working memory deficits, smooth pursuit eye movement dysfunction, schizophrenia-related psychometric deviance on the Minnesota Multiphasic Personality Inventory (MMPI), executive functioning deficits, dysfunctional anti-saccade performance, subtle formal thought disorder, clinical schizotypal and paranoid personality features, schizophrenia-related social cognition deficits, exteroceptive and proprioceptive somatosensory deficits, psychomotor abnormalities, and candidate polymorphisms (e.g., ZNF804A, Val158Met-COMT, neuregulin-1). That schizotypic persons manifest such a panorama of deficits, similar in nature albeit less in degree to those seen in schizophrenia, argues for a connection or common underlying construct for conditions defined phenotypically (i.e., schizotypic subjects vs. schizophrenia-affected subjects).

An area of continued speculation concerns the underlying structure of schizotypy and the precise nature of the variation expressed in that latent construct. Considerable statistical evidence, using a variety of latent structure methods, points to the existence of possible underlying discontinuities or severe threshold effects in schizotypy, and work in this area continues. Such evidence stimulates the caveat, to wit, that the use of continuous measures to assess phenotypic manifestations of schizotypy does not *ipso facto* mean that the underlying (or latent) schizotypy construct is fully quantitative or uniformly graded by degree.

The course and clinical outcome for those designated as harboring schizotypy remains an area of active inquiry. It is entirely conceivable that many individuals possessing schizotypy may traverse the life course escaping psychotic illness as well as other diagnosable schizotypic manifestations. The expectation that some people validly at risk for schizophrenia may never manifest the illness is well established in the reality of discordant monozygotic twins, in which one twin is affected by schizophrenia and the co-twin is not psychotic (perhaps not even diagnosable as having a non-psychotic, but detectable, clinical schizotypic condition like schizotypal or paranoid personality disorder).

Individuals that achieve elevated scores on psychometric measures of schizotypy have been shown to be at increased risk for schizophrenia and schizophrenia-related psychoses later in life, as well as a variety of other related outcomes. Such individuals also display poorer psychosocial functioning, lower rates of marriage, increased use of psychiatric medications, and increased utilization of psychiatric services[2]. It is entirely conceivable that many individuals designated as "prodromal" for schizophrenia, but who do not convert to schizophrenia (which is 60-70% of such subjects), are in fact harboring schizotypy and will, even if not psychotic, show impairments across the life span, perhaps adopting an eccentric or odd manner of personality functioning.

The schizotypy model has helped to adjust the boundaries of schizophrenia phenotype in the DSM-5 (e.g., schizotypal pathology is now included with schizophrenia). Furthermore, illuminating the nature of schizotypy may aid in unraveling the current puzzle of the very low conversion to schizophrenia rates seen in "prodromal" schizophrenia research[9].

Finally, I have argued that the schizotypy framework may be useful in understanding *configurations* (rather than simple additive summation) of genes relevant to schizophrenia variants[2], an idea that is beginning to gain traction. There is no doubt that incorporation of schizotypy indicators into genomic studies of schizophrenia increase their statistical power.

The advantages of a cleaner unit of analysis (the schizotype), free from the effects of medication, institutionalization and neurocognitive decline, are axiomatic. However, the understanding (and misunderstanding) of the schizotypy model as well as alternative approaches to the construct require vigilance, in order to ensure that the approach continues to yield the fruit that it can.

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The value of polygenic analyses in psychiatry

The last decade of genetics research in psychiatry (and in other fields) has been dominated by genome-wide association (GWA) studies, in which common variants across the genome are tested for association with a trait or disorder. These studies have shown that polygenicity is the rule, i.e., psychiatric disorders are influenced by many (likely thousands of) genetic variants, each with a small effect[1].

This is best illustrated by the flagship GWA meta-analysis on schizophrenia, which is the first disorder that has achieved the sample size needed to detect the effect sizes that have been dealt by nature's hand. By analysing 37,000 cases and 113,000 controls, 108 associated regions were identified[2]. However, the significant variants together only explained 3.4% on the liability scale for schizophrenia, indicating there are many more vari-

ants involved. This high degree of polygenicity means that everyone harbours risk variants, but those affected likely carry a higher, and possibly unique burden of risk factors, which is fully consistent with the spectrum of clinical presentations.

Still, because of the small effect sizes, the usefulness of the results of GWA analyses has been questioned. In this paper, we show the value of the identification of genetic variants in psychiatric disorders and illustrate how analyses of GWA data have further advanced our knowledge, beyond the identification of associated genetic variants.

One major problem in psychiatry is that there have hardly been any new drugs developed in the last decades[3]. Even though effect sizes are small, significantly associated genetic variants can point to new drug targets, as shown for other diseases[3]. With 108 regions associated and no immediate knowledge about the functional effects of the far majority of the hits, further analyses are necessary, but could lead to new targets.

Functional annotation of genetic variants associated with psychiatric disorders using bioinformatic analyses is an active area of research[4]. This includes analyses that aim to explore which trait-associated genetic variants are also associated with inter-individual variation in gene expression levels, and gene-based analyses investigating which biological pathways are enriched with genes harbouring associated genetic variants[3]. For psychiatric disorders, neuronal, immune and histone pathways are reported to be involved[5], and these analyses will become more informative with new technologies, such as single cell gene expression studies.

GWA data can also be used to increase knowledge on the mechanisms underlying the frequent comorbidity within psychiatric disorders or between psychiatric disorders and other traits. This is interrogated by polygenic analyses, investigating the joint effect of genetic variants[1,4]. Traditionally, to demonstrate a genetic relationship between disorders was difficult, especially for the rarer disorders, because recording of psychiatric diagnoses was needed on large samples of twins or families to demonstrate the increased risk of a second disorder in family members of those affected by a first disorder. However, direct measurement of DNA variants has allowed direct measures of genetic sharing using independently collected case-control samples.

It has become apparent that psychiatric disorders not only share genetic risk with other psychiatric disorders, but also with somatic diseases and traits such as educational attainment[6]. If genetic correlations between disorders and traits are identified, a key question is whether the association reflects shared biological pathways (pleiotropy) or if there is a causal relationship. Using two-step Mendelian randomization, it has been shown that cannabis initiation does result in a small increase in risk to develop schizophrenia, but that schizophrenia leads to a larger increase in risk for cannabis initiation[7]. More insight into directions of effect and causality can direct the development of prevention programs.

Such knowledge is also important for research aiming to develop treatments targeted to children at high risk that their disorder develops into an adult psychiatric disorder, either the same or a different one. A polygenic risk score is an estimate of the cumulative genetic risk of an individual. In schizophrenia research, polygenic risk scores have been found to predict various psychiatric traits during childhood and adolescence, indicating that genetic variants play a role in the transition from internalizing or externalizing symptoms during childhood or adolescence to schizophrenia later in life[8].

These polygenic risk scores cannot be used as diagnostic predictors of psychiatric disease, as risk to psychiatric disorders is only partly explained by genetic risk factors, and, to date, only a small proportion of genetic risk has been identified. Nonetheless, out-of-sample prediction explains about 7% in liability to schizophrenia[2], so those with highest polygenic risk scores have an increased risk approximately equivalent to having a first-degree relative affected.

While this has little clinical utility in the general population, it may have clinical application in the context of prodromal presentation at a mental health clinic. Recently, an individualized risk calculator has been developed that with reasonable accuracy could predict the conversion to psychosis[9]. Predictors included were already existing symptoms and poorer functioning on cognitive tests. Possibly, risk prediction can be improved by adding further variables to the model, including, but not limited to, genetic risk scores[10]. Based on these profiles, individuals could be stratified into high and low risk groups for transition into a severe mental illness[10] and the effects of different treatment programs for these groups could be tested.

Overall, the progress in genetic research has substantially increased our insight into the etiology of psychiatric disorders. Genetic discoveries in schizophrenia have been achieved by large sample sizes, and the current data show that, with larger samples, similar results can be obtained for other disorders. Genotyping technologies are no longer the limiting factor (500,000 DNA variants can be measured for less than $100/person). The limiting factors are availability of large samples with consistently measured clinical symptoms and environmental risk factors. International collaborations, such as the Psychiatric Genomics Consortium (PGC) (www.med.unc.edu/pgc) and the EArly Genetics Lifecourse Epidemiology consortium (EAGLE) (www.wikigenes.org/e/art/e/348.html), and long-term planning are required for cost-effective generation of the data sets needed to deliver on the promise of precision or stratified medicine in psychiatry.

The new genetic discoveries of the last five years are opening previously unknown avenues of research. If ultimately these lead to new treatments, as in other fields of medicine, these treatments could be specific to stratified patient groups.

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The promise and challenges of drug repurposing in psychiatry

The term "repurposing" literally means to give a new purpose or use to a drug. Some researchers have sub-classified repurposing into "reformulation", which is the development of a different formulation for the same drug, and "repositioning", which is the process of identifying a new therapeutic use for an already known drug[1]. One may argue that only repositioning is closely aligned with the term repurposing. Therefore, the focus of this paper will be only on the repositioning form of repurposing.

Drug repurposing is viewed as an approach to rediscovering value in "old molecules" and finding new therapeutic uses, particularly in areas with high risk of failure, such as psychiatry. It is considered a cost-effective and de-risked strategy[2]: having already established the safety and tolerability of a compound diminishes the risks of further development.

The importance of repurposing was recently acknowledged by the European Commission, which formed the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). STAMP aims to recognize the importance of comprehensive investigation of different opportunities that a molecule could bring to patients, with faster development times, and at reduced costs and risk for pharmaceutical companies[3].

The scope and extent of drug repurposing in the central nervous system (CNS) area has been recently reviewed[4]. The authors performed an extensive search of compounds, with the initial and target indication and the type of repurposing strategy (repositioning, reformulation or both). Their study identified 118 source products which were repurposed 203 times, with 80 products repurposed once, 16 products repurposed twice and 22 products repurposed three times or more[4].

Among products repurposed multiple times, over two thirds (68%) came from the CNS area, and half of the new indications (102 cases) were approved[3]. Most of the cases were repositioned (N=171), while only 16 were reformulated, and 16 were reformulated and repositioned at the same time[4]. Among new therapeutic indications, Alzheimer's disease was targeted most often (22 cases), followed by substance dependence (alcohol, opioids, tobacco), bipolar disorder, depression, neuropathy/neuralgia, multiple sclerosis and schizophrenia, with 10 or more cases each[4].

A prototypical example of a repurposed drug in psychiatry is valproic acid/valproate[5]. The anticonvulsant properties of N-dipropylacetic acid (valproic acid) were discovered in 1967 and the drug quickly became widely used in epilepsy, generally in the form of sodium valproate. Antimanic and prophylactic activity in bipolar disorder was only subsequently demonstrated for both valproic acid and sodium valproate, with divalproex (an equimolar combination of valproic acid and sodium valproate) being approved by the US Food and Drug Administration (FDA) in 1995 for this new indication[5].

Traditionally, there have been three major approaches to drug repurposing/repositioning.

One approach is the discovery at the bedside, where a clinician observes/discovers the benefit in a given condition of a compound approved for a different condition. A classic example is bupropion for smoking cessation. Bupropion was first approved by the FDA for the treatment of depression in the 1980s. L. Ferry, at the time Chief of Preventive Medicine at the Loma Linda Veterans Hospital, and her colleagues tried the drug in the mid 1990s in a small group of smokers, with impressive results, as about half were able to quit smoking for at least a year. This led to a series of positive placebo-controlled trials and to the approval of bupropion for smoking cessation in 1997[6].

Another approach involves leveraging the knowledge of the potential benefits of specific pharmacological actions in certain conditions, and identifying compounds initially developed for the treatment of other conditions and sharing similar pharmacological actions. A clear example of this is atomoxetine. This compound, a norepinephrine reuptake inhibitor, was originally developed for the treatment of depression and then abandoned despite good tolerability. T. Spencer, J. Biederman and colleagues, whose group at Massachusetts General Hospital had shown the efficacy in attention deficit disorder of desipramine[7], a tricyclic antidepressant with norepinephrine reuptake inhibition properties, approached the maker of atomoxetine about testing it in this condition, and showed it to be effective[8]. Atomoxetine was subsequently approved by the FDA in December 2002 for the treatment of attention-deficit/hyperactivity disorder.

The third approach to drug repurposing comes from the advances in the understanding of the neurobiology and genetics of psychiatric disorders. The identification of specific neu-