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Clinical Staging and Pluripotent Risk: Implications for Ethical Arguments in Prodromal Research

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Abstract

The identification and treatment of young people at heightened risk of psychosis has not been without controversy. A central feature of this has been debate about the ethics of intervening in this stage of psychotic disorder, prior to the point at which a diagnosis, at least a psychotic diagnosis, can be provided. In this article, we briefly canvas the main ethical issues, including stigma, over-treatment, and paternalism. We then outline the clinical staging model and the concept of pluripotent risk and how these emerging concepts address many of the ethical issues in prodromal research. The clinical staging model and pluripotent risk concepts take a broader approach to syndrome development. We argue that this provides a framework for researching transdiagnostic risk and treating early, diffuse symptom presentations, as well as addressing many of the ethical issues raised in psychosis prodrome/at risk research.

Key words: prodrome, ethics, stigma, clinical staging

Introduction

The identification and treatment of young people at heightened risk of psychosis has not been without controversy. A central feature of this has been debate about the ethics of intervening in

this stage of psychotic disorder, prior to the point at which a diagnosis, at least a psychotic diagnosis, can be provided. In this article, we briefly canvas the main ethical issues, including stigma, over-treatment, and paternalism. We then outline the clinical staging model and the concept of pluripotent risk and how these emerging concepts address many of the ethical issues in prodromal research.

Psychosis Prodrome Research

Eighty percent of people who suffer from schizophrenia and other psychoses experience a prodromal phase, which can last from months to years, preceding their first episode of psychosis (Yung & McGorry, 1996a, 1996b). This period is characterised by non-specific psychiatric symptoms such as depressed mood and anxiety, functional difficulties, anomalous self-experience and, closer to the onset of a psychotic episode, attenuated psychotic symptoms, such as perceptual disturbances, overvalued ideas, and subtle disturbances in speech and language. These symptoms intensify and crystallise into overt psychotic symptoms, accompanied by a diminution of reality testing and insight.

The prodromal period, along with first episode psychosis, has been a cornerstone of early intervention research and establishment of phase-specific clinical services over the last several decades (McGorry et al., 2008). Twenty years ago, criteria were introduced for prospectively identifying young people who may be experiencing a psychotic prodrome. The “close in” strategy that formed the basis of these so-called “ultra high risk” criteria (otherwise referred to as “clinical high risk” or “prodromal” criteria) were based on identifying help-seeking people in the age range for highest risk of a first psychotic episode (mid-teens to early adulthood) who were experiencing attenuated or brief psychotic symptoms, or who had a trait vulnerability to psychosis (family history

of psychosis in combination with functional decline) (Yung et al., 1996). Approximately a third of young people meeting the ultra high risk (UHR) criteria proceed to develop a psychotic episode over one to three years after identification, while a third experience ongoing attenuated psychotic symptoms (not reaching threshold-level psychotic disorder), and a third demonstrate symptom remission (Addington et al., 2011b; Lin et al., 2015; Schlosser et al., 2012).

Although a range of predictive models have been developed (Cannon et al., 2008; Nelson et al., 2013; Nieman et al., 2014; Ruhrmann et al., 2010), a reliable set of predictors for identification of UHR patients who will progress to psychotic disorder remains elusive, as has the identification of biomarkers for this true positive group. This is complicated by the issue of intervention possibly averting (or at least delaying) the onset of psychotic disorder in UHR patients [i.e., "false false positive" cases (Yung & McGorry, 1996b)], making it difficult to distinguish lack of risk from treatment responsiveness. Twelve intervention trials have now been conducted in the UHR population and several meta-analyses of their results have appeared (Preti & Cella, 2010; Stafford et al., 2013; van der Gaag et al., 2013). The interventions trialled have included cognitive behaviour therapy, integrated psychosocial interventions, antipsychotic medication, family therapy and omega-3 fatty acids. Overall, these interventions are associated with a 54% reduction in risk of transition to psychotic disorder at 12 months and a Number Needed to Treat (NNT) of 9 (van der Gaag et al., 2013). At 24 to 48-month follow-up, the interventions are associated with a risk reduction of 37% and a NTT of 12 (van der Gaag et al., 2013).

Prodromal research and clinical care has always been associated with some degree of ethical debate (McGorry et al., 2001). However, this intensified in the context of discussion as to whether to include a diagnosis in DSM-5 to capture this clinical group (the precise formulation and name for this diagnosis went through a number of iterations). The Attenuated Psychosis Syndrome

was ultimately placed in DSM-5's Appendix as a condition requiring further study, principally due to a failed field trial of applying the diagnosis in ordinary clinical settings without special expertise and structured interviews (Carpenter, 2014). The ethical concerns have mainly been to do with stigma, over-treatment, and paternalism. These will be addressed briefly here before discussing clinical staging and the broader risk concept as changing the complexion of these ethical issues.

Stigma

There has been concern that the identification or label of being at heightened risk of psychotic disorder may be associated with stigma in various ways: external stigma (discrimination from others, including peers or organisations, such as schools or insurance companies); shame (possibly leading to a label of "psychosis risk" being kept secret from others); internalised stigma (self-identification as being defective or hopeless in some way); and identity engulfment (the person regarding psychosis risk as defining their identity) (Corcoran, 2016; Link & Phelan, 2001). The concerns about stigma are heightened by the age range of the UHR group (teenagers and young adults), a crucial period for identity development (Corcoran et al., 2010). Families might also react to the identification of psychosis risk in an overly protective manner, discouraging healthy risk-taking in their child due to a fear that stress could trigger psychosis.

A number of empirical studies of stigma in the UHR group have now been conducted. Amongst college students, public stigma elicited by a clinical vignette describing attenuated psychotic symptoms was similar regardless of whether the diagnosis was psychosis risk or schizophrenia, apart from when the psychosis risk label was accompanied by several sentences explaining that the real risk of psychosis was 35% in 2.5 years, which greatly reduced public stigma (expressed as a desire for social distance) associated with these vignettes (Yang et al., 2013). In

another study, family members of young people identified as being at risk of psychosis had low associative family stigma, they reported that at-risk youths should be encouraged to vote and work, and they denied any sense of shame about their family members or need to conceal their symptoms (Wong et al., 2009).

Other recent studies in UHR patients found that, after adjusting for age, gender, symptoms, and functioning, self-labelling as mentally ill was associated with greater stigma stress (perceived harm of mental health stigma in excess of perceived resources to cope with it) and reduced well-being (Rusch et al., 2014a; Rusch et al., 2014b), more suicidal ideation (mediated by social isolation) (Xu et al., 2016b), and higher rates of developing schizophrenia (Rusch et al., 2015), although self-labeling was also associated with more positive attitudes toward treatment (Xu et al., 2016a). These studies certainly indicate that self-labeling as mentally ill can be harmful for the UHR group. Another recent study, albeit in a first episode psychosis group, found that the impact of self-stigma extended beyond social and occupational withdrawal and undermined a subjective sense of community belonging (Berry & Greenwood, 2017). However, as discussed by Corcoran (2016), it is possible that self-labeling and associated stigma stress derive from the very symptoms that place young people at risk of psychosis, rather than from an external label of psychosis risk provided by a clinician or researcher. In fact, another recent study found that UHR patients reported significantly more shame and discrimination related to their symptoms than to a “psychosis risk” label itself, which instead was associated with more positive emotions, such as feeling understood, hopeful, and relieved (Yang et al., 2015). Our own recent work (Kim et al., 2017) in fact indicated that patients were less likely than clinicians to believe that there was stigma associated with the terms “UHR” and “Attenuated Psychosis Syndrome (APS)”, underlining the fact that assumptions amongst clinicians may at times blind them to the actual experience and views of help-seeking young people.

Together, these studies suggest: the importance of explaining the label “psychosis risk” and the potential for misinterpretation if not accompanied by an explanation; that the “psychosis risk” label need not be harmful and may in fact confer benefit, as it provides an explanatory framework for symptoms and can guide treatment and potential strategies for minimising risk; and that stigma associated with psychosis risk labels can be greater amongst clinicians than amongst patients themselves.

Over-Treatment

Another point of ethical debate has been whether identification as UHR for psychosis may result in over-treatment of this clinical population, particularly with antipsychotic medications, which are currently not advocated in clinical guidelines for this group. While this may not be the case in specialised research clinics, it may be more of a concern in general psychiatric services where the label of attenuated psychotic symptoms or psychosis risk may easily be misperceived as a label of actual psychosis (Corcoran, 2016). Indeed, UHR/prodromal clinics have reported substantial rates (13-30%) of young people being referred already on antipsychotic medication, although never having met diagnostic criteria for a psychotic disorder (Cadenhead et al., 2010; Cannon et al., 2008; Yung). This issue is particularly salient given the reducing rate of transition to psychotic disorder observed in recent UHR cohorts, i.e. the increasing rate of false positives, because this means that more UHR patients not in fact on the trajectory to develop psychotic disorder (or for whom psychosocial interventions are sufficient for delaying or preventing psychosis onset (Nelson et al., 2016)) will inappropriately receive antipsychotic medication.

Paternalism

Given concerns about labelling and stigma, there has been consideration as to whether

information provided by clinicians to patients and families about attenuated psychotic symptoms and psychosis risk should be limited in some way. This may particularly be indicated given that motivation for help-seeking and the main source of clinical distress is often not the attenuated psychotic symptoms themselves, but rather other clinical concerns, such as depression, anxiety, etc. (Falkenberg et al., 2015; Power et al., 2015). However, this is a form of paternalism (attempting to protect individuals by censoring or filtering information), which is generally not adopted across medical fields and is inconsistent with ethical principles of patient autonomy and informed consent. In addition, avoiding terms such as "schizophrenia" or "psychosis" can actually feed into the stigma associated with such terms by implicitly conveying the message that such terms/diagnoses should be kept secret or should be seen as a source of shame (McGorry et al., 2001). Also, in the online age it is not realistic to protect young people or their families from certain medical information, as most clinics, researchers, or psychiatric symptoms can easily be researched online. To illustrate, it was the recent experience of one of the authors that within minutes of seeing a new patient for the first time, the patient asked, "I see online that you research risk for psychosis…so why on earth are you seeing me?"

One way of addressing the ethical issues around the psychosis risk concept and the increasing rate of false positives in UHR cohorts (although see discussion of false false positives above) is to regard it as a syndrome in its own right, rather than as a risk state. This is the approach adopted in the DSM 5 category, Attenuated Psychosis Syndrome. This effectively sidelines concerns about labelling *risk* of developing a more severe form of disorder and concentrates clinical formulation, diagnosis, and treatment on currently presenting symptoms. Another approach that minimises ethical concerns is taking a broader scope in identifying risk states and outcomes of interest, which we will now address.

Clinical Staging & Pluripotent Risk

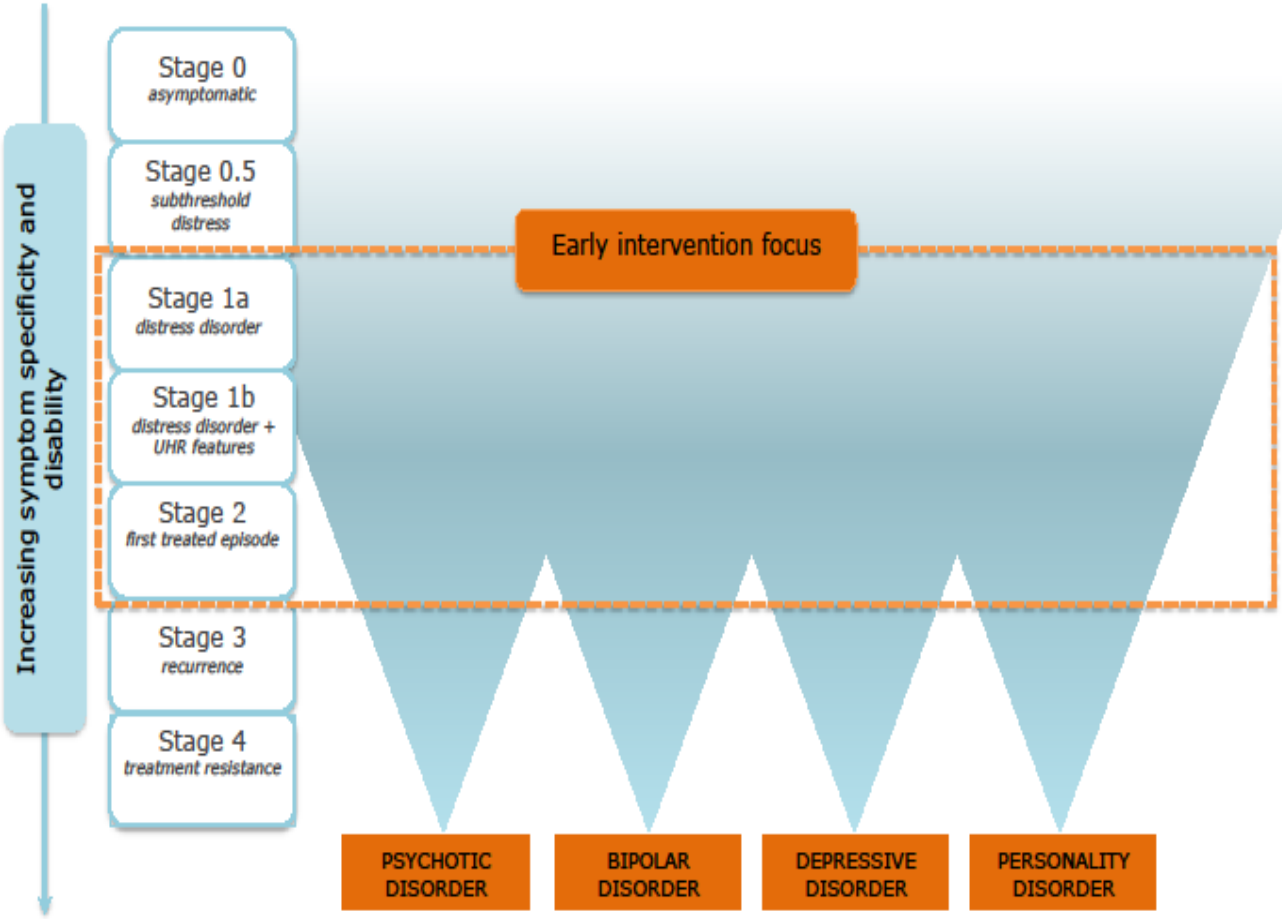
The clinical staging model, which parallels staging models in general medicine (e.g. cancer or kidney disease), moves beyond the traditional dichotomous approach to psychiatric diagnosis by defining *the extent of disease progression* based on severity, duration, and course of symptoms (see Figure 1). The model attempts to determine the position of an individual along a *continuum* of illness, defined according to stages: Stage 0 = no current symptoms, Stage 1a = help-seeking with distress, Stage 1b = attenuated (i.e., sub-threshold) syndrome, Stages 2-4 = full threshold disorder with varying degrees of recurrence and severity. This is also referred to as a "trunk and branch" model, with the trunk representing the pluripotent risk of symptoms, crystallising over time into particular syndromal branches (Hickie et al., 2013; McGorry, 2007a; McGorry et al., 2006). The concept of pluripotent risk stems from general medicine and refers to clinical signs and symptoms that are not fixed as to their potential development – that is, they may evolve into a range of different syndromes. The differentiation of early and milder clinical phenomena from more severe and chronic phenomena lies at the heart of the clinical staging concept, and allows the clinician to select appropriate treatments according to stage (Hickie et al., 2013; McGorry, 2007a; McGorry et al., 2006). An appropriate intervention for a Stage 3 disorder, for example, is probably not appropriate for a Stage 1b disorder. Interventions should be proportionate to need and risk of extension of the clinical phenotype.

Staging also moves outside the current diagnostic boundaries to include the full spectrum of symptoms and disorders. While highly congruent with notions of an extended phenotype for individual disorders (Berk et al., 2014; van Os & Linscott, 2012), involving continuity with the healthy population, it places strong diagnostic emphasis on where a person sits in the evolution of the clinical phenotype *transdiagnostically.* This broad, transdiagnostic approach to clinical staging takes

a life course perspective that transforms the impression of multiple lifetime psychiatric comorbidities (measured cross-sectionally), recognising that many of these may in fact be artifactual or transitory (Shah & Scott, 2016). This approach is based on the understanding of clinical symptoms as heterotypic continuities, with early, *less specific* stages of disorder potentially evolving into more specific diagnoses. The approach is consistent with the current trend in psychiatry to think beyond traditional diagnostic categories, reflected in the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) approach (Cuthbert & Insel, 2010, 2013) and continuum models of mental disorder (van Os et al., 2001). Clinical staging also has a longer-term goal of facilitating links between biological and neurocognitive illness markers and clinical phenotypes, as well as developing cross-domain predictive models (Nelson et al., 2017). The clinical staging model has mainly been a heuristic strategy to date in order to organise thinking about disease extension and severity, to guide treatment decision making, and to link psychopathological, psychological, and neurobiological variables across stages of disorder. Empirical data are now becoming available to empirically test and validate the model (Hartmann et al., 2017; McGorry et al., 2014a; Purcell et al., 2015a; Purcell et al., 2015b). The notion of a ‘stage’ or a ‘step’ (implying some degree of discontinuity) remains a hypothesis, since each stage may merely represent an arbitrary boundary drawn on essentially continuous phenomena (McGorry et al., 2014a). Nevertheless, the ‘stage’ notion already has clinical utility from the perspective of aiding treatment decision making (McGorry, 2013).

Figure 1

Title: Hypothesized Clinical Staging Model and Pluripotent Risk



Note. This is a heuristic model. The outcome disorders (Stage 2 and beyond) included are for illustrative purposes. Other Stage 2 disorders (e.g., anxiety disorders, substance dependence) could also be listed. UHR = ultra high risk.

The clinical staging model accommodates the pluripotent nature of early clinical phenotypes of mental disorders. Emerging mental disorders manifest diffusely and non-specifically in their early

stages (Fusar-Poli et al., 2014; McGorry, 2014). Prodromal symptoms of the various syndromes overlap substantially and wax and wane in intensity over time. This is well illustrated by the UHR for psychosis criteria: these criteria not only have a strong valence for subsequent psychosis, but also predict other syndromal and functional outcomes (Addington et al., 2011a; Lin et al., 2015). A long term follow-up study by our group revealed that 70% of UHR patients who did not develop psychosis (non-transitioned cases) had *non*-psychotic disorders over a 2-14 year follow up period, mainly mood disorders (49%) and anxiety disorders (35%) (Lin et al., 2015). Similar figures have been reported in US samples (Addington et al., 2011a). This supports the notion of the pluripotency of the early clinical phenotypes of mental disorders.

While the UHR criteria already identify young people at risk of a range of disorders, the identification of risk for a range of serious mental disorders (a general risk state) can be improved by broadening and refining these criteria (McGorry & Nelson, 2016). This approach identifies a degree of distress and need for care warranting clinical intervention, but which does not attempt to define a particular target outcome syndrome, such as psychotic disorder. This is consistent with concepts in developmental psychopathology of equifinality (many paths to one disorder) and multifinality (many disorders from one pathway) (Cicchetti & Rogosch, 1996). Our research group is currently trialing a broader set of risk criteria (identifying young people at stage 1b disorder according to the clinical staging model), based on and expanding the UHR approach of sub-syndromal syndromes (*forme fruste* disorder) (Hartmann et al., 2017). The identification approach may be expanded in due course to include other predictive variables and risk factors (clinical, demographic, biological characteristics, etc.). Importantly, the pluripotent risk identification approach is also more efficient with regard to power to conduct prediction and intervention studies in relatively low incidence disorders, such as schizophrenia or bipolar disorder (Cuijpers, 2003), because although a reasonably low rate of

transition to a particular disorder may be observed, the onset of one or more of a range of Stage 2 or DSM-diagnosable disorders may be substantial. Early data from our current study validating the broader risk criteria indicate a substantial rate of transition to more serious Stage 2 disorder (psychosis, bipolar disorder, severe depression, borderline personality disorder) of 20-30% by 6 month follow up (Hartmann et al., 2017).

Implications for Ethical Arguments

The clinical staging model and the pluripotent approach identifies risk for multiple psychiatric outcomes (i.e., is transdiagnostic in the outcomes of interest) and therefore decreases the risk of false positives inherent in at-risk approaches to any single disorder. Although of course all risk identification approaches involve identification of some false positive cases, this rate is likely to be substantially lower when the outcome is broader (i.e., any Stage 2 disorder). The ethical concern of the low transition rate/high false positive rate in UHR samples is therefore mitigated. The labelling associated with this broader risk state would not be psychosis-specific and would therefore not carry the stigma that can (unfortunately) be attached to schizophrenia and other psychotic diagnoses. While stigma can certainly be present for mental disorders more broadly (i.e., is not limited to psychotic disorders) (Link, 2001; Link et al., 2001), the clinical staging model directs treatments that are stage-specific and proportionate to presenting problems, as well as providing treatments to reduce risk of progression to more severe disorder. While this has always been the case in UHR intervention (McGorry et al., 2001), the emphasis on treating *current* symptoms and distress is possibly even stronger in the context of the clinical staging model. To use a medical analogy, the shift is akin to diagnosis and clinical care of angina or chest pain rather than risk/prevention associated with hypercholesterolemia (Carpenter et al., 2014). This conveys the message of dealing with present distress and reason for help-seeking rather than emphasising risk for more severe

disorder, as has sometimes been a concern with the UHR approach and the terminology used in this field (Frances, 2011; Frances & Widiger, 2012). Broad-spectrum relatively benign interventions can be applied at an early stage of disorder such as Stages 1a and 1b (e.g., stress management, cognitive behaviour therapy (CBT), practical case management, neuroprotective agents such as omega-3 fatty acids), with more specific and targeted interventions (e.g., antipsychotic and mood stabilizing medications) reserved for more severe stages of disorder (Stage 2 onwards) (McGorry, 2007a, 2010; McGorry et al., 2010). This approach of matching treatment to stage of disorder avoids concerns about inappropriate treatment of false positive cases and overtreatment of young people at risk for psychosis. Defining this broader, pluripotent at risk group also allows refining the identification of risk by allowing us to accurately identify young people who require intervention and who may progress to more severe stages of disorder and differentiating these from young people who will follow a more benign trajectory without intervention (Patton et al., 2014).

The concerns about stigma are also significantly diminished if treatment is provided in youth-specific services especially designed to have easy access and be non-stigmatising, such as the Headspace services established in Australia. These youth-specific services are provided in an accessible, community-based, non-judgmental, and non-stigmatising setting in which young people feel comfortable, have a say in how their care is provided, and feel a sense of trust (McGorry et al., 2013; McGorry, 2007b; McGorry et al., 2014b). Similar youth-specific service models have been implemented in other countries, such as the UK, Ireland, Denmark, France, and Singapore, and are proposed for Canada, the USA, and Israel (McGorry et al., 2014b).

With regard to concerns about paternalism, the clinical staging model and pluripotent risk concepts support a transparent approach to providing information to patients and families about treatment for the existing stage of disorder and discussion of the multiple possible symptom

trajectories (progression from a mixture of mild clinical symptoms to more specific and severe symptoms, which may warrant a change in treatment approach, remission of symptoms, etc.). While this involves a degree of uncertainty (not being able to say with certainty which clinical trajectory an individual is on or how effectively the person will respond to treatment), which is not uncommon in medicine, it promotes a collaborative, hopeful approach to clinical care and does not involve censoring or filtering information. As research into pluripotent risk factors and transdiagnostic preventative intervention progresses, risk prediction can be refined and personalised and this can be reflected in information provided to patients and families.

This discussion of implications of clinical staging and pluripotent risk for ethical issues in the field is based on reasoned argument that should be tested in empirical studies. For instance, studies should test whether the explanation of current symptoms and distress in the context of the clinical staging model, as described above, is in fact less potentially distressing and/or stigmatising to patients and families than other methods of explaining clinical risk. Empirical work should also investigate the way that patients and families understand and react to health care providers conveying the limitations of our current understanding of individual patient trajectories (Simmons et al., 2017).

Summary

The UHR/prodrome field has been a particular focus of ethical debate, which intensified in the discussion about whether to include a diagnostic class in DSM 5 capturing this pre-psychotic state. Some of these points of debate included stigma, over-treatment, and paternalism. While we believe that these ethical issues can be effectively dealt with in UHR services and research studies (McGorry et al., 2001), the broader and agnostic approach with regards to specificity of syndrome

development captured in the clinical staging model and pluripotent risk concept meets these ethical challenges even more effectively and provides a framework for treating early, diffuse symptom presentations and researching transdiagnostic risk. Empirical work is currently underway to further test and validate the clinical staging model and pluripotent risk concepts.

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