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Opinion

Reframing anorexia nervosa as a metabo-psychiatric disorder

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Anorexia nervosa (AN) is a serious and often fatal illness. Despite decades of research, investigators have failed to adequately advance our understanding of the biological aspects of AN that could inform the development of effective interventions. Genome-wide association studies are revealing the important role of metabolic factors in AN, and studies of the gastrointestinal tract are shedding light on disruptions in enteric microbial communities and anomalies in gut morphology. In this opinion piece, we review the state of the science through the lens of the clinical presentation of illness. We project how the integration of rigorous science in genomics and microbiology, in collaboration with experienced clinicians, has the potential to markedly enhance treatment outcome via precision interventions.

Highlights

Anorexia nervosa (AN) is a severe and frequently lethal illness for which there are no biologically informed evidence-based interventions, notwithstanding decades of research.

Genome-wide association studies have identified significant loci that have been previously implicated in metabolic traits as well as robust significant genetic correlations between anorexia nervosa and psychiatric, anthropometric, and metabolic traits.

An imbalance in the intestinal microbiota (dysbiosis) of individuals with anorexia nervosa has been reported. Studies of intestinal morphology also suggest disturbances in gut villus architecture and a decrease in intestinal permeability in the gastrointestinal systems of individuals with AN, both of which might impede recovery.

Integrating the study of human genomics and the intestinal microbiota, with input from experienced clinicians, has the potential to develop and deploy precision nutrition approaches to improve AN renourishment interventions and sustain meaningful recovery.

Shifting paradigms in understanding and treating AN

AN rests squarely on the psyche–soma border; however, etiological theories and treatments have historically focused on psychological, family, and societal factors. A conceptual shift is underway. The latest **genome-wide association study** (GWAS; see Glossary) for AN [1] suggested reconceptualizing AN as a 'metabo-psychiatric disorder'. In addition to identifying eight significantly associated genomic loci, a rich panel of genetic correlations underscored the role of psychiatric, anthropometric, and metabolic factors in the etiology of this highly lethal disease.

We provide a blueprint for clinical translation of these findings by summarizing GWAS findings, describing the **endocrine** and metabolic setting and sequelae of AN, discussing the role of the intestinal microbiota and intestinal morphology in AN, and exploring how integration of these three important sources of information may advance our understanding of AN etiology and enhance its treatment (see Figure 1, Key figure). We cautiously introduce **nutritional psychiatry**, focusing on nutrigenomics and **precision nutrition**, underscoring the importance of separating hype from science in calibrating hope and guiding future research and precision interventions.

Clinical presentation of AN and outcome

AN is characterized by extremely low body weight, fear of weight gain, behaviors to impede weight gain, and an inability to recognize the seriousness of the condition [2]. Two subtypes exist: (i) restricting, marked by restrictive eating, dieting, fasting and excessive exercise, and (ii) binge eating/purging, in which either or both binge eating and compensatory behaviors accompany restriction. Clinically, AN is difficult to treat, with only 30% of adults recovering fully [3]. Mortality is significantly elevated (typically direct sequalae of malnutrition or suicide) [4,5] with most individuals achieving partial recovery (i.e., a sustainable but low weight and some cognitive and behavioral symptoms of the illness), placing them in perilous risk of relapse [6]. Therapeutic renourishment and weight restoration are essential first steps in treatment and are core treatment goals in most clinical guidelines and evidence-based interventions [e.g., **family-based treatment (FBT)** [7], **specialist supportive clinical management** [8], **Maudsley**

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model of anorexia treatment for adults (MANTRA) [9], and cognitive–behavioral therapy [10]]. Yet, surprisingly few studies have addressed the optimal renourishment strategy in AN, especially for adults. Renourishment approaches reflect clinical experience and are conducted in collaboration with dietitians trained in eating disorders. The key challenge in AN management is ensuring maintenance of restored weight. Far too often, inpatient or residential weight restoration is followed by rapid post-discharge weight loss. Repeat cycles may result in severe and enduring AN marked by prolonged suffering, lifestyle interruption, and even death. The rapid loss of restored weight has historically been psychologized, citing the fierce determination of individuals with AN to reach and maintain a low body mass index (BMI); however, that perspective has not yielded improvements in treatment outcomes or reductions in mortality.

Urgency exists to advance understanding of the biology of AN. No medications are effective or approved in its treatment. Moreover, both the United States [11] and Europe [12] face a crisis in care, and access to care for those with the most severe forms of the illness is limited. Highly specialized centers have emerged to stabilize the most critically ill patients [13], but for many, these life-saving options are inaccessible.

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Key figure

Integration of genetic and microbiology science on anorexia nervosa encourages precision nutrition approaches that target the gut–brain axis to restore healthy weight and gut function and reverse hormonal dysregulation and entrenched cognitions that maintain the illness and contribute to relapse

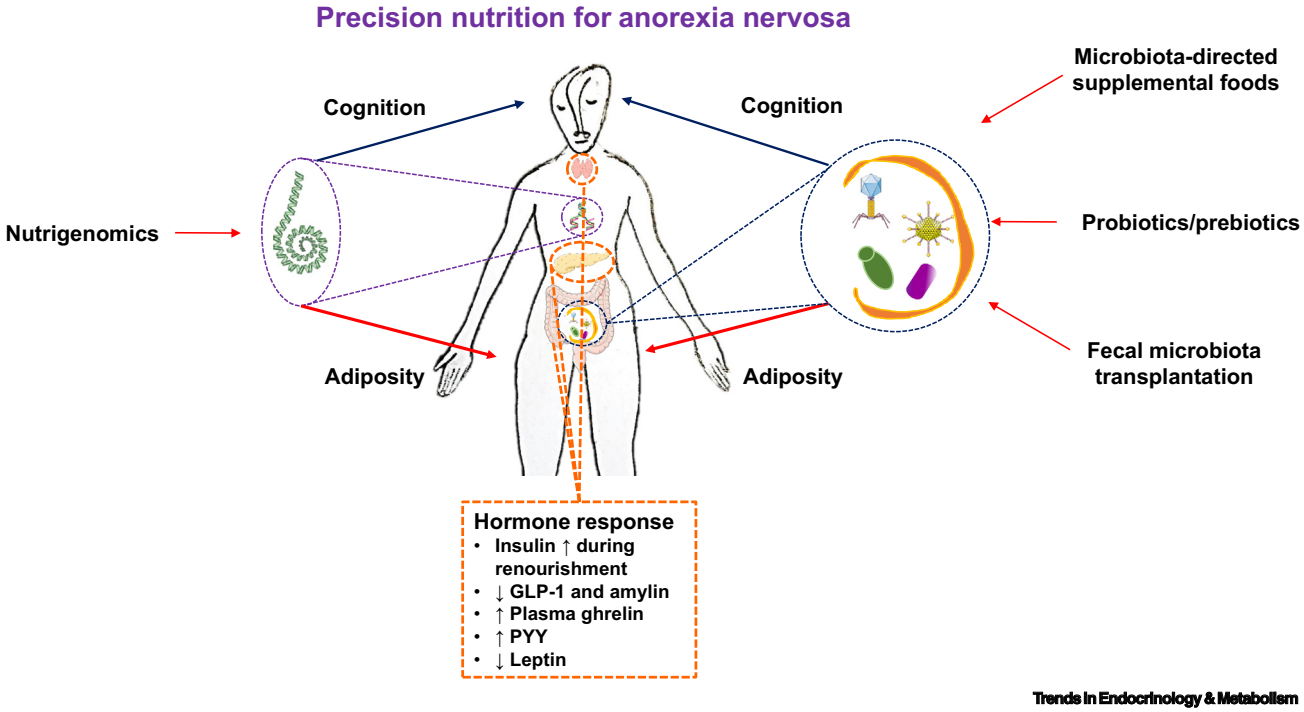

Figure 1. Abbreviations: GLP-1, glucagon-like peptide; PYY, gut hormone peptide YY.

The endocrinological and metabolic setting of AN

To direct further investigations of the role of endocrinology and **metabolism** in AN etiology and treatment, a full appreciation of the biological setting of the illness is essential. The endocrine and metabolic setting of AN is complex and occasionally counterintuitive because the clinical findings are not always as would be expected in a state of prolonged malnutrition. Multiple adaptive or reactive changes in the endocrine system and metabolism are observed that occur at the hypothalamic–pituitary level and at the level of specific endocrine glands. Some common endocrine changes are detailed in Box 1.

Metabolic disruptions are evident across almost all body systems, but most aberrations revert to normal or near normal with renourishment and weight restoration. Box 2 discusses the impact of AN on bone, and Box 3 presents common metabolic disturbances observed in AN. Key to advancing understanding of metabolic contributions to AN will be clearly demarcating changes that are inherent to disease etiology from those that are simply expected sequalae of starvation and reversible upon renourishment.

How the study of genetics has reinvigorated our interest in the role of metabolic factors in AN

Psychiatric genomics has led to unprecedented advances in our understanding of the biology of mental illnesses, including AN [14]. Under the auspices of the Psychiatric Genomics Consortium, a series of increasingly powerful GWAS analyses have pointed toward the important role of metabolic factors in the etiology of AN [1,15,16]. The latest AN GWAS yielded significant loci that had been previously implicated in several metabolism-relevant traits, including BMI,

Box 1. Endocrine findings in AN

Pervasive endocrine disruption is observed in AN.

Thyroid: the euthyroid sick syndrome [low serum thyroxine (T) and triiodothyronine (T), high reverse T , and normal thyroid-stimulating hormone (TSH)] is nearly universal with BMIs of <16 kg/m^2 [59], resulting in reduced resting energy expenditure (REE) and kilocalorie (kcal) conservation. The thyroid gland atrophies with progressive weight loss [60] and normalizes with weight restoration. Hypermetabolic periods during renourishment [61,62] may represent a reversion from euthyroid sick to euthyroid, as total T and T levels rise and REE increases.

Adrenal: cortisol secretion is elevated and renal clearance of cortisol is reduced, resulting in high serum cortisol levels that adversely affect bone mineral density (BMD). This may metabolically induce insulin resistance and counteract hypoglycemia. These changes are driven by increased adrenocorticotropic hormone secretion from the anterior pituitary [63]. Aberrations in the pituitary–adrenal axis are not fully elucidated [64].

Gonadal: fertility is impaired due to pituitary and gonadal changes, as reproduction is deprioritized during malnutrition. This originates both at the level of the hypothalamic–pituitary axis (HPA) and at the gonadal target organs in both males and females. Testosterone, estradiol, luteinizing, and follicle stimulating hormone serum levels are consistently reduced and further propagated by low serum leptin [65]. Amenorrhea occurs, although menstruation persists in some patients even at very low BMIs [66].

Pituitary: secretion of antidiuretic hormone (ADH) from the posterior pituitary can be abnormally high or low. Elevated ADH yields the syndrome of inappropriate antidiuretic hormone, causing the kidney to reabsorb excess free water, resulting in dilution of serum sodium and hyponatremia [67]. Critical hyponatremia can emerge because patients with AN also tend towards hyponatremia due to reduced solute load being delivered to the distal renal tubules and inability to clear free water. Abnormally low ADH secretion has also been described and results in diabetes insipidus with concomitant hypernatremia [68].

Growth hormone: growth hormone (GH) secretion is elevated, which, as an anabolic hormone, should promote weight gain and growth. However, GH resistance occurs, and low levels of insulin-like growth factor-1 (IGF-1) necessitate higher GH pulsatility. Although GH resistance reverses with weight restoration, elevated GH may be adaptive since GH is a potent stimulus for gluconeogenesis and hypoglycemia avoidance [69]. An abnormality in the posterior pituitary gland also occurs, affecting oxytocin secretion, a hormone involved in mood, energy homeostasis, and bone metabolism. Abnormal oxytocin secretion can reduce appetite and BMD [70].

Glossary

Dysbiosis: imbalance in a microbial community.
Endocrine: refers to glandular secretion of hormones.
Family-based treatment (FBT): evidence-based intervention for AN in youth marked by parental control of renourishment.
Genome-wide association study (GWAS): scanning markers across complete sets of DNA or genomes from large samples of people with and without a particular disease to identify genetic variations associated with the target disease.
Gnotobiotic: germ-free mice (or gnotobiotic mice) are bred in isolators to keep them completely free of detectable microorganisms, including those that are typically found in the gut.
Insulin resistance: impaired response of the body to insulin, resulting in elevated levels of glucose in the blood.
MANTRA: Maudsley model of anorexia treatment for adults; evidence-based intervention for adults and adolescents with AN.
Metabolism: complex set of human body systems that control usage of calories and weight.
Microbiota-directed complementary foods (MDCF): specially formulated foods designed to target depleted microbial taxa.
Moderate acute malnutrition (MAM): wasting (weight-for-length *z* scores between less than –2 and –3 compared with World Health Organization child growth standards) and/or mid-upper-arm circumference greater than or equal to 115 mm and less than 125 mm.
Nutragenomics: study of reciprocal interactions between genes and nutrients at a molecular level.
Nutritional psychiatry: therapeutic use of food and supplements to provide essential nutrients as part of treatment for mental health disorders.
Osteopenia: reduced bone mass (of lesser severity than osteoporosis).
Osteoporosis: loss of bone mineral density.
Phenome-wide association study (PheWAS): systematic approach to analyze the many phenotypes potentially associated with a specific genotype.
Precision nutrition: stratifying people on the basis of biomarkers related to metabolic variation to better estimate subgroups' dietary requirements and

Box 2. The impact of AN on bone

AN has marked and severe adverse effects on bone metabolism. **Osteopenia** and **osteoporosis** are two of the most deleterious physical consequences of AN and are permanent complications of AN even after successful weight restoration [71]. These, in turn, result in a life-long increased risk of fragility fractures. The etiology of this profound and aggressive loss of BMD in AN is multifactorial, including low sex hormone levels, high cortisol, GH resistance, and low leptin and oxytocin levels [72]. The decrease in BMD found in AN is a very unique form of bone loss marked by 'uncoupling' with both increased bone resorption and decreased bone formation. Nutritional deficiencies are also core to the etiopathogenesis of bone loss in AN.

enabling better dietary recommendations and interventions.
Specialist supportive clinical management (SSCM): evidence-based intervention for AN in adults.
Thyroid: gland in the neck that impacts many different body systems.

high-density lipoprotein (HDL) levels, and several other obesity and body fat-related traits [1]. GWAS affords analytic opportunities far beyond the identification of implicated loci. Statistical techniques that enable the calculation of genetic correlations [15,17] have allowed us to create disease atlases that clarify the nature of the relation between and among diseases and traits on a genomic level. This approach expanded our conceptualization of AN as a psychiatric disorder to AN having both psychiatric and metabolic origins. As expected, given its long characterization as a mental illness, we consistently observed strong positive genetic correlations between AN and other psychiatric disorders and traits (e.g., obsessive–compulsive disorder, anxiety, and major depressive disorder). This panel of correlations clearly mirrored what clinicians observe to be comorbid in individuals with AN and in their family members. However, a less-expected set of metabolic and anthropometric genetic correlations also emerged that became increasingly robust with expanding sample size [1,15,16] and that are more pronounced than what is seen in other psychiatric disorders [18]. Specifically, significant negative genetic correlations (same genes, opposite direction of effect) were observed between AN and fat mass, fat-free mass, BMI, obesity, type 2 diabetes, fasting insulin, **insulin resistance**, and leptin. The sole significant positive genetic correlation with a metabolic trait (same genes, same direction of effect) was between AN and HDL cholesterol. Importantly, these associations remained significant after parsing out the effect of BMI, meaning that AN shares genetic variation with these metabolic phenotypes that may be independent of BMI. The authors concluded that metabolic dysregulation

Box 3. The metabolic setting of AN

Paradoxically, insulin levels are elevated early on in the renourishment process. In fact, high insulin levels, which may represent an early stage of insulin resistance, likely cause the development of edema in patients with restricting AN who otherwise do not have elevated aldosterone levels, which characterize Pseudobartter's edema physiology commonly found in the AN binge-eating/purging subtypes [73]. In addition, high insulin levels may influence the emergence of hypoglycemia, a poor prognostic finding in AN that impacts the vicious cycle of recurrent hypoglycemia, frustrating attempts at treatment via glucose tablets. The situation is further complicated by a quizzical lack of expected neuroglycopenic signs and symptoms in AN that typically manifest as hypoglycemia worsens in typical people. Covert hypoglycemia may contribute to the profound lethality of AN [74]. However, gastrointestinal hormones such as glucagon-like peptide (GLP-1) and amylin, which normally stimulate insulin release from pancreatic beta cells, are low in AN, which may be an appropriate adaptive response to starvation to prevent further hypoglycemia [75].

All forms of plasma ghrelin levels are elevated in acute AN [76], and resistance develops to the orexigenic hormone, which is produced by the stomach and acts on the HPA, affecting secretion of gonadotropin-releasing hormone, adrenocorticotropic hormone, and GH. The resultant lack of motivating feeding response to ghrelin, despite hunger sensation, supports an altered reward circuit, which may contribute to both onset and maintenance of AN [77]. Elevated ghrelin may impact glucose homeostasis in an adaptive manner, and its secretion may vary with insulin levels [78].

Peptide YY (PYY), an anorexigenic hormone released by L cells in the intestine after eating, acts at the hypothalamus to decrease appetite. However, PPY levels are also elevated in AN, which might be involved in the etiopathogenesis of disease and its recidivism [79].

Adipocytokines, secreted by adipose tissues, such as adiponectin, leptin, and resistin, normally regulate energy metabolism and insulin sensitivity. Leptin levels are expectedly low in AN [80] and contribute to amenorrhea and restlessness. By contrast, the other adipocytokines have varying serum levels in patients with AN. These discrepant levels suggest that confounding factors may be operative, and further inquiry is still needed to elucidate their status [81].

may contribute to the exceptional difficulty that individuals with AN have in maintaining a healthy BMI (even after successful weight restoration) and underscores the importance of more fully elucidating the precise nature of metabolic dysfunction that influences risk for and maintenance of AN.

The future clinical translation of these genomic findings may clarify the occasionally inconsistent endocrine and metabolic picture seen in individuals with AN.

Additional clues about the role of metabolism from genetic studies of AN

Several follow-on analyses have used innovative analytic approaches to further explicate the role of metabolism in AN. Notably, AN also has one of the most disproportionate sex ratios of any mental illness, with women up to nine times more likely to suffer from the illness than men [2]. Hübel *et al*. [18] shed light on this imbalance showing that the genetic correlation of AN with body fat percentage in females (r_g = –0.44) was significantly stronger than in males (r_g = –0.26). This observation suggests that AN and body fat percentage may share a sex-dependent set of genomic variants that could partially account for the disproportionate number of women and girls afflicted with the illness.

A second downstream functional analysis, transcriptomic imputation, allows for the translation of single-nucleotide polymorphisms (SNPs) into regulatory mechanisms. This can then be used to assess the functional outcome of genetically regulated gene expression through the use of **phenome-wide association studies (PheWAS)**. A PheWAS functionally queries an electronic health record (EHR) to identify associations of a trait of interest (i.e., AN) with the clinical phenome (i.e., all of the disease and medication codes included in the EHR). Exploring the phenotypic associations with AN genetic architecture can isolate how GWAS variants functionally contribute to AN disease risk, symptomatology, and clinical presentation [19]. Several PheWAS of AN are currently underway.

Genomics findings summary

The study of the genomics of AN is accelerating. Initial GWAS findings convincingly pointed toward the importance of focusing on aberrant and unique metabolic factors underlying the illness. Follow-on analyses have begun to hone the observations to address the imbalanced sex ratio and potential implicated metabolic mechanisms. Nonetheless, this research is nascent. Rapid increases in sample size are underway, and follow-on functional analyses are planned to optimize resultant data and maximize translational potential of genomic findings.

The role of the intestinal microbiota and intestinal morphology in understanding the role of metabolism in AN

The past decade has also witnessed an explosion of studies of the role of the intestinal microbiota in a remarkable range of illnesses, including AN. Sifting through early findings in an emerging field is challenging, especially before method standardization. Bearing this in mind, we summarize findings to date and explore how the study of the intestinal microbiota and intestinal morphology may hold promise for developing treatments for AN.

Intestinal microbiota

The intestinal microbiota is a complex community of microbes (including archea, bacteria, fungi, protists, and viruses) that reside in the mammalian gastrointestinal (GI) tract [20]. Microbes within this complex community slightly outnumber human cells by a 1:1.3 ratio [21], with the gut microbiome (the cumulative genomes of the intestinal microbiota) outnumbering human genes 1000-fold [22]. The intestinal microbiota's contribution to host health has been well established

[20], with studies reporting the importance of gut microbial communities in harvesting energy from the diet [23] and predicting an individual's postprandial glycemic index [24]. An imbalance in this microbial community, often termed a **dysbiosis**, has been associated with multiple disease states, including obesity, diabetes, and inflammatory bowel diseases [25–27]. The term dysbiosis implies the presence of a gut microbiota with the potential to damage the host; however, an abnormal gut microbiota could simply be the consequence of an altered GI environment and not the cause of disease. As diet can rapidly change the composition of the intestinal microbiota [28], depriving enteric microbial communities of nutrients is likely to impact both their composition and function. Therefore, whether the changes in the intestinal microbiota found in patients with AN influence specific clinical hallmarks of the illness (i.e., weight dysregulation) or are merely a consequence of a nutrient-deprived environment warrants careful exploration. To date, most studies investigating the role of the gut microbiota in AN have compared gut microbial communities between patients with AN and unaffected controls [29–34]; however, only two studies have attempted to determine the influence of gut microbiotas from patients with AN on the host, with contrasting results [35,36].

A recent systematic review investigating the composition and diversity of the intestinal microbiota in AN reported specific microbial taxa (*Alistipes*, *Parabacteroides*, and *Roseburia*) that distinguished patients from controls. Additionally, decreased butyrate-producing (*Roseburia*) and increased mucin-degrading bacteria (*Akkermansia muciniphila*) were consistently observed in the gut microbiotas of patients with AN [37]. To address whether the gut microbiota harbored in patients with AN can negatively influence the host, Hata *et al*. [35], transplanted fecal samples from AN patients and unaffected controls into germ-free (GF) mice (mice raised in the absence of microbial associates). The GF mice colonized with an AN microbiota exhibited decreased weight gain compared with mice colonized with non-AN control microbiotas. By contrast, Glenny *et al*. [36] reported no differences in weight gain, fat or lean mass, or food consumption between GF mice colonized by gut microbiotas from AN patients and unaffected controls. Although both studies used a **gnotobiotic** (Greek; 'gnotos' meaning known and 'bios' meaning life) approach to address the same question, multiple technical differences could explain the diverging results. Observed inconsistencies highlight the need for standardization in investigations regarding the causative effect of AN-associated gut microbiotas. Nonetheless, clinical translation of these findings is underway as case reports of fecal microbiota transplantation in AN have begun to emerge in the literature, although it is premature to draw conclusions about efficacy [38,39].

Intestinal morphology

One potential explanation for the inefficacy of current renourishment strategies is requiring consumption of a sustained high-calorie diet, which is psychologically and physically challenging to patients and seriously jeopardizes long-term recovery [40,41]. The gut GI tract, the primary site of nutrient absorption, has been poorly investigated in AN. The gut epithelium is the gatekeeper of body metabolism due to its central role in the absorption of nutrients; however, little is known about the impact of severe and prolonged caloric restriction in AN on intestinal epithelial function. Nutrient deprivation in individuals with AN could impact gut function and ultimately lead to a global reduction in the absorptive capacity of the gut. Although weight gain and weight maintenance are major hurdles for AN recovery [42], scant information exists about the absorptive capacity of the gut in AN patients. Indeed, the limited number of studies of intestinal epithelial alterations reported disturbances in gut villus architecture and a decrease in small intestinal surface area and permeability in individuals with AN [43–45]. These observations support the concept of a dysfunctional GI tract and encourage further science because the existence of an AN-associated dysfunctional intestine has important implications for renourishment strategies and could impede weight maintenance. Renourishment interventions are poised to fail if the

patient is unable to absorb calories and gain weight. Consistent with this concept, it has been postulated that children experiencing malnutrition are unable to absorb what they consume during renourishment [46]. In the case of malnutrition, novel approaches are being developed to restore gut function via the gut microbiota in parallel to renourishment [47].

Summary

Despite the centrality of eating to the pathology of AN and of renourishment to its treatment, strikingly, little research has addressed optimal renourishment strategies and the role of GI morphology in weight gain and maintenance. Randomized controlled trials comparing renourishment approaches are scant. Rapid advances in the study of the intestinal microbiota and longitudinal studies of intestinal function and morphology across stages of illness and recovery may hold promise for developing more effective interventions for AN.

Integrating clinical, genetic, and microbial findings to guide future research and treatment

A shift in treatment paradigms for patients with AN is critical to achieve better outcomes in this life-threatening disorder. Harnessing metabolic, genomic, and gut microbiota approaches has the potential to generate novel, safe, and effective treatments for these patients, especially with reference to maintaining restored weight. We argue that work in these fields has the potential to inform precision nutrition interventions encompassing **nutragenomics** and **microbiota-directed complementary foods (MDCFs)** under the general umbrella of nutritional psychiatry [48].

Precision nutrition (not to be confused with personalized nutrition) centers around stratifying individuals into subgroups based on biomarkers of metabolic variation and estimating each subgroup's dietary requirements [49]. Applying a precision nutrition strategy to AN treatment would categorize patients based on the multiple biomarkers discussed herein (e.g., hormonal profile, polygenic risk scores or specific genetic variants or SNPs, specific gut microbial taxa) and create targeted dietary recommendations or renourishment strategies for subgroups of individuals.

Nutrigenomics refers to the effects of genetic variation on the metabolic response to nutrients. Indeed, genetically guided nutrition is not novel. Widely known examples include phenylalanine-restricted diets for individuals with specific mutations in the phenylalanine hydroxylase gene [50], ketogenic diets for children with epilepsy [51], and gluten-free diets for individuals who are genetically predisposed to celiac disease [52]. Ultimately, tailored renourishment regimens could be developed for subsets of patients with AN classified by specific genetic profiles.

Another precision nutrition approach to promote recovery from AN could treat the biological consequences of nutrient deprivation on the GI tract via MDCFs. The premise of this approach is based on the success of using MDCFs in children with **moderate acute malnutrition** (MAM). Like AN, the treatment of MAM relies on renourishment to promote weight gain; however, it typically focuses on increasing caloric intake without careful consideration of the nutritional composition of the food consumed. Based on previous studies reporting specific microbial taxa that are depleted in children with MAM [53], MDCFs have been formulated to restore the abundance of these microbes. MDCFs have been reported to be superior to established renourishment approaches for children with MAM in Bangladesh [54]. Children with MAM on an MDCF diet consumed fewer calories than children on a diet composed of traditional ready-to-use supplementary foods; yet, they exhibited better weight-for-length and weight-for-age *z* scores at the end of the study. Given that nutrient deprivation is common between MAM and AN, albeit with discrepant serum albumin levels, a precision nutrition approach [49] using

MDCFs to renourish patients with AN has the potential to be more effective and enduring. *Faecalibacterium*, *Ruminococcus*, *Clostridium*, and *Lactobacillus* species have been reported to be depleted both in patients with AN and in children with MAM. Developing an MDCF for AN would potentially restore a normal microbial ecosystem, correct a dysfunctional intestine, and lead to more effective and tolerable renourishment and sustainable weight gain.

Nutrigenomics and MDCFs represent surgical approaches to the emerging field of nutritional psychiatry [48], which broadly proposes to identify which nutrients and food types are essential for mental health and to incorporate nutritional management into psychiatric practice. The importance of thorough scientific vetting of nutritional psychiatry approaches as well as careful explications of underlying efficacy mechanisms has been thoroughly explored [55]. We contend that both genomics [56] and the intestinal microbiota [57,58] are important avenues to identify mechanisms underlying the efficacy of any nutritional psychiatry interventions, not just for AN. Of all of the mental illnesses, nutritional psychiatry is perhaps most relevant to eating disorders, and we are well positioned to materially advance the field provided that we accept the premise and the challenge.

Concluding remarks

We have failed to improve and consistently achieve outcomes for patients with AN, especially in adults, over the past decades. Treatment for children has improved somewhat primarily due to FBT, which fundamentally presents a no-negotiation approach to parental renourishment of their children (i.e., focus on renutrition and perhaps metabolism). To be sure, individuals with AN have a fierce desire to be thin. But believing that their strength of will is stronger than all of our efforts to treat them is hard to swallow. Much more likely is that we are missing something fundamental underlying the unrelenting drive for thinness that so often kills. Today, with the emergence and convergence of genomic and intestinal microbiota research, it is like seeing land for the first time after being at sea for decades with this disease. However, the picture is not yet wholly clear (see Outstanding questions). We encourage rapid, thoughtful, and integrated scientific advances in these fields in close collaboration with expert clinicians who have puzzled over the complex biology of AN for decades. As cautioned by Adan *et al*. [55], science must lead, and hype must be contained to allow families and patients to accurately calibrate hope.

Outstanding questions

How can genomics and the study of the intestinal microbiota help us understand the perplexing and unique endocrine and metabolic findings in AN?

Which functional genomic analyses are best positioned to further explicate the observed contribution of metabolic factors to AN?

What steps need to be taken in the study of the intestinal microbiota of patients with eating disorders to standardize approaches that will enable sufficiently large studies to be performed successfully and yield clinically meaningful convergent results?

What designs will allow us to best distinguish among physical–organic sequelae of malnutrition versus causal biology in AN?

How can we rigorously evaluate precision nutrition and nutritional psychiatric interventions to ensure that needed emerging treatments for AN are evidence based and do not offer false hope through untethered novelty and hype?

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