Expert Study. *Front Psychiatry*. 2018;14(9):151.