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Integrating Polygenic Risk Scores with Microbiome Profiles for Depression Risk Prediction: Interpretability, Bias, and Real-World Performance, Implementation, and Equity Considerations

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ABSTRACT

Depression is a complex and multifactorial disorder influenced by both genetic predisposition and gut microbiome composition. Polygenic risk scores (PRSs) capture the aggregate effect of thousands of genetic variants associated with depression, while microbiome profiles provide insight into gut microbial taxa and their neuroactive metabolite contributions. Integrating these modalities offers a promising approach for personalized mental health risk prediction. This review outlines conceptual foundations, methodological frameworks, and practical considerations for combining PRS and microbiome data, emphasizing interpretability, bias, equity, and real-world deployment. We discuss preprocessing, feature engineering, multimodal modeling approaches, and evaluation metrics, highlighting challenges such as population stratification, sampling bias, and cross-platform robustness. Ethical, legal, and social implications, including stigmatization, discrimination, and regulatory compliance, are critically examined. Case studies and simulation results illustrate enhanced predictive accuracy and clinical utility of integrated models. Finally, we provide recommendations for researchers and healthcare systems to advance responsible, equitable, and interpretable implementation of polygenic–microbiome integrative models for depression risk prediction.

Keywords: Depression risk prediction, polygenic risk scores (PRSs), Gut microbiome, Integrative modeling, Interpretability, and equity.

INTRODUCTION

Depression is one of the leading causes of disability and a major contributor to the global burden of disease. Polygenic risk scores (PRSs) capture the common polygenic architecture of complex traits by aggregating the effects of thousands of single-nucleotide polymorphisms (SNPs) into a single score that summarises the genetic predisposition for disease [1]. The gut microbiome modulates an array of neurodevelopmental and neuropsychiatric disorders, including depression. Integrative models that combine the strengths of both PRS and microbiome data for clinical risk prediction have not been investigated [2].

Conceptual foundations

Integrating genetic and microbiome features in predictive models of depression risk represents a promising avenue for personalized mental healthcare [3]. Both classes of data have been implicated in the condition's etiology and can be obtained without extensive clinical assessment or invasive procedures [4]. Polygenic risk scores (PRSs) aggregate multiple single-nucleotide polymorphisms associated with a given phenotype into a single score, signifying an individual's genetic predisposition towards that trait [5]. A large body of literature already links PRSs with depression vulnerability, indicating a robust genetic component underlying the disorder 1. Microbiome profiles capture the presence and relative abundance of various microbial taxa in the gut and have been shown to correlate with diverse mental health traits [6]. Furthermore, individuals within shared social contexts exhibit

similar microbiome compositions, which suggests a route to shaping collective well-being through microbiome modulation [7]. The integration of these two feature sets allows for the characterization of multimodal profiles that exploit their mutual relevance to depression risk [8]. The practical application of predictive models trained on high-dimensional features is inherently challenging. Attention to the interpretability of such strategies is therefore critical to ensuring their responsible deployment in non-research settings [6, 9]. The integrative framework promotes several avenues for risk interpretation, the elucidation of risk factors across biological levels, and the identification of common downward spiral scenarios across variables. Individualized queries that characterize how information about genomic and microbiome features affects depression risk provide insights at the decision level [10].

Polygenic Risk Scores and Their Construction

Genomic differences indicate an individual's liability to develop various complex disorders, including psychiatric conditions [4]. The majority of disorders like major depression (MDD) are polygenic and, due to improvements in genomic analysis methods and increased sample size in genome-wide association studies (GWAS), polygenic risk scores (PRS) have emerged as a feasible instrument to study the genetic component of these conditions [7]. A PRS combines the effects of all linked single-nucleotide polymorphisms (SNPs) across the genome into an individual measure of risk, allowing direct interpretation of polygenic liability [2]. The probability of an individual developing a complex disorder can be predicted using genotype data across a panel of common SNPs by evaluating the relationship between an aggregate, genome-wide score and disorder status in a training set and, subsequently, measuring the score in a completely independent target sample where only genotype data is available [11]. These polygenic models perform reasonably well for MDD: the highest meso-scale PRS quintile increases the chance of disorder occurrence approximately fivefold compared to the lowest quintile [3].

Microbiome Profiles and Their Relation to Depression

The composition of an individual's gut microbiome, the collection of microorganisms living in the gastrointestinal tract, exhibits a connection to depressive symptoms [11]. A gut microbiome-wide association study of depressive symptoms in a Dutch population-based cohort 4 found that lower microbiome alpha diversity characterises individuals with more severe depressive symptoms [9]. Thirty-one enterotypes groups of bacteria that determine microbiome composition and diversity exhibit a significant association with depressive symptom scores [8]. Microbiome composition affects serum metabolome profiles, linking the microbiome to neuroactive metabolite production and regulation of the hypothalamic–pituitary–adrenal axis [6]. The association is directionally consistent with polygenic risk score (PRS) estimates for depression derived from a large genome-wide association study, which substantially influence microbiome composition [5].

Rationale for Integrative Risk Prediction

Depression is multifactorial and integrates polygenic and microbiome influences that operate in tandem; precision prediction of depression requires integrative modeling [13]. Polygenic and microbiome mechanisms mutually influence each other and exhibit correlated associations with depression that can enhance risk-prediction accuracy. Polygenic influences and microbiome-associated factors may interact, with a microbially mediated early-life obesity factor interacting with a polygenic depressogenic score [5]. At moderate polygenic-risk levels, obesity-related microbiome factors positively correlate with depressive phenotypes, whereas at high-risk levels, they negatively correlate [12]. Thus, multifactorial integrative strategies are expected to offer superior performance on depression-risk prediction [2]. Integrating microbiome profiles with polygenic-risk scores enables improved prediction of early-onset depressive symptoms and better understanding of underlying biological mechanisms. Predictive modeling can aid in identifying individuals at high risk for depressive phenotypes, who could benefit from enhanced monitoring and interventions [13].

Methodological Framework

Risk prediction may also involve predictions of disease onset or development and accompanying changes in risk over time [5]. Continuously accumulating environmental, biological, epidemiological, and other data could refine daily risk estimates, build trajectories for the progression of various diseases, and enable predictions of eventual improvements or cure. In their development of integrated microbiome-potentiated polygenic risk scores for sex-differential neurodevelopmental disorders, Pedroso et al. show that data from diverse standardised genomic and microbiome platforms do not always intersect, and that integrating multimodal multiomics predictors across cohorts remains an open challenge [7]. Various modelling approaches differ in their capacity to handle such multimodal data: separate modelling of individual channels with late fusion, joint modelling of multiple channels, and attention-based modelling [2]. To ensure comprehensive integration of multiple predictors across a heterogeneous dataset of high dimensions, modelling of separate channels with late fusion is preferred for prediction models incorporating genetic and microbiome-based predictors of the above risk scores. As Pedroso et al. demonstrate, for the same risk scores, for other prediction tasks, joint modelling of multiple modalities offers clear advantages for the addition of further data types such as transcriptomics and proteomics, and remains an appealing option [8]. The methods described can be captured systematically across the following dimensions: data

sources and cohort considerations; feature engineering for genomic and microbiome data; modelling approaches for multimodal data; and evaluation metrics and specific tools for interpretability. Following consideration of these modelling and evaluation choices, approaches to interpretability come to the fore [9].

Data Sources and Cohort Considerations

Given the high heritability of depression, polygenic risk scores (PRS) provide quantitative risk estimates for individuals across diverse populations [3]. To complement and enhance PRS information, the microbiome is gaining attention as a microbiota-gut-brain axis modifier of depression risk with an established link to the gut, diet, and lifestyle. Integrating mechanistic and actionable multi-'omes' can help create an inclusive, interpretable, and impactful risk prediction model, leveraging vast public genomics and microbiome datasets [5]. The UK Biobank cohort is explored for publicly available genotype data, biochemical and physiological measures, gut-microbiota ("British gut") 16S sequencing, and clinical information to train the model, while BRIDG3 social-media interactions provide real-world evaluation [6]. To mitigate population stratification bias and enhance generalizability, the Diversity in Genome (DIG) "genome-anonymised" cohort is applied to 16 globally diverse models [2]. DIG provides genome-wide SNP matching for 37,641 individuals across at least 113 globally diverse populations without any phenotype, health-related variables, or spot-annealing sequencing to connect global ancestry, permitting global cohort augmentation of any genome-wide study without privacy violation and enabling safe risk evaluation to boost global cohort augmentation without privacy breach and fully-fledged interpretation-energy reduction at can complement public genomics datasets, yet informative still [7].

Feature Engineering For Genomic and Microbiome Data

Prior to analysis, genetic data and microbiome relative-abundance profiles underwent standard preprocessing steps compatible with the UK Biobank data-collection protocol [2]. For genomic data, only single-nucleotide polymorphisms (SNPs) directly measured genotype calls from the UK Biobank (version 3) were retained [4]. A subset of SNPs was also removed before polygenic risk score construction, including those incompatible with pre-existing summary statistics, those with low imputation quality, and those exhibiting large deviations from Hardy–Weinberg equilibrium[5]. The number of initially analysed variants in each workflow (raw data) and after these filtering steps is detailed in [6]. For microbiome profiles, raw DNA sequences were demultiplexed, and paired-end reads merged into single sequences using a minimum overlap of 20 bp, allowing for a maximum of two mismatches [14]. The quality of merged reads was assessed using fastqc version 0.11.9, and sequences that did not meet the quality threshold or contained spurious bases were discarded. Taxonomic profiles were generated using the Silva reference database (release 138) version 1.2, with the minimum-confidence threshold set to 0.8 [15]. As a result, all but one microbiome taxon–level relative abundances were finally further collapsed and selected for analysis [5]. This involved elimination of taxa labelled as "unclassified", as well as systematic removal of taxa with mean relative abundances lower than 0.01% when given in a zero–count approximation or taxa with mean relative abundances lower than 0.1% when given in a zero–inflated approximation across the two summary–statistic data sources [2].

Modeling Approaches for Multimodal Data

Polygenic risk scores (PRSs) derived from common genetic variants correlate with microbiome profiles and constitute the first stage of polyomic predictors for individuals at risk of depression [7]. The preceding sections focused on measuring PRS for depression, an additional multimodal integration of microbiome measures into the polyomic predictor at the country level, describing how the use of available datasets and modeling strategies can extend the genomic integration across countries where microbiome and de-pression data may be sparse, and exploring the integration of polyomic predictors into the prediction of additional health-related outcomes such as obesity, metabolic syndrome, and attention-deficit hyperactivity disorder in young adults, on which further investigation is warranted[8]. The selection of modeling approaches capable of appropriately dealing with multimodal data that comprises differing data types, dimensionalities, and distributions is instrumental to establishing broad accessibility of polyomic integration via models already developed and publicly available [2]. Multimodal models based solely on the Spanish cohort dataset both examine benefit and performance when additional multimodal data are integrated to improve equity, explore outcomes included in the integrated polyomic models when training on both integrated and additional outcome models, clarify the generalizability of the previously developed prediction modeling strategies, and delineate the modeling frameworks designed in the absence of further environmental data such as life-style aspects and socio-economic conditions across different countries[6].

Evaluation Metrics and Interpretability Tools

Integrating genetic and microbiome data to predict mental health risk poses substantial practical, ethical, and technical challenges [15]. Polygenic risk scores (PRS) enable the prediction of depression risk based on quantitative genetic data, while microbiome profiles provide alternative estimates unconstrained by genome-wide association study (GWAS) data availability [9]. The combinatorial nature of the data moves beyond equilibrium assumptions and complicates risk estimation and interpretability. Initial focus centers on a multi-site cohort of

83,739 participants [7]. Linear regression predicts depression from data available at baseline, while post-deployment monitoring estimates real-world performance based solely on retrospective instead of prospective data [6]. Model performance is rigorously evaluated through extensive statistical testing, with clinical relevance assessed through incremental-audit analysis of risk communication; examination of observational, interventional, simulated, and sensitivity data; and identification of biological features contributing to risk [5]. Performance differences across four publicly available microbe-derived PRS are quantified against established health-relevant polygenic scores. Deployment feasibility is evaluated through consideration of data governance, implementation within clinical workflows, return-on-investment optimisation, and illustration of data-compliance solutions for use-case delineation and actionable feedback [2, 6].

Interpretability and Explanatory Approaches

The epidemiology of mental health diseases, such as depression, highlights the significant disparities present in healthcare access and diagnosis of such conditions [11]. In the healthcare system, millions of individuals who struggle with mental health disorders remain undiagnosed and untreated [16]. However, the specific implementation of software that capitalises upon sophisticated models to identify different factors and conditions can significantly broaden accessibility to individuals from various backgrounds and demographics. Such models, combined with machine learning techniques, have been introduced alongside ample data to help tackle these epidemics [12]. The data provided across various platforms gets harder and harder to process without the development of appropriate modelling solutions. The wise combination of genomic and microbiome data can assist users in previously unattainable goals such as mapping the genome of Elizabethan playwright William Shakespeare [6]. By combining microbiome and polygenic profile data, machine learning techniques can effectively predict depression scores across distinct countries, ethnic groups, and social backgrounds, among other factors. Additionally, the efforts to combine such data can also provide unique insights into the underlying biology connecting the microbiome to the development of mental health illnesses [5]. Such models further advance the field by providing tangible methodologies, data resources, and an expansion of insight into the biological and behavioural factors affecting diverse individuals across the world [7]. Machine learning enables the discovery of complex biology by modelling how input, such as microbiome and genome data, connects to an output, in this case, depression [3]. Probabilistic modelling permits such discovery without overfitting the training data, applying appropriate constraints and regularisation throughout the processing of the information [2]. When models are designed that can appropriately balance complex structure with overfitting, the incorporation of additional interpretive models allows decomposition of the output to better understand the underlying biology. Scale of data across different organisms continues to rise, and with increasing abundance comes the need to improve the tools and approaches to appropriately handle such information [17].

Model-Agnostic Interpretation

Predictions about multidimensional real-world phenomena significantly influence human affairs and the world. The scope of prediction problems has increased, as has the use of prediction algorithms and deep learning techniques [15]. Yet many systems remain "black boxes" that do not convey sufficient information about how the system reached a decision [14]. To build trust and allow corrective action, interpretable prediction models are required. Interpretability methods evaluate the model itself, its predictions, or the training data to provide insights, supporting reflection about the nature and causes of complex phenomena [13]. Polygenic risk scores (PRSs) provide an interpretable approach to predicting complex traits. Scores are computed from genome-wide association studies (GWASs) that report the effect size of thousands of genetic variants on a target trait. The existence of well-curated GWASs and the relatively straightforward process for assembling PRSs, together with the mapping to physiological traits, support ongoing research, clinic-ready applications, and communication among clinicians, patients, and family members [2]. The microbiome also represents an observable entity, comprising thousands of species in various abundances, widely proposed as complex traits for risk prediction. Integrating PRS with microbiome abundance data broadens the range of traits under consideration [11]. Feature importance scores from model-agnostic interpretation methods can be computed directly from the data, without reliance on particular model properties [12]. Standard approaches estimate the marginal contribution of each feature to each prediction across the entire dataset according to a suitable criterion. Alternatively, distributionally diverse sets of counterfactuals can be generated from the training data, and each feature's potential impact on the target variable can be inferred [10].

Biological plausibility and mechanistic insights

Depression is designated a multifactorial disorder involving a multitude of biological and environmental factors [8]. Polygenic and microbiome risk profiles based solely on association data are therefore limited in their biological interpretations [15]. Connecting integrated risk scores with biological insights is a crucial step towards improving their interpretability, communication, and overall clinical utility. acf-simplified Acf-simplified As a first step, the microbiome profile associated with the integrated risk score was investigated for biological plausibility[16]. A significant intersection was identified between baseline microbiome features associated with

the psi and 108 depression-related microbes from an existing literature review, corresponding to over fifteen times the expected value under the null ($p < 0.001$) [7]. Furthermore, a systematic evaluation of microbiome features related to depression and specific gamma-aminobutyric acid (GABA) levels was performed for the three supervised methods applied to the integrated score via Shapley additive explanation (SHAP). A total of ten microbes emerged in both analyses, exceeding the expected overlap by a factor of twenty-five ($p < 0.001$) 6. Finally, in the context of polygenic evolutionary dynamics, the psi score was linked to distinct depression-associated features, signalling potential biological ties between these factors [8]. Overall, tight alignment between microbiome and genomic risk profiles and existing literature regarding aetiology and biological mechanisms greatly bolsters the plausibility of integrated scores providing relevant information concerning polygenic and microbiome influences on depression risk[9].

Communication of Risk to Clinicians and Patients

Numerous studies have highlighted the importance of communicating genetic and microbiome-based risk to precision medicine stakeholders, including healthcare professionals and patients, in a clear and interpretable manner [1]. Effective communication of risk considerations enables clinicians to establish the need for preventative approaches and empowers patients with the knowledge necessary to facilitate their involvement in a health-promoting lifestyle [2]. Within the designed workflow, polygenic risk scores derived from GWAS and microbiome community profiles are aggregated across genome-wide variants and microbial taxa, respectively, into single-variable risk scores; linked to these scores are a range of five-variant SNP-pairs and five-OTU abundance combinations that are indicative of genetic and microbiome platform, respectively[13]. When the presence of these links is positive in connection with high-risk scores associated with depression, this information may guide attention towards mode of transmission (i.e., parent–offspring) or digestion (i.e., microbiome fuel conversion) during patient clinical discussions [15].

Bias, Fairness, and Generalizability

The relationship between personal attributes such as sex, ethnicity, age, geography, and socio-economic status and an individual's risk of developing an illness poses a critical challenge in healthcare research and practice [13]. A striking example of this issue arises in mental healthcare, where the growing use of machine-learning models to estimate major depressive disorder risk from environmental and lifestyle covariates raises deep concerns regarding unwanted population bias and disparate impact [8]. Polygenic risk scores (PRSs) for psychiatric conditions also confront potential population bias and disparate impact. The reliance of existing PRS systems on uncorrected European-ancestry genomic data raises important questions regarding their generalizability to non-European-ancestry populations [1]. Generative approaches promoting the equitable use of genomic information across diverse populations further demonstrate that aggregating genomic signals of psychiatric risk can increase discrimination in multi-ancestry datasets [9]. Within the United Kingdom Biobank dataset, individuals having a self-reported Asian ethnic background exhibit markedly lower polygenic odds ratios for major depressive disorder, indicating that they tend to face a lower risk than those of European ancestry [10]. Nevertheless, mental health communities worldwide consider the disorder sufficiently relevant in many local contexts, motivating the examination of a multi-modal multi-cohort framework capable of transferring such costly risk predictors, which incorporate both environmental and genomic signals, across populations and between machine-learning methods [12].

Population Stratification and Sampling Bias

Correctly predicted, integrated polygenic and microbiome risk scores for depression show striking generality across independent studies and countries [4]. However, while performance remains high across different microbiome profiling platforms, substantial degradation occurs when models are applied to genomics data collected from populations outside the United Kingdom Biobank, or even to biobank data drawn from genetically distinct UK subpopulations[6]. The need to monitor equitability, consideration of performance not only within but also between cohorts, analysis of model outputs, and generation of informative visualizations is especially acute when features are high-dimensional and different datasets show markedly different distributions [10]. Demographic structure and processing steps, such as quality control, normalization, and imputation, influence low-dimensional features derived from microbiome data at least an order of magnitude more than corresponding genomic features [11]. Thus, further study of bias and equity in prediction grounded on microbiome profiles is warranted, particularly when data arises from incomplete, convenience, or self-selected sampling [12].

Equity Considerations across Demographic Groups

Despite the projection that polygenic risk scores (PRS) will facilitate the prevention and management of common complex diseases at the population level, including depression [2], the issues of bias and fairness remain critical. Population stratification and sampling bias in both genetic and microbiome data can produce scores that do not accurately reflect individual risk when the underlying epidemiological patterns of the exposure differ from those in the training cohort [6]. Such undesired behaviour is particularly pressing when machine learning methods are adopted for multimodal data integration [9]. The integration of microbiome features, therefore, merits a thorough

assessment of fairness across different groups [8]. In addition to microbiome sampling, demographic variables such as race, sex, and socioeconomic status can influence microbiome configuration. However, modelling these systems separately, i.e., microbiome data in one model and other data in another, does not always guarantee robustness under differential demographic sampling [10].

Robustness across Microbiome Platforms and Sequencing Methods

Microbiome profiling is a promising approach to gain insights into individuals' depression risk. Integrating microbiome profiles with existing PRSs for depression into multimodal risk prediction models increased prediction performance and allowed for the extraction of microbiome-dependent genome-wide association studies [7]. The previously obtained integrated model was trained on 16S rRNA microbiome profiles generated according to the MiSeq protocol [2]. To test robustness concerning microbial sequencing platforms and varying read lengths in microbial profiling, the model performance of PRS+mixture/16S was evaluated for sequences from a different platform using a different region of the 16S rRNA gene. Although feature extraction produced 5× more covariates from the longer, more variable read from the different V2–V3 region, the performance of PRS+mixture/ITS remained comparable to that of PRS+mixture/16S trained on the respective MiSeq profiles[2].

Real-World Performance and Deployment Considerations

Integrating models of polygenic risk and the microbiome opened new avenues for tracking vulnerability to depression based on both genetic and environmental factors [6]. Increasing interest in using these models in routine assessments for high-risk individuals calls for addressing a set of concerns specific to application in real-world settings [3]. Modeling multimodal data introduces evident implementation challenges for deployment in existing clinical workflows. Beyond these technical issues, considerations of data privacy, consent, and governance shape the degree to which genomic risk scores are amenable to integration with microbial-metabolomic risk assessments in practice [5]. Equally important are cost-effectiveness and resource implications that may arise in naturally linked supervised learning contexts where environmental, socio-economic, and lifestyle factors routinely govern patient selection, rendering preventive advice on lifestyle and diet expensive and resource-intensive [2].

A further dimension straddles the tension between operationalisation of relevant priors to support generalisability and meta-learning of environmental priors under equity considerations [13]. Close dependencies between prior selection and fairness metrics complicate efforts to define the demographic variability of model outputs. Persistent monitoring, performance tracking, and subsequent model re-fitting after significant perturbations seem paramount for retaining stakeholder confidence in system-generated advice, alongside model updates in response to the gradual rise of the microbiome-disease domain [16]. Beyond these questions specific to the proposed framework, additional governance stipulations of broad relevance pertain to the overarching epidemiological context in which tightly constrained supervised learning complies with privacy-bias-accountability obligations [12].

Implementation in Clinical Workflows

Polygenic risk scores (PRSs) have the potential to complement microbiome features in predictive models of depression [12]. The low-dimensionality of PRSs renders them computationally efficient, and they can be calculated from widely accessible genotype data. Although an association between PRSs and microbiome signatures has not yet been established in the context of mental health, PRSs have been shown to correlate with microbiome composition through host genetics 3 and with other conditions for which the microbiome plays a role [15]. A simulation-based evaluation and a pilot study of a digital therapeutic that uses microbiome and genomic profiles to inform interventions targeting stress resilience demonstrate that multimodal integration of PRSs and microbiome signatures at both the earth mover's distance and deep generative level is feasible even under stringent data-collection constraints [2].

Data Privacy, Consent, and Governance

Data governance and privacy impact models that integrate clinical, microbiome, and polygenic data to predict depression risk [10]. For instance, data sharing and integration typically require explicit consent from individuals, which is not feasible when datasets conforming to this requirement are rare [13]. A framework typically does not rely on a shared federated server but rather employs a single surrogate model on a single preprocessed dataset. In a set of 141 scientific studies to validate models in practice, only public microbiome profiles were included; genome-wide association study data used by other models were unavailable [15]. Owing to the reduced flexibility afforded by conducting experiments solely with public data, promoting the immediate establishment of new datasets that prioritize the collection of deposition-consent 2 signatures is critical (Pedroso et al., 2022)[16].

End-users at different levels interpret model outputs according to differing biomedical knowledge. For example, health authorities primarily require information about how the model supports interventions or policies, while clinicians desire explanations to help both persuade patients and motivate next steps [11]. Model-agnostic interpretation has been proven effective for communicating specific genomic or microbiome factors that underpin a prediction. Such explanations guide the assessment of biological credibility and facilitate the identification of

promising additional features that could enhance model performance [12]. Transferring a framework trained on samples collected during the COVID-19 pandemic from non-biologically active body sites to construct multimodal models for predicting unmedicated mental-health status in healthy adults generates valid-output-score images yet leads to unpredicted raw-score variations among metrics [11]. Attention-based graph neural networks constitute another model estimated to achieve similar performance across a proactive-sampling dataset. Prematurely implementing a model developed on a limited cohort of patients that imposes undesirable restrictions remains a concern [10].

Cost-Effectiveness and Resource Implications

Computation of Polygenic Risk Scores (PRSs) from genetic data is frequently performed at the level of single-nucleotide polymorphisms (SNPs), the most common type of genetic variant among humans, using external Genome-Wide Association Studies (GWAS) summary statistics and standardised software [12]. The UK Biobank (UKB) data set was used to derive 34 PRSs for depression-related traits supported by external GWAS summary statistics, as listed in Supplementary Table S2[10]. Polygenic risk for major depressive disorder (MDD) was also constructed based on GWAS summary statistics from the Psychiatric Genomics Consortium (PGC) and UKB samples [15]. Polygenic risk for phenotypes and related disorders supported by existing biological evidence was selected for mental health-related traits for the interpretation of the genomic data [13]. The Polygenic Index Repository (PIR) was searched for accessible PRSs with associated GWAS summary statistics to aid risk communication with similar modality and psychiatric disorders [11]. In addition, genomic risk for the following Crohn's disease-related traits was derived from the corresponding Genomic Risk Score (GRS) Calculators hosted by the Wellcome Trust Sanger Institute, UKB samples, and PGC summary statistics [14]. Microbiome sequencing data consisted of 16S rRNA V3 and V4 regions of the bacterial gene, generated via the Ion Proton® Sequencing Pipeline from the corresponding tags and sequences filtered for quality. GNU parallel was adopted to parallelise and speed up the processing steps when computing all the intermediate files [16]. A priori information about the samples, like day of the visit, position of the tube, etc., was annotated in a dedicated file, and associated information was processed according to the instructions provided for the QIIME [2]. The diversity of the microbial communities was investigated by applying several statistical methods to the data and samples. These analyses were performed at uninformed levels (OTU dominant taxa) to ensure the greatest possibility of sharing information in the downstream modelling and interpretation [8]. Sophisticated phylogenetic analyses linked to a large reference genomes catalog (PATHDB available at the NCBI bioproject PRJNA419273) were also conducted to predict a putative function at the species level [9].

Monitoring, Updating, and Maintaining Model Performance

A model introduced to integrate polygenic risk scores with microbiome profiles to predict depression risk from DNA can be continuously monitored and updated to maintain performance in different real-world settings. Monitoring can include model drift analysis and performance measurement [15]. Model drift may be triggered by sampling bias in follow-up cohorts, ruling out environmental factors or biological processes that substantially shift the microbiome, or when sequenced data is constituted of different samples on the ML platform. Performance measurement involves monitoring standard metrics such as the area under the receiver operating characteristic curve (AUC) or the Brier score on the follow-up cohort [12]. The performance of the integrated model in the original cohort could be tracked during the model reference period before implementing control measures in new cohorts. Model and data updates can involve a re-thought of the population of focus or implementations of new data generation processes through additional sequencing steps [11]. An operator responsible for monitoring and updating the model can sharpen its focus on the datasets that remain optimum to deliver continuous output [2].

Ethical, Legal, and Social Implications

The substantial increases in the availability and accessibility of polygenic risk scores (PRSs) and microbiome measurements for epidemiological studies targeting depression lead to the practical integration of these two modalities into a joint score that characterizes multifactorial risk [12]. This integration directly addresses the question of whether and how poorly understood and indirect linkages between the two biological systems can be meaningfully exploited for predictive modeling [15]. The specific solutions developed provide a pathway toward data-driven modelling of other paired but loosely coupled biological systems relevant to complex societal questions [13]. The Joint PRS–Microbiome Model (JPM), a general-purpose framework for fusing polygenic and microbiome data, has been developed. JPM is versatile enough to accommodate both low-dimensional and high-dimensional polygenic data, different families of microbiome features (taxon count, taxa presence/absence, and Common Soil Coordinate Analysis), low-dimensional and high-dimensional microbiome data under various kernel types, environments serving as direct precursors of risk or bench-markers of unmeasured sociocultural cruces [1], and active learning for the arrayed microbiome data representing momentary snapshots that evolve over time as a function of diet and metainformation [13].

Potential for Stigmatization and Discrimination

The integration of biological data, polygenic risk scores for major depressive disorder (MDD-PRS), and gut microbiome composition into a predictive model for the onset of major depressive episodes enables the clinical identification of at-risk individuals [12]. However, the purported predictive framework is accompanied by ethical, legal, and social implications related to the combined MDD-PRS and microbiome profile. Concerns about stigma and discrimination arise with respect to such sensitive biological information [11]. The accumulation of rich biological data streams is anticipated to fuel discrimination and stigmatization by insurers, employers, or groups advocating gene-based superiority and against historically marginalized minority groups [8]. Stigmatization and discrimination are catalysts for health inequity, leading to more care avoidance and worse health outcomes for already marginalized groups [7]. Polygenic risk scores (PRS) for health-related traits are emerging tools that project the genetic predisposition of individuals, with positive and negative societal ramifications [1]. At-risk individuals need to be made aware of the respective biological determinism potentially stalling the uptake of relevant mental healthcare pathways and treatments by health jurisdictions [8]. These specific equity considerations form part of a broader agenda that privileges safety and equity for biological risk predictors of mental and physical disorders such as COVID-19, obesity, breast cancer, or miscarriage [6]. Registration of clinical discovery and dataset captions regarding the nature and frequency of biological measurement from distinct populations contributes to a better understanding of equity, along with additional acknowledgement of biases or exposure risk covariates pertaining to at-risk groups [5].

Regulatory Landscape and Compliance

Regulations and standards related to polygenic risk prediction are under development. Early efforts are represented by the draft guidance from the Food and Drug Administration (FDA) for ANS, including polygenic risk models [3]. These regulatory frameworks are concerned with the quality, interpretability, equity, societal impact, and utility of the pronominal risk assessment for populations, ethnicities, and optional population subgroups. Regulatory and standards developments help prevent misuse, allow the ethical use of polygenic risk models, and avoid new forms of disparity or discrimination for ethnic minorities [5]. For instance, regulatory agencies need to clarify which risk categories encompass pronominal, population, individual, and ecology. Annotating the biological basis of polygenic risk models helps make them interpretable. Risk modeling should avoid new ethical concerns, follow regulations, and meet facility standards. Selecting only applicable covariates, population, ethnic, or optional subpopulations needs to be pronounced [5]. In other cases, regulatory frameworks can speed up the implementation of new polygenic risk scores in practical applications. When regulations permit polygenic risk models to be used as approved, pronominal risk models developed on different data sets or data types only require assurance of basic, prior requirements and allow free use of these risk aspects in combination with existing systems or tools [14]. Specific examples of pronominal, population, individual, and ecological risk modeling help clarify the roles of systemic drivers, available risk models, appropriate deposit storage of inputs and modeling, population, ethnic, or subgroup specification in the risk modeling process, and whose signatures or summary statistics are permitted within each risk model, thereby preserving the intended regulatory support measures [13].

Stakeholder Engagement and Patient Autonomy

Models for polygenic risk scores (PRSs) and microbiome features trained on independent, heterogeneous cohorts maintain comparable predictive performance and differentially emphasize specific features, indicating that joint training on a diverse multisource dataset could improve generalizability and equity, even across assessment platforms [15]. Predictive modeling of microbiome features trained solely on studies with individual-resolved data enhances performance and leads to a feature set aligned with clinical investigators' priorities, while training on datasets lacking such information reduces performance, suggesting that independent datasets with records at the individual level provide valuable opportunities for improved learning[11]. In contrast, microbially based models exhibit better generalization across sequencing technologies, larger longitudinal temporal distributions, multiple analytical choices, and diverse population structures, whereas PRS models show a greater propensity for overfitting, mandating increased attention to the accompanying pipelines and protocols [9]. A current study investigates the ethical, legal, and social implications (ELSI) associated with implementing genetic testing based on polygenic scores (PGS) for multifactorial conditions, a topic frequently discussed in academic literature. To elucidate these ELSI aspects, the research analyzes data from a genetic testing implementation project that incorporated continuous feedback from key stakeholders over 4 years [10]. Given the considerable media coverage of PGS testing for diseases such as Alzheimer's, PCOS, or breast cancer, and the ongoing general interest in genomic information acquisition, the study represents an important contribution to the ongoing discourse on the ELSI considerations surrounding PGS testing in established projects [12]. Stakeholders express a positive perception of the integration of genetic risk assessment into clinical settings. Perceived benefits include enhanced disease understanding, increased proactivity in managing personal lifestyles and environmental factors, and motivation to pursue preventive measures [16]. For adult-onset conditions, stakeholders prefer to receive genetic

risk evaluations at adulthood, after they reach maturity; however, PGS testing targeting psychiatric and allergy diseases manifesting during childhood is still needed [12]. Stakeholders acknowledge the demand for aggregated genetic testing eligibility throughout life, recognizing that they require access to testable information based on cumulative genetic knowledge at the time of their own test [10]. Engaging stakeholders, such as participants, patients, or the general population, in genomic implementations plays a vital role in shaping future directions and optimizing research and healthcare organization efforts, driving resource allocation toward initiatives that address stakeholder requests[9].

Case Studies and Simulation Results

Integrating microbiome profiles and polygenic risk scores (PRS) enables individuals at high risk of depression to be identified more accurately [12]. Such systems provide greater interpretability through accompanying feature contributions, enable improved efficiency through smaller input sizes, and are more widely applicable because their biological pathways do not overlap [13]. A proof-of-concept study was carried out with publicly available data to demonstrate the practical utility and accessibility of multiomics models. Employing nested five-fold cross-validation, DepDScr was compared with single-modal genomic and microbiome models based on AUC, precision-recall curves, and the validity and relevance of microbiome and genomic features [14]. Additional experiments investigated the effects of input size and total training set size, underscoring the value of polygenic affordance augmentation. Simulations of two intervention strategies, a baseline policy increasing polygenic affordance by 0.1, and an augmentation-targeted policy stimulating microbiome and polygenic affordance simultaneously, were also conducted [15].

Practical Recommendations for Researchers and Healthcare Systems

Integrated prediction models combining genomic and microbiome features show great promise for enhancing precision mental health care, yet numerous questions surrounding equity, interpretability, bias, and real-world applicability remain unresolved [19]. These challenges reinforce the critical need for continued scrutiny of existing frameworks as well as proactive development of guidelines to advance responsible research on multimodal and integrative risk prediction approaches [13]. Several directions can help facilitate the adoption of integrated modelling while ensuring ethical safeguards and attention to relevant considerations. First, researchers and practitioners should give particular emphasis to preprint and conference publications that not only detail the predictive advantages of multimodal genomic–microbiome prediction but also conduct comprehensive investigations into the accompanying risks and limitations of such methods [20]. Sharing case studies that apply integrated polygenic and microbiome prediction to publicly available cohorts could help in negotiating the balance between clinical deployment timelines and responsible participant sampling. Beyond considerations of sampling, detailed reporting of model performance variability across diverse genomic ancestries and microbiome sequencing platforms remains paramount in guiding equitable implementation [21]. Further engagement with government, private-sector, and third-sector stakeholders to broaden both the scope of input and reach of communication will enhance the clarity and quality of the accompanying discourse [22].

CONCLUSION

Integrating polygenic risk scores with microbiome profiles represents a significant advance in precision mental health care, providing a more comprehensive understanding of depression risk than either modality alone. Multimodal predictive models enable early identification of high-risk individuals, inform intervention strategies, and elucidate biological mechanisms underlying depression. Nevertheless, challenges related to interpretability, bias, population generalizability, and ethical considerations remain critical for responsible deployment. Ensuring robust model performance across diverse cohorts, microbiome platforms, and sequencing methods, while maintaining equity and mitigating potential stigmatization, is essential. Future research should prioritize longitudinal studies, continuous monitoring, stakeholder engagement, and development of regulatory-compliant frameworks to facilitate the translation of integrative polygenic–microbiome risk prediction into real-world clinical settings. By addressing these considerations, integrated models hold promise for enhancing mental health outcomes, promoting equity, and advancing biologically informed precision psychiatry.

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