The aggregation of marginal gains: a pragmatic philosophy of clinical care in psychiatry

The cliched opening sentence of many articles in the psychiatric field bemoans the limited efficacy of individual treatments. However, this singular truth is far from the whole truth. The theory of aggregation of marginal gains, also known as the "1% improvement theory", suggests that small, sustained, incremental improvements in multiple areas can lead to substantial overall progress in a given field[1]. This theory has been applied in various areas, including sports, business, and health care, and appears to be relevant to psychiatric clinical practice.

This approach was famously adopted by the Sky British Cycling Team. The team's management implemented multiple small changes and improvements to diverse aspects of the team's operations, including training, nutrition, sleep, equipment and recovery. The goal was to combine these individually small improvements to achieve a significant overall increase in performance. This alchemy successfully transmuted leaden failures into golden victories in the Tour de France. The concept of "aggregation of marginal gains" has since been widely adopted in other fields, and has become a popular approach to achieving continuous improvement[1]. This notion is concordant with the view of Stein et al, put forward recently in this journal[2], that progress in psychiatry will likely not be driven by a singular transformative paradigm, but by "incremental progress and iterative integration".

An approach to the aggregation of marginal gains in psychiatry can be based on the concomitant utilization of interventions that target specific risk factors or operative pathways for an individual. As argued by Kendler[3], psychiatric disorders are highly multicausal, with as many as 37 potential risk factors identified, for instance, for depression. Additionally, Borsboom et al[4] show that the complex network interaction of multiple factors results in complex psychiatric syndromes, which cannot be explained by reductionist models.

Similarly, Loscalzo and colleagues[5] used the mathematics of networks to show that the interactions between all relevant factors (the "interactome") and all the changes that can lead to a diseased state (the "diseaseome") form stable networks. These networks, when perturbed by therapeutic interventions, will adapt and can lead to a healthy state (the "healthyome"). However, this healthy state tends to be temporary, and the network will tend to revert to the diseased state "unless multiple interventions lock the network into the healthy state"[5].

Furthermore, by modelling those factors which cause other factors (e.g., insomnia can cause fatigue), clinicians can identify the most important areas to target interventions[2]. Here, the "Swiss cheese" model of risk mitigation[6] can be illustrative of a path forward. Widely used in the public health sphere, such an approach focuses on incremental improvements across several imperfect interventions to provide a sum effect greater than any one intervention alone.

Attempts to conceptualize and manage psychiatric disorders as monocausal or simply linear have generally been unsuccessful. By extension, approaches that leverage the above multicausal complex network models into treatment are now needed. This also has the potential to pragmatically personalize therapy. Precision medicine approaches have largely focussed on biomarkers and other singular factors capable of stratifying care. In contrast, clinical formulation aims to understand and explain the diversity and network of multiple predisposing precipitating and perpetuating factors leading to an individual's problems and symptoms[7]. These span genetic loading, different etiological factors for those with earlier or later age of onset, the impact of early or ongoing life events and stressors, lifestyle and environmental factors; comorbid substance use, medical or psychiatric conditions; early life experiences, development and subsequent cognitive schemas, personality strengths and difficulties, and current relationships and supports[7,8].

Merging the constructs of aggregation of marginal gains and complex clinical formulation is a pragmatic way to identify an individual's risk pathways and combining the multitude of possible and available treatments.

Furthermore, a subtractive approach focuses on eliminating factors that might be detrimental to care. Two potentially malleable factors include the treatment gap, whereby individuals with disorders do not have access to care, and the evidence-practice gap, which refers to the gap between treatment received and the evidence base[2]. Health care systems are complex interconnected chains, with disruption at any link capable of adversely impacting clinical outcomes. A continuous improvement approach involves regularly evaluating the patient's progress and iteratively identifying new areas for improvement. By continuously making small systems-level and individual improvements and adjusting the treatment plan as needed, clinicians can help their patients make ongoing progress in their health.

Lifestyle factors operate across the spectrum of psychiatric and non-communicable physical disorders. There is now abundant evidence that smoking increases the risk for several psychiatric disorders and worsens outcomes; there is equal evidence that smoking cessation, previously thought of as too difficult, represents a clinical low-hanging fruit, being associated with improvement in many domains of mental health. The same is true of increased physical activity, improved sleep and diet, and reduced screen time: improvements in these domains are associated with better outcomes in multiple mental health and comorbid physical disorders. Moreover, pharmacogenomic testing might produce a marginal gain for a subgroup of people, as may digitally augmented phenotyping and therapies[2].

In addition to their direct effects, diseases and their symptoms erode people's capacity to engage in meaningful, rewarding and purposeful activities. Activity scheduling, encouraging hobbies and activities, supporting occupational engagement, volunteering,

and enhancing social networks can increase resilience and supports, as does supporting caregivers and meaningful relationships.

Thus, multidisciplinary approaches focusing on small improvements in various areas can help significantly improve overall health. Seemingly small benefits at a point in time have nevertheless the capacity, through compound interest, to become large benefits over time. Each gain is a small victory that subtly enhances hope and boosts confidence and self-efficacy, which increases the capacity of the individual to take on further tasks. Just as compound interest in investing does not appear to do a lot in the first years, but does a huge amount over decades, each clinical gain amplifies other gains, and increases the possibility of further improvement in a self-reinforcing cycle.

A further and synergistic construct is that of persistence. A recent paper suggested that most people who persisted with up to 10 different treatments showed meaningful clinical improvement [9]. This conclusion is supported by epidemiological data showing that people who received specialized, multi-sector care were more likely to report being helped "a lot"[2]. The obvious caveat is time: the six- or eight-week timeframe of clinical trials is not sufficient for meaningful improvement for most people, and realistic expectations need to be set. Meaningful clinical improvement for most people is generally measured in months, if not years.

In conclusion, the theory of aggregation of marginal gains can be a pragmatic and optimistic philosophy of clinical care. Because of the complexity of psychiatric disorders, there are few silver bullets. By focusing on multiple small, incremental improvements in various areas germane to an individual, clinicians can help their patients progress significantly in their overall mental health. Using clinical formulation to tailor the plethora of available options to the individual's needs, aided by a multidisciplinary and continuous improvement method, clinicians can further enhance the effectiveness of this approach.

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The NIMH supports more comprehensive and inclusive genomic studies in psychiatry

The inclusion of diverse populations in genomic studies is key to generate more comprehensive findings, as well as to ensure equitable research. However, most genomic studies have been conducted as yet on cohorts of European ancestry, with minimal representation of other populations worldwide[1,2]. To address this historical gap, the US National Institute of Mental Health (NIMH) has established the Ancestral Populations Network (APN), through two funding opportunities[3].

The APN was formed with the overarching goals of: a) accelerating genetic discovery for psychiatric disorders in cohorts of non-European ancestry; b) advancing global mental health discovery and equity; c) facilitating measurement and data analytic harmonization efforts to enhance rigor and reproducibility; and d) generating a resource for network members and the scientific community. The APN also presents a distinctive global perspective toward reducing inequities and disparities in mental health research, by supporting strong in-country leadership representation, strengthening research capacity, and promoting the development of early-stage career researchers.

Overall, the APN will collect and analyze data from 200,000 participants (cases, controls and families) from over 25 sites worldwide, through seven projects.

The Populations Underrepresented in Mental Illness Association Studies (PUMAS) will use the newly developed blended genome exome (BGE) sequencing technology for genetic characterization of severe mental illnesses (SMI), including individuals with schizophrenia spectrum and bipolar disorder, in Africa, South America and the US. The project aims to create the largest to date phenotypic and genomic resource of people with non-European ancestry with SMI data.

The Genomics of Schizophrenia in the South African Xhosa (SAXII) will characterize the genomic architecture of schizophrenia in the native Xhosa population of South Africa, using a combination of long-read and short-read whole genome sequencing (WGS) methods to identify new classes of damaging mutations. Using these innovative genomic technologies, the project will provide deeper insights into the genomic structure of individuals with schizophrenia and serve as a resource for other case-control comparison studies across ancestral populations.

The Latin American Trans-Ancestry Initiative for OCD Geno-