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Analysis

The potential of precision psychiatry: what is in reach?

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Summary

Progress in developing personalised care for mental disorders is supported by numerous proof-of-concept machine learning studies in the area of risk assessment, diagnostics and precision prescribing. Most of these studies primarily use clinical data, but models might benefit from additional neuroimaging, blood and genetic data to improve accuracy. Combined, multimodal models might offer potential for stratification of patients for treatment. Clinical implementation of machine learning is impeded by a lack of wider generalisability, with efforts primarily focused on psychosis and dementia. Studies across all diagnostic groups should work to test the robustness of machine learning models, which is an essential first step to clinical implementation, and then move to prospective clinical validation. Models need to exceed clinicians' heuristics to be useful, and safe, in routine decision-making. Engagement of clinicians, researchers and patients in digitalisation and 'big data' approaches are vital to allow the generation and accessibility of large, longitudinal, prospective data needed for precision psychiatry to be applied into real-world psychiatric care.

Keywords

Precision psychiatry; machine learning; biomarkers; risk assessment; treatment response.

The past decade has seen substantial investment in the field of data science to develop precision healthcare for the treatment and prevention of mental illness. Precision healthcare promises to move away from a 'one-size-fits-all' approach to treatment decisions by using objective and replicable psychosocial and/or neurobiological measures. Interventions would ideally be tailored to these individual profiles and address unique characteristics of individual patients by maximising clinical response.[1] The drive to embrace data science results from core challenges that psychiatry has not yet been able to resolve: how we define illnesses, develop accurate diagnostic categories, identify biomarkers and predict outcomes, together with how we understand and manage the heterogeneity that is the norm in mental health populations. Finding accurate prediction models and defining meaningful phenotypes or biologically informed groups could be transformative. However, although considerable investment has resulted in progress and several key achievements, caution is clearly still needed. Although a number of machine learning studies to date have potential for real-world application, some are closer to bedside testing than others and many steps are still needed before data-driven precision healthcare is in place to aid everyday clinical care. We present here an analysis of the current position of machine learning research that is closest to real clinical practice, covering prognostic risk, diagnostic stratification and treatment response, with critical insight into current gaps and challenges (Fig. 1).

Prognostic risk

Mental disorders with onset in early adulthood frequently lead to enduring disability.[2] Disorders occurring later in life, such as dementia, result in significant burden on family members and institutional care in the last decades of life. Early detection could reduce this burden by enabling increased support and preventive interventions. Recently published machine learning studies bring some hope for this goal, as they show partially generalisable multimodal prognostic models able to predict individual functional outcomes with some accuracy.[2] Using algorithmic pattern recognition, this work showed better accuracy than human prognosis. The North American Prodrome Longitudinal Study (NAPLS) individual risk calculator for development of psychosis from the clinical high-risk (CHR) state[3] has been recently validated in more broadly defined CHR groups from multiple countries,[4] including patients with recent-onset depression from the PRONIA consortia. This valuable generalisable model points to younger age at onset and reduced cognitive processing speed as increasingly relevant risk markers in broader risk cohorts. Harmonised models from PRONIA and NAPLS are based on a concise pattern of demographic, clinical and neuropsychological variables, in addition to attenuated psychotic symptoms, that can be more easily applied in clinical practice.

Currently, evidence suggests that neurobiological data may add some predictive accuracy to clinical models for risk prediction, yet at present this may not be at the level of significance to warrant everyday use.

Higher specificity sometimes seen in neurobiologically based models, when compared with solely clinical data, may remain important in identifying underlying aetiological processes or new staging, given the heterogeneity in clinical phenomenology.[2] The added value of neurobiological data becomes more evident in older patients, for example when predicting fast progression from mild cognitive impairment to Alzheimer's dementia. Cerebrospinal fluid, cerebral amyloid or tau and, in particular, neurodegenerative markers so far prove to be key neurobiological predictors[5,6] that have been validated in a number of muticentre dementia studies.[7]

Genetic data may be similar to neuroimaging data, in that they could improve overall accuracy of models, but are not able to deliver self-standing findings, i.e. at present they only complement clinical data. For over a decade expectations were directed at the level of single candidate genes, for example *COMT* for schizophrenia or *ApoE4* for Alzheimer's dementia, but contemporary research of prediction relies on polygenic risk scores.[8] Recent advances from the Psychiatric Genomics Consortium–UK Biobank–23 and Me genome-wide association study report that polygenic risk scores may be useful for prediction of vulnerability to depression and resilience under stress.[9] Similarly, studies on prognostic flows[10] applied in psychotic disorders agree that polygenic risk scores slightly augment the performance of models based on clinical cognitive data, yet remain insufficient for risk screening in the general population.

These multimodal prognostic flows may be extended to cohorts of young adolescents and adults, although a similar caution should be taken. Most recent multisite longitudinal adolescent studies, for

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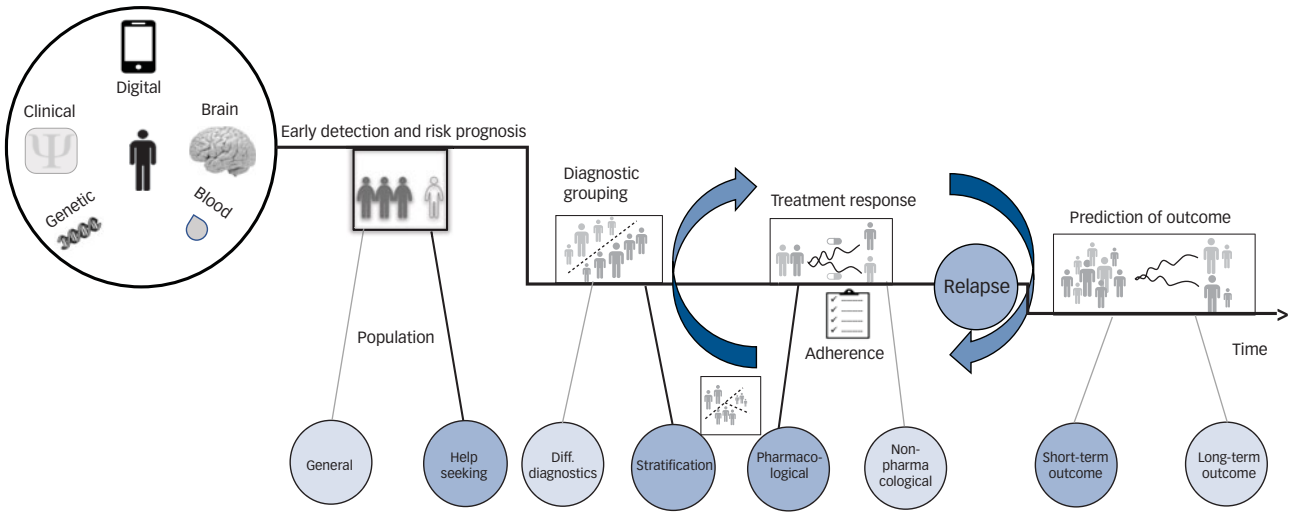

Fig. 1 Individual prognosis along the disease trajectory.

Black lines indicate fields with stronger translational potential due to a larger number of validation studies; grey lines indicate fields of research with currently less translational perspective, owing to a sparse number of studies and validation attempts. Diff. diagnostics, differential diagnostics.

example IMAGEN,[11] emphasise the relevance of a risk pattern for depression in adolescence driven by baseline depressive symptoms, female gender, neuroticism and stressful events, accompanied by surface reduction in the supramarginal gyrus. A broad population-based study, the Philadelphia Neurodevelopmental Cohort (PNC),[12] pursued clinical and neurobehavioural characterisation of genotyped youths for the prospective emergence of psychiatric illness. The PNC has so far delivered a solid normative ground for cognitive milestones and neural development in children and adolescents from age 8 to 21 years. However, the full potential of sufficiently validated developmental biomarkers identified through epidemiological cohorts is yet to be confirmed, and challenges include the infrequent nature of target outcomes, which mean that very large prospective samples are needed.

Diagnostic classification and stratification

Early supervised machine learning studies were driven by the idea that different diagnostic categories have distinct neurobiological underpinnings that can be used to identify biomarkers for psychiatric diseases, similar to those in physical health conditions.[13] Long clinical interviews would become obsolete and techniques such as structural magnetic resonance imaging (MRI) would be used to deliver a robust psychiatric diagnosis and facilitate an accurate prognosis and treatment choice. However, less algorithmic precision than initially expected has been achieved, with predictive accuracies in ranges that would fail validation tests.[14] This has led to further scepticism regarding discrete diagnostic categories and also the potential of machine learning methods.[15] Distinct mental disorders often have many individual symptoms in common, and similarly the majority of neurobiological substrates are present across diagnostic categories. Although diagnostic categories help to conceptualise the high variability of symptoms, we need to be able to accurately stratify patient subgroups on the basis of both reliable clinical and relevant biomarker data to foresee clinical outcome and facilitate the development of selective and indicated treatments. Depression is arguably the one of the most heterogeneous conditions, with differing disease trajectories and treatment responses, and there has been some success with machine learning models defining subgroups based on large-scale population and clinical data.[16]

Recent research has demonstrated the utility of data science in stratification of psychosis and discovery of new targets.[2] It has been estimated that 60% of young people who experience a first episode of psychosis never fully recover[17] and over 20% will develop severe treatment-resistant schizophrenia (TRS). In schizophrenia, unsupervised clustering has found and replicated subgroups with greater structural brain changes (cortical and subcortical volume reduction) associated with chronicity and cognitive dysfunction.[18] In early-onset disorders, supervised machine learning models aimed at interrogating diagnostic weight and boundaries suggest a transdiagnostic signature of poorer outcome across depression and psychosis.[19] Subgroup identification using blood-based biomarkers builds on univariate and group-level approaches that have identified that 35–50% of people with schizophrenia show some evidence of immune dysfunction, as assessed by circulating pro-inflammatory cytokines.[20] Further, Boerrigter et al used a recursive two-step cluster analysis to define subgroups of people with psychosis based on pro-inflammatory cytokine mRNA levels.[21]

Similar work combining multimodal data is advancing stratification of mild cognitive impairment and dementia. Young and colleagues report the working pipeline to uncover stage and subtype of dementias with fine-grained patient stratification, enabling advanced prediction of progression patterns.[22] However, in all aspects of stratification, complex interactions at individual level and acknowledgement of environmental and illness layers remain a challenge.

Prediction of treatment response, adherence and relapse

There has been a large growth in published models able to predict treatment response and treatment resistance in schizophrenia and depression in recent years. Potentially, tools developed from data science may be embedded into clinical practice, so that a clinician and patient can be guided in treatment choice, rather than trial-and-error prescribing. Prediction of treatment response can be framed either in predicting broadly determined non-response (e.g. in TRS or treatment-resistant depression (TRD)) or in predicting specific response to individual interventions (e.g. response to specific antidepressants).

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Prediction of risk for TRD and TRS could potentially provide alerts for increased monitoring and timely use of existing treatments (e.g. clozapine, electroconvulsive therapy). Pigoni recently reviewed prediction of TRD with eight studies, five of which focused solely on clinical and demographic data.[23] Most studies reported reasonable predictive accuracy, including those with external validation samples. Leighton et al developed and externally validated a supervised model based on clinical data from the UK national EDEN study, able to predict symptom remission with an area under the curve (AUC) of 0.70.[24] Legge et al used clinical and genomic data with a conditional inference forest model to predict treatment-resistant psychosis, finding a lower accuracy of prediction (AUC = 0.59): young age at onset, family history, IQ, and poor social and occupational functioning at baseline were significant features, whereas genetic liability was not associated with treatment resistance.[25]

In this issue, Lee et al[26] review 13 studies presenting models that predict outcome after first-episode psychosis, only one including early treatment resistance,[27] with multimodal models to date largely built to predict broad outcomes after a first episode of psychosis (e.g. functioning, recovery) rather than TRS or transition to psychosis from the CHR state.[2]

In terms of individual response to a specific treatment, there is more research activity in depression than in disorders such as schizophrenia or dementia, perhaps owing to the lack of diversity in medication options for those conditions (e.g. all current antipsychotics act as dopamine antagonists). Several models have been developed for antidepressant response, including those originating from the STAR*D trial, for example Chekroud et al[28] and Laje et al,[29] with an externally validated model to predict response to citalopram. Recent advances in pharmacogenetic biomarkers, including gene expression profiles and single nucleotide polymorphisms, hold promise in predicting adverse drug reactions and response to antidepressants.[30]

Recent studies have also aimed to disentangle the response to non-pharmacological treatments (e.g. ELECT-TDCS, involving transcranial direct current stimulation in major depression)[31] and models predicting response to cognitive–behavioural psychotherapy (CBT)[32] and cognitive training.[33] Moreover, digital psychotherapeutic interventions are increasingly common, and machine learning approaches have been used to predict symptom change in response to an internet intervention for depression.[34] Their predictions outperform linear regression models and use easily accessible clinical data, increasing the potential for clinical implementation.

Prediction of treatment response is tightly connected to the prediction of adherence, hospital readmission and side-effects. In this issue, Bannemann et al[35] compare different machine learning algorithms to identify the most clinically useful model that predicts response to CBT in naturalistic settings. The authors report that tree-based and boosted algorithms that include a variable selection process are the most well-suited to predict drop out from CBT. The highest AUC (of 63. 4%) was found for lower education and younger age, as well as strongly pronounced negativistic and antisocial personality traits in contrast to less pronounced compulsiveness traits. Work has also been done on the predicting of hospital readmission within 2 years of follow-up in patients with depression[36] that indicates that again models based on a combination of biomarkers and clinical data outperform models based on clinical variables alone.[2,10] The most far-reaching in terms of multi-centre generalisability is the prediction of readmission to hospital, with up to 74% balanced accuracy (BAC), using data from the European First Episode Schizophrenia Trial (EUFEST).[37]

Predictive models for the early identification of the risk for developing a disorder, relapse, therapy response or adherence may provide prompter identification of individuals requiring close clinical monitoring.[38] Digital approaches such as the experience sampling method (ESM) could be used to actively monitor self-rated mental states, and passive digital phenotyping (phone messages, keyboard use, etc.) also have potential to inform machine learning models, adding real-time data.[39] Most digital measures, either active or passive, are acquired in a longitudinal manner. As such they may be more ecologically valid then symptom rating acquired in traditional cross-sectional studies and they bypass difficulties in bringing patients to the clinical setting. However, no systematically validated prediction models using ESM and digital data are currently available, and ethical considerations, including data protection, are still to be addressed.

Finally, deep learning models may bring the most future promise by outperforming more classic machine learning algorithms. This is possibly due to the suitability of deep neural networks (DNNs) for the high-level representations with minimal domain-specific knowledge and prior feature construction.[40] DNNs require large data-sets containing thousands of data points to provide enough material for the models to learn. As psychiatry is generally struggling with the scale of data-sets needed, the implementation of deep learning paradigms would require coordinated efforts of clinicians, researchers and healthcare providers to deliver faster progress in this field.

Conclusions

Advanced multimodal data science utilising clinical, neuroimaging, proteomic, genomic and digital biomarker data has the potential to address key challenges in psychiatry. This includes the identification of subgroups for novel targeted treatments, improved individual targeting of existing treatments and identification of those at risk of developing a disorder or relapse of existing conditions. However, the routine use of machine learning to guide clinical judgement has not yet come to fruition, and its independent use has yet to surpass the ability of clinicians' best guesses. However, this may not be the fundamental flaw of precision psychiatry, but the present challenge of data availability for already developed, highly performing models which now need to be applied in prospective real-world conditions. The gap is in this last, but most profound step in translation. Coordinated research-ready mental health services are needed to support the scale of clinical, sociodemographic, biomarker and intervention data that would allow the advancement of precision psychiatry to equal that achieved in other areas of precision medicine.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

L.K.-I. and R.U. jointly conceptualised this analysis piece, selected the content and drafted the manuscript. N.K. was involved in conceptualisation of the piece and commented on the manuscript draft.

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