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The potential of precision psychiatry: what is in reach?

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Abstract: Progress in developing personalised care for mental health disorders is supported by numerous proof-of-concept machine learning (ML) studies in the area of risk assessment, diagnostics and precision prescribing. The majority of ML applications still primarily use clinical data, however models may benefit from additional neuroimaging, blood and genetic data to improve accuracy. Combined, multimodal models may additionally offer potential for stratification of patients for treatment. However, the implementation of ML into real world 'bedside' application is presently impeded by a lack wider generalizability, with such efforts primarily focused in psychosis and dementia. Studies across all diagnostic groups should work to test the robustness of ML models, which is an essential first step to clinical implementation, and then move to prospective clinical validation. ML models need to exceed clinicians' heuristics to be useful, and safe, in routine decision making. Engagement of clinicians, researchers and patients in digitalization 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. Together we may confront this challenge with sustained, collaborative effort in times ahead.

Introduction

The past decade has seen substantial investment in the field of data science to develop precision health care for the treatment and prevention of mental illness. Precision health care promises to move away from 'one-size-fits-all approach' for treatment decisions by using objective and replicable psychosocial and/or neurobiological measures. The succeeding treatment interventions would ideally be tailored to these individual profiles and finally address unique properties of individual patients by maximizing 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, whilst considerable investment has resulted in progress and several key achievements, clear caution is still needed. Whilst some ML 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 health care is in place to aid every day clinical care. We present here an analysis of the current position of ML research that is closest to real clinical practice, covering prognostic risk, diagnostic stratification and treatment response with critical insight into current gaps and challenges. (see Figure 1)

Prognostic Risk

Mental health 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 preventative interventions. Recently published ML studies bring some hope to this goal, as they are able to show partially generalizable 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 this clinical high risk state (CHR)[3] has been recently validated in a more broadly defined clinical high[4], including patients with recent onset depression from the PRONIA consortia. This valuable generalisable model points to younger age of onset and reduced processing speed as increasingly relevant for 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. In this themed issue Rosen et al., demonstrate how detailed clinical phenotyping is valuable for prediction of clinical risk and functional outcomes. Their prognostic models in clinical high risk and recent onset depression generalize across geographically and structurally diverse health care systems in absence of neurobiological data.

Higher specificity sometimes seen in neurobiologically based models, when compared to solely clinical data, may remains important in potentially identifying underlying aetiological processes or new staging, given the heterogeneity in clinical phenomenology[2]. The added value of neurobiological data becomes more evident in the older patient population, 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 multiple muticentric dementia studies)[7].

Genetic data may be similar to neuroimaging data, in that it could improve overall accuracy of models, but is not able to deliver self-reliant findings; ie complements 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, whilst contemporary research of prediction relies on polygenic risk scores (PGRS)[8]. Recent advances from the Psychiatric Genomics

Consortium–UK Biobank–23and genome-wide association study report that polygenic risk scores may be useful for prediction of vulnerability to depression and resilience under stress[9]. Similarly, prognostic flows[10] applied in psychotic disorders agree that PGRS slightly augment the performance of models based on clinical-cognitive data[10], yet, remain insufficient for risk screening in general population.

These multimodal prognostic flows may be extended to cohorts of young adolescents and adults, however a similar caution should be taken. Most recent multisite longitudinal adolescent studies, for example IMAGEN[11] emphasize relevance of a risk pattern for depression in adolescence, driven by baseline depressive symptoms, female gender, neuroticism, stressful events accompanied by surface reduction in the supramarginal gyrus. In a broad population based study, The Philadelphia Neurodevelopmental Cohort (PNC)[12] pursued clinical and neurobehavioral characterization of genotyped youths for the prospective emergence of psychiatric illness. The PNC cohort has so far delivered a solid normative ground for cognitive milestones and neural development in children and adolescents from 8 to 21. 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 very large prospective samples are needed.

Diagnostic classification and stratification

Early supervised ML 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 eg structural Magnetic Resonance Imaging (MRI) scans 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 skepticism regarding discrete diagnostic categories, and also the potential of ML methods[15]. Distinct mental disorders often have many individual symptoms in common, and similarly the majority of neurobiological substrates are present across diagnostic categories. Whilst diagnostic categories help to conceptualize the high variability of symptoms, we need to be able to accurately stratify patient subgroups based on reliable clinical *and* relevant biomarker data to foresee clinical 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 ML models defining subgroups based on large scale population and clinical data[16]. In this issue, Arathimos et al focus on Bipolar Disorder, and identify replicable subclass structure for mania symptoms including grouping individuals based on symptoms experienced during periods of manic and/or irritable mood identified five latent classes with varying genomic loading and impact, including and extensively affected active and inactive restless. Although there is still some distance from clinical application, future work aimed at the better characterization of psychopathology and position within the Bipolar 1 or 2 may lead to novel targeted treatments.

Recent research has demonstrated the utility of data science in psychosis stratification and new target discovery[2]. 60% of young people who experience a first episode of psychosis (FEP) 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 (ref needed). In early onset disorders, supervised ML models aimed at interrogating diagnostic weight and boundaries suggest a transdiagnostic signature of poorer outcome across depression and psychosis[18]. Sub-group identification using blood- based biomarkers builds on univariate and group level approaches that have identified 35-50% of patients with schizophrenia show some evidence of immune dysfunction, as assessed by circulating proinflammatory cytokines[19] . Further, Boerrigter et al use a recursive two step cluster analysis to define subgroups of people with psychosis based on proinflammatory cytokine mRNA levels[20].

Similar work combining multimodal data is advancing stratification of in 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[21]. However, in all aspects of stratification, complex interactions at individual level and acknowledgement of environmental and illness layers will 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 choice, rather than trial-and-error prescribing. Prediction of treatment response can be either framed in predicting broadly determined non-response; eg treatment resistant depression (TRD) or schizophrenia (TRS) or in specific response to individual interventions; eg response to specific antidepressants.

Prediction of risk for TRD and TRS could potentially provide alerts for increased monitoring and timely use of existing treatments (eg clozapine, ECT). Pigioni recently reviewed prediction of TRD with eight studies, five of which focused solely on clinical and demographic data[22]. 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 AUC of 0.70[23]. Using multimodal data Legge et al[24] used clinical and genomic data with a conditional inference forest model to predict treatment resistant psychosis, finding a lower accuracy of AUC 0.59, with young age of onset, family history, IQ, poor social and occupational functioning at baseline significant features in the model- genomic data not adding predictive accuracy (ref needed). In this edition, Lee et al. review 13 studies presenting models predicting outcome after first episode psychosis, only one including early treatment resistance[25], with multimodal models to date largely built to predict broad outcomes after FEP (eg functioning, recovery) rather than TRS, or transition to psychosis from clinical high risk[2].

In terms of individual response to a *specific* treatment, there is more activity in depression than for other disorders such as schizophrenia or dementia, perhaps the result of the lack of diversity in medication options in these conditions (eg all current antipsychotics acting as dopamine antagonists). A number of models have been developed for antidepressant response including those origionating from the STAR-D* trial, for example Perlis et al. [26] and Chekroud et al.[27], with a developed and externally validated model to predict response to citalopram. Recent advances in pharmacogenetic biomarkers, including gene expression profiles and single nucleotide polymorphisms, hold promise to predict adverse drug reactions and response for antidepressants [28].

Recent studies have also aimed to disentangle the response non-pharmacological treatments such as the ELECT-TDCS (Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study)[29] and models predicting response to cognitive behavioral psychotherapy CBT[30] and cognitive training [31]. Moreover, digital psychotherapeutic interventions prove to be increasingly halpful and ML approaches have been used to predict symptom change in response to Internet intervention for depression[32]. Their predictions can 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, rehospitalization and side effects. In this regard, Bannemann et al., compare different ML algorithms to identify the most clinically useful model that predicts response to CBT in naturalistic settings. The authors discuss that tree- based and boosted algorithms that include a variable selection process are the most well-suited to predict CBT dropout. The highest AUC of 63. 4% was based on lower education and younger age, as well as strongly pronounced negativistic and antisocial personality traits in contrast to less pronounced compulsiveness traits. Further work has been done in the prognostication of re-hospitalisation within 2 years of follow-up in patients with depression[33] that indicates that again a combination of biomarkers and clinical data outperform models based on clinical variables alone [2,10]. The most far reaching in terms of multi-center generalizability is the prediction of readmission to hospital, with up to 74% BAC, with data from the European First Episode Schizophrenia Trial (EUFEST) study[34].

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[35]. Digital approaches such as 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 ML models adding real-time data[36]. 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 bypass difficulties in bringing patients to the clinical setting. However, until today no systematically validated prediction models using ESM and digital data are available, and as yet ethical considerations including data protection are still to be addressed (ref?).

Finally, deep learning models may bring the most future promise by outperforming more classical ML algorithms. This is possibly due to the deep neural networks (DNN) suitability for the high-level representations with minimal domain-specific knowledge and prior feature construction[37]. DNN requires 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 health care providers to deliver faster progress in this field.

Conclusion

Advanced multimodal data science, utilizing 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, identification those at risk of developing a disorder or relapse of existing conditions. However, the routine use of ML to guide clinical judgement has not yet come to fruition, and its independent use has yet to surpass the ability of clinician's best guess. However, this may not be the fundamental flaw of precision psychiatry, but the challenge of data availability for developed, highly performing models which need to be applied in prospective real-world data at scale. The gap is in this last, but most profound step, in translation. Coordinated research and 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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Figure 1. Individual Prognosis Along the Disease Trajectory. Dark grey lines indicate fields with stronger translational potential due to a larger number of validation studies whereas light grey lines indicate fields of research with currently less translational perspective due to a sparse number of studies and validation attempts.