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Outcomes of a Precision Digital Care Program for Obesity and Associated Comorbidities: Results in Real World Clinical Practice

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Abstract

Background: Obesity is a multifactorial disease with a complex pathogenesis and several prevalent and debilitating associated comorbidities. New genome and microbiome based diagnostic and therapeutic strategies (i.e., personalized medicine) are increasingly guiding the treatment of obesity in clinical settings, but clinical outcomes of precision digital therapeutics require critical examination.

Objective: To conduct a follow-up of participants who lost at least 5% of their weight using a precision digital care program, and to specifically examine the effect of the intervention upon participants' fasting blood glucose, hemoglobin A1c, hypertension, and symptoms of gastrointestinal distress, all of which are risk factors for metabolic illness.

Methodology: A precision digital care program was delivered online and leveraged participants' physiological data, genetic and gut microbiome profiles, and lifestyle habits alongside a mobile app and personalized health coaching to manage weight loss. Individuals who lost at least 5% of their starting bodyweight within 100 days of program commencement were sent a survey on comorbidities and symptoms and incentivized to report back within a week.

Results: Participants reported remission or reversal in presenting comorbidity symptoms, namely two of the most physically and financially debilitating obesity-associated comorbidities: insulin-related disorders and gastrointestinal distress. Those with insulin-related disorders experienced an average reduction of fasting blood glucose level by 17.55% and an average reduction of HbA1c level by 6.27%. Overall, gastrointestinal symptoms decreased by 7.5%, and specific symptoms were alleviated by 40-70% on average.

Conclusion: Weight loss guided by precision digital therapeutics may also improve obesity associated comorbidities, resulting in drastic healthcare savings and quality of life improvements. Further larger scale and longer-term investigations are needed to provide key insights and improve clinical guidelines for the monitoring and treatment of obesity and associated comorbidities.

Introduction

Skyrocketing obesity rates in the U.S. are driving a rapid shift in the landscape of American healthcare [1,2]. The medical system is faltering under the exponentially rising costs of managing obesity-related metabolic illnesses and comorbidities such as diabetes, cardiovascular disease, and mental health [3,4]. Obesity is a multifactorial disease with a complex pathogenesis and several prevalent and debilitating associated comorbidities [5]. In particular, biological factors interact with behavioral factors and demographic influences such as socioeconomic status, or even cuisine, to influence obesity risk [6]. Obesity-associated biological factors include, but are far from limited to, genetics and epigenetics, microbiomic composition, age, circadian rhythm disruption, pharmaceutical interactions, and comorbidities and their management [6,7].

Most current clinical interventions for obesity management focus on lifestyle and dietary adaptation with varying levels of professional guidance and involvement, short- or long-term pharmaceutical therapies, or also bariatric surgery [8]. Individual responses to

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these therapeutic interventions are confounding (for clinicians and patients alike) and heterogeneous for multifactorial reasons [9], making imperative the need for personalized, precision medicine courses of treatment. Eventually researchers hope to elucidate the genetic patterns that influence individual obesity and concomitant illness susceptibility, risk of progression, and response to therapy, to afford patients maximal treatment.

Why Precision Medicine?

Traditional medicine has long focused on caring for patients by preventing and treating symptoms of disease. With the completion of the human genome project, however, the 21st century has heralded the advent of personalized medicine—identification and treatment of disease based upon a patient's individual genetic and microbial makeup [10]. In the mid-nineties mutations in two genes, BRCA and BRCA II, were shown to have such strong correlation with breast and ovarian cancer that today, results of mutational screens in women with family histories of breast cancer now drive important medical decisions such as whether to preemptively excise breasts or ovaries [11,12].

Analysis of a person's individual genetics as a tool for both screening and treatment, from illnesses ranging from cancers to obesity and obesity-associated comorbidities, is becoming increasingly relevant as mechanisms of disease are further elucidated [12]. Targeted pharmaceuticals specific to the molecular basis of a condition, such as obesity, can also reduce side effects [8]. Furthermore, in the healthcare community, a major cost is patient non-adherence, especially relating to chronic diseases where no adherence also frequently exacerbates underlying conditions. Effective personalized therapies with fewer side effects can have the effect of greater patient compliance, greatly improving the efficacy of therapies for chronic diseases and better controlling overall healthcare costs [12]. Personalized nutrition and digital therapeutics, leveraging the power of genetic and microbiomic information that can now be sampled on an individual basis, are altering clinicians' capacity to effect weight loss in patients.

Obesity Associated Comorbidities

Three notable comorbidities, themselves with serious health implications indicative of the current health landscape in the U.S., are insulin-related disorders (namely pre-diabetes and Type 2 Diabetes), gastrointestinal disorders [13] and hypertension (high blood pressure). All three of these comorbidities experience demonstrable reduction upon weight loss [14-16]. With all three of these comorbidities, more weight loss produces more improvement, but even just moderate weight loss (5–10%) is associated with reduction in health care costs [15]. Subjects who lose between 5% to 10% of their initial body weight show the same reduction in blood pressure as those who undergo an intensive year-long lifestyle management program [14]. Even just 5-7% can prevent progression of impaired glucose tolerance (pre-diabetes) into Type 2 Diabetes [15]. Weight loss even has implications for gastric health - in one study, 5-10% weight loss was associated with an 8% reduction in prevalence of IBS [16].

Insulin-related disorders

More than 30 million adults, almost 10% of the U.S. population, suffer from diabetes [17]. A further 84 million American adults (more than a third of the population) are suspected to suffer from prediabetes. In 2014, there were more than 14 million emergency room visits and 7 million hospitalizations linked to insulin-related disorders (diabetes - both non-insulin dependent and insulin-dependent, prediabetes, and gestational diabetes); the disease is of major public health concern costing close to $250 billion in annual health expenditures [17]. The etiologies of prediabetes and Type 2 Diabetes (non-insulin dependent) are closely linked with both obesity and inflammation. More than 80% of diabetes patients in the western world are obese [18], and the inhibition of adiponectin associated with fat accumulation contributes to the insulin resistance that is a hallmark of diabetes [19].

The current standard of care for pre-diabetics (per the Centers for Disease Control and Prevention) involves a "one size fits all" approach to increasing physical activity and decreasing caloric and glycemic intake while undergoing a year-long lifestyle coaching program [20]. Only about 40% of those who have successfully completed an intervention such as the CDC's "Prevent T2" program are able to lose 5% or more of their body weight in that year [21]. Furthermore, only about a quarter of those who have successfully completed a calorie restrictive weight loss program such as Weight Watchers are able to maintain their full weight loss for a year beyond program completion; in fact, more than 20% of Weight Watchers participants are unable to maintain even 5% of their weight loss beyond a year [22]. The diagnosis and progression of pre- diabetes and Type 2 Diabetes are skyrocketing in the U.S., indicating a need for novel approaches to halting the progression of these diseases. In recent years, increasing evidence correlating inflammation with the gut microbiome has emerged, and there are indications that dietary interventions aimed at altering the composition of gut microbiota can be used to target inflammatory disease such as diabetes [23].

Gastrointestinal disorders

Digestive, or gastrointestinal, diseases related to obesity include gastro esophageal reflux disease (GERD), as well as its progression into Barrett's esophagus and esophageal cancers; other carcinomas such as colon polyps and cancers, cholangiocarcinomas, pancreatic cancers, and hepatocellular carcinomas; other liver-related ailments such as nonalcoholic fatty liver disease and hepatitis C-related disease; and gallstones. Diseases such as these annually affect more than 60 million Americans [24]. Every year, gastrointestinal ailments are associated with close to 5 million hospitalizations, more than 70 million ambulatory care visits, over 200,000 deaths, and close to $150 billion dollars in direct and indirect costs [24].

Recent research has elucidated the relationship between commensal gut microbiota and a spectrum of digestive disorders, primarily via up-regulation of inflammatory pathways [25]. Microbial diversity has been shown to be a hallmark of gut health, and perturbations to the microbial environment, especially those that result in reduced diversity are commonly known as gut dysbiosis; dysbiosis, in turn, is shown to be related to a variety of gastric conditions including chronic Irritable Bowel Syndrome and diarrhea [26]. Recent evidence indicates that management of both obesity as well as gut microbiome to alleviate dysbiosis can be instrumental in improving gastrointestinal health [25].

Hypertension

Epidemiological studies have shown a correlation between body weight and blood pressure in obese populations [27]. Although the relationship between obesity and hypertension is well established in children and adults, the mechanism by which obesity directly causes hypertension is poorly understood [28]. Obesity accounts for 65-75% of hypertension risk, and research has clearly established that BMI and blood pressure are directly proportional to one another. In fact, an obese individual tends to have a higher blood pressure than an otherwise identical person but of a lower body weight [27]. A recent study showed how a 3 month weight loss intervention with an average weight loss of 5% helped to normalize BP levels in 49% of participants [29].

Hospitalizations due to primary and secondary hypertension more than doubled since the 1970s and 80s, and the attendant annual costs have risen from $40 billion in the early 80s to $113 billion (15.1% of total hospital costs) in the mid 2000s [30]. Today, a third of American adults suffer from hypertension [30], and although that number stabilized somewhat in the last two decades [31], the estimated number of years of life lost to hypertension-related diseases in 2010 included: ischemic heart disease 7.2 million;

stroke 1.9 million; chronic kidney disease, other cardiovascular and circulatory, and hypertensive heart disease 2.2 million combined [32].

The objective of this study was to conduct a follow-up review on participants enrolled in a precision digital care program who lost at least 5% of their weight within the first 100 days of commencement and who reported at least one of the three comorbidities; insulin-related disorders, gastrointestinal distress and hypertension, and to specifically examine in these participants the association of weight loss upon fasting blood glucose, hemoglobin A1c, hypertension, and symptoms of gastrointestinal distress, all of which are risk factors for metabolic illness.

Methodology

Digbi Health is a Precision Digital Care company that operates online value-based programs using gut microbiome, genetic, and blood metabolite risk signals in an effort to deliver improved health outcomes and financial savings to payers and clinicians. Value-based programs, which are growing to replace the traditional fee-for-service model, reward care providers with incentive payments for the quality of care by moving from a model based on quantity to value-based reimbursement, based on quality. Digital precision care interventions are delivered online in order to expand the accessibility, safety and effectiveness of health care. Digbi Health's DNA and gut microbiome based health program is geared primarily toward individuals who are overweight or obese, with or without a comorbidity, and functions as a weight loss and management tool. The program is currently covered by a large California based health insurance payor for their qualifying members through its obesity management wellness platform.

For this study, we identified 265 Digbi Health participants who enrolled in the program between June 12, 2019 - Dec 13, 2019 and were shipped their DNA kits. Participants were prescribed the program either through a physician or self-enrolled through their health insurance. The Digbi Health research study was approved by the Ethical and Independent Review Services West Coast Board, Corte Madera, California, reference IRB00007807. All participants agree to the Digbi Health terms and conditions and privacy policy when enrolling in the program. From among these participants, we identified 112 (42.26%), all overweight or obese at program onset, who lost at least 5% of their bodyweight within the first 100 days of joining. Of them, 24% reported suffering from digestive disorders, 25.6% from insulin-related disorders (prediabetes, gestational diabetes, Types I and II Diabetes), 25.8% suffered from concurrent skin-related comorbidities, and 22.9% from hypertension (Table 1) (Figure 1).

While skin-related comorbidities were the most frequent amongst individuals enrolled in the Digbi Health program, literature associating dermatologic conditions with obesity indicates that the relationship is less than clear. However, the focus of this brief review is to show the impact of weight management via this personalized program upon the most physically and economically debilitating obesity-associated comorbidities--diabetes, hypertension and digestive disorders and also explore the linkage between inflammation and the most frequently seen comorbidities in the participant cohort.

Upon enrolling in the Digbi Health program participants were provided with online login credentials and were mailed a bluetooth compatible digital weighing scale and saliva and stool biosampling kits. App usage consisted of daily tracking of weight (via the bluetooth scale), dietary intake (uploading photographs of all food items consumed), and tracking wellness associated metrics (sleep quality and quantity, exercise type and duration, stress and meditation, energy levels, cravings, and recommended foods consumed/avoided).

Sample collection

Individual's DNA was collected via buccal swab [Mawi Technologies iSwab DNA collection kit, Model no. ISWAB-DNA-1200 is used to collect the DNA sample]. Saliva DNA extraction, purification, next-generation sequencing (NGS) library preparation and sequencing is performed as per the Illumina standard protocol [32] by Akesogen Laboratories in Atlanta, GA. The results presented in the genetics section of the report were determined by the number of markers and risk genotypes present in the genomic raw data and the Digbi Health reports were loaded to the app. Individuals' gut microbiome was collected via fecal swab [Mawi Technologies iSWAB Microbiome collection kit, Model no. ISWAB-MBF-1200 is used to collect the stool swab]. Sample processing and 16S rRNA-targeted next generation sequencing was performed at Akesogen Laboratories in Atlanta, GA. Sequence data was processed using an open-source microbiome analysis pipeline and publicly available database capable of detecting various microbes in the gut with high specificity. Based on analysis of these genetic and gut microbiomic risk profiles, the Digbi Health Total Wellness Report is generated, and the results are systematically reviewed with the participants 1:1 by the health coach over a 12-week period at regular, pre-determined, weekly and bi-weekly intervals.

Genetic report

The exact gene polymorphisms analyzed for each trait and algorithms that weight each of these SNPs are proprietary to Digbi Health's product, but example genes and information are related as follows. Based on an individual's fat intake, one may have a genetic propensity for elevated BMI on a diet high in saturated fats versus polyunsaturated fats (PUFAs) or monounsaturated fats (MUFAs). The risk related to weight gain with increased saturated fat intake was determined by looking at genetic markers in the $APOA_2$ and FTO genes [33,34], high PUFA intake risk was assessed based on markers

Markers	Risk	Remarks
Akkermansia	High Risk	This genus has shown potential to combat weight gain and inflammation
Bacteroides	Low Risk	This genus has shown potential to combat weight gain
Bifidobacterium	High Risk	This genus has shown potential to combat weight gain
Anaerostipes	High Risk	Associated with weight loss and leaner body types
Coprococcus	High Risk	Associated with weight loss and leaner body types
Roseburia	Low Risk	Associated with weight loss and leaner body types
Eubacterium	High Risk	Regulates weight and appetite
Ruminococcus	High Risk	Regulates weight and appetite
Alistipes	Low Risk	This genus has shown potential to promote weight gain and inflammation
Clostridium	Low Risk	This genus has shown potential to promote weight gain and inflammation
Faecalibacterium	Low Risk	High abundance increases risk of obesity/metabolic disorder
Lactobacillus	Low Risk	High abundance increases risk of obesity/metabolic disorder
Prevotella	Low Risk	High abundance increases risk of obesity/metabolic disorder
Obesity Risk Index	2(1 = Lowest risk; 3 Highest Risk)	Moderate Risk

Table 1: Breakdown of Digbi Health Total Wellness Report Obesity Risk "Microbiome Section". This table was taken from our published case study for the male subject

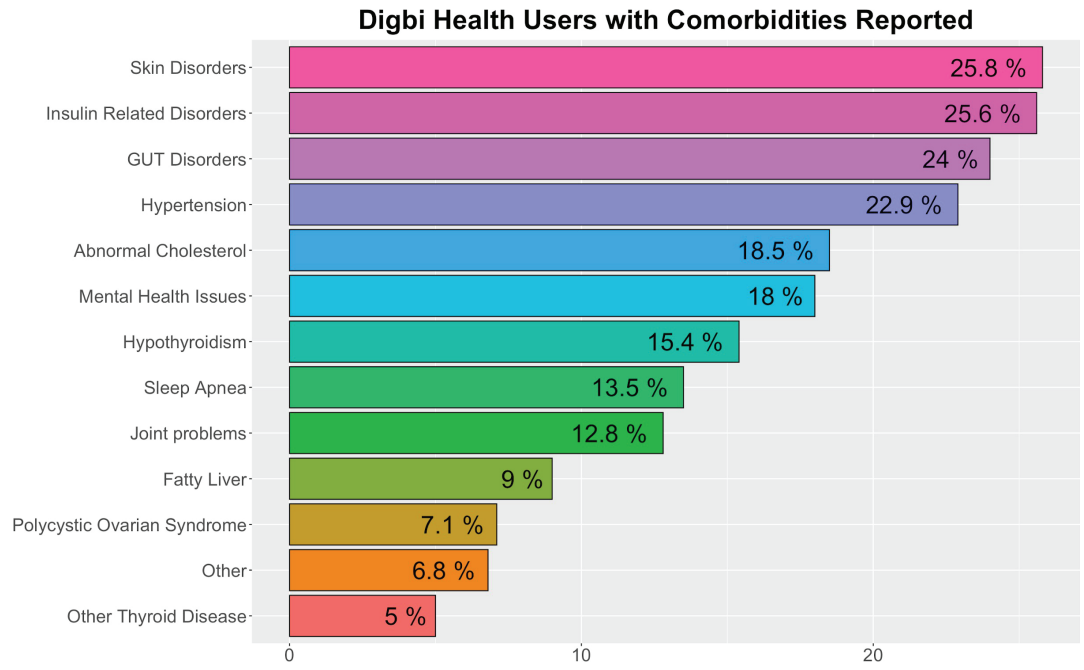


Figure 1: Digbi Health users with comorbidities self-reported between June 12, 2019 and December 13, 2019

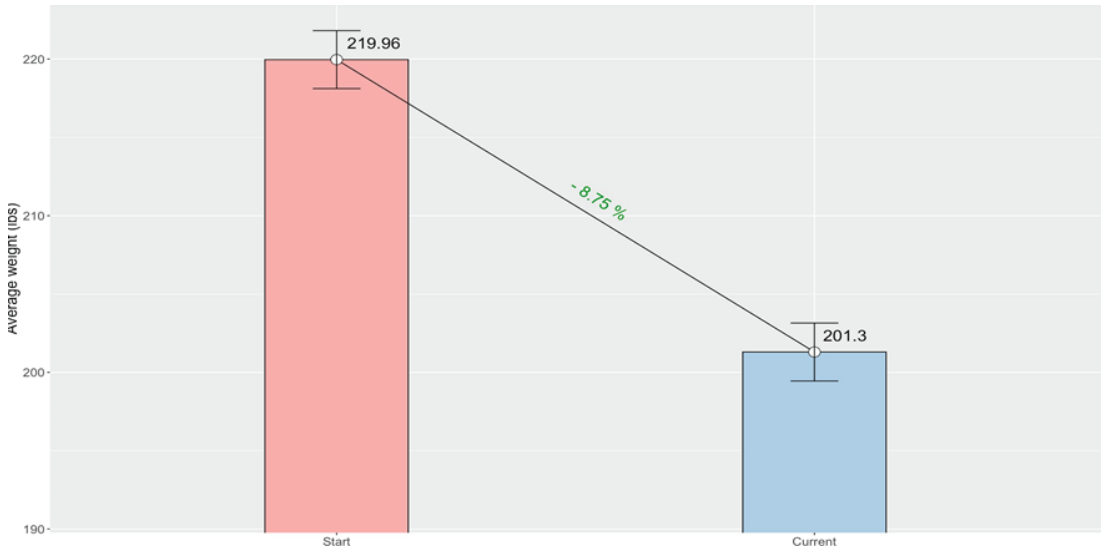


Figure 2: Average Weight Loss of Survey Participants

in the BDNF gene [35], and high MUFA intake risk was determined based on genetic markers in the PPARG gene [36], among others. The Digbi Health Total Wellness Report (genetic section) advised subjects to personalize their diets by adjusting cooking oils and fat consumption to incorporate their individualized genetic findings; for example, someone at high risk for MUFA consumption and low risk for saturated fat consumption would be advised to shift from using olive oil as a cooking medium to using coconut oil or ghee (clarified butter).

Exercise generally improves insulin sensitivity, but this improvement can be dependent upon genetic subtype. Insulin sensitivity with response to exercise was determined by genetic markers in the LIPC gene [37]. Subjects whose insulin sensitivity was predicted to be responsive to exercise were, for example, advised to schedule workouts shortly after meal-times.

Gluten sensitivity, lactose intolerance and caffeine metabolism are three main dietary sensitivities that direct the course of the program's recommendations. The genetic markers were analyzed looking at (among others) the HLA DQ gene for gluten sensitivity [38], MCM6 gene for lactose intolerance [39] and the CYP1A1 gene [40] for caffeine metabolism. People of certain genetic types may have lower tolerance to gluten, a protein found in wheat, barley and rye. Some people experience symptoms like abdominal cramps, bloating, headaches, musculoskeletal pain, diarrhea or constipation, or chronic fatigue when they include gluten in their diet but may not test positive for serological determination of celiac disease. When gluten is removed from such subjects' diets, these symptoms subside, indicating they have a condition known as non-celiac gluten sensitivity [41].

People of certain genetic types stop producing the enzyme lactase in late childhood. Lactase is needed to break down the sugar lactose, present in milk. These individuals may experience gastrointestinal symptoms upon consuming large quantities of milk as adults [42].

Certain individuals are of a genetic type that renders them likely slow metabolizers of caffeine, causing them to experience symptoms such as palpitations and anxiety upon consuming more than 1 to 2 cups of coffee a day. These individuals may also be at a higher risk of heart disease with increased coffee intake [43]. Eliminating gluten for those who are sensitive, eliminating or reducing lactose for those who are intolerant, and eliminating or reducing caffeine for those who are slow to moderate metabolizers can potentially reduce systemic inflammation in these clients, alleviating side-effects and symptoms and promoting weight loss [44].

The Digbi Health program also assesses the feasibility of treating hypertension by looking at genes related to two features: 1) for some people, increased dietary intake of sodium is linked with high risk for hypertension (and others are at moderate or low risk related to sodium consumption), 2) for a subgroup of people, increased dietary consumption of riboflavin (Vitamin B2) is associated with lowered risk for hypertension. The predicted response related to Riboflavin and blood pressure response were determined by looking at genetic markers in the MTHFR gene [45] and the SGK1 gene [46] amongst others for salt intake related to blood pressure sensitivity.

Gut microbiome report

In addition to using genetic risk profiles to guide the course of subjects' precision care, the Digbi Health program also analyzes gut microbiomic profiles (collected from stool sampling) to guide the course of care. The Digbi Health Total Wellness Report (gut microbiome section) looks at overall microbiomic diversity as an indicator of gut health [47], and also looks at abundance of various probiotic and anti-inflammatory microbes. Certain probiotic bacteria are associated with healthy digestion, metabolism, and immunity. A high abundance of associated bacteria such as Akkermansia, Bacteroides, Bifidobacterium, amongst others helps to combat weight gain, inflammation, regulates weight, appetite, fat accumulation. A high abundance of bacteria that contribute to increased obesity risk, for example Alistipes, Clostridium, Faecalibacterium, amongst others, promotes weight gain, inflammation and metabolic disorders. A lower abundance of these bacteria are beneficial and reduces the risk of gaining weight and inflammation [48].

In the report, an individual's obesity risk profile is represented by an obesity risk score for each individual. The Digbi Health Total Wellness Report includes information on the presence, absence, and relative proportions of gut microbes associated with health and various conditions. These microbes are identified in the report as either negatively or positively associated with health outcomes by taking into account a large number of peer-reviewed studies. Positively associated microbes found to be underrepresented in a subjects' sample are considered "high risk," and dietary interventions are recommended to improve microbial diversity and probiotic representation; if those same microbes are found to be well-represented, then the status is "low risk". Similarly, negatively associated microbes found to be underrepresented in a subject are "low risk" whereas if over-represented, they are then "high risk" and dietary interventions are recommended to decrease levels of those organisms.

Lifestyle

The Digbi Health program is a 24-week program which uses body metrics, gut microbiome and genetic profiles, and personalized health-coaching to manage weight loss. Participants use the Digbi Health app to track 10 key lifestyle and wellness markers (weight, sleep, hunger, cravings, stress, meditation, super foods, morning energy, foods to avoid, and exercise) on a daily basis, take photos of the food they consume, and are assigned a health coach who works personally with the participant through 12 guided sessions at various intervals to interpret the personalized wellness reports generated from sampling participants' DNA and gut microbiota. The reports also provide a breakdown of obesity risk based on individuals' genetic and gut microbiome profiles. The program is geared toward participants losing at least 5% of their starting body weight by week 16 of the 24-week program. To achieve this goal, the program seeks to nudge participants towards making incremental lifestyle changes focused around reducing sugar consumption, timing meals to optimize insulin sensitivity, reducing systemic inflammation by identifying possibly inflammatory and anti-inflammatory nutrients via genetic testing, establishing a base level of physical activity and doing so in a manner that reduces inflammation, optimizing gut health based on microbiomic testing, and most importantly, making these behavioral modifications supported by health coaching and the app so that the changes are sustainable long-term. The genetic profile of Digbi Health users identifies several nutrients/foods that have associations with obesity, comorbidity, or inflammatory risk (e.g., gluten sensitivity, lactose tolerance, caffeine sensitivity, fatty acid metabolism, blood pressure response to salt or riboflavin intake, reduced insulin resistance with exercise, etc.).

Survey

The group of Digbi Health participants who achieved at least 5% weight loss within 100 days were sent a survey to determine if they showed an improvement in any of their comorbidities' symptoms. The survey was sent via email, respondents were given 1 week within which to complete the survey, and survey completion was incentivized by entering respondents into a randomized drawing for an Amazon gift certificate. Forty four individuals responded to the survey, out of 112 possible respondents. The survey invitation was sent via email; 72 of email recipients clicked to open the email, and of those who opened the email, 44 responded in the required time frame. Email recipients were given ten days in which to respond. In a further analysis of these 44 survey participants, the respondents' Digbi Health's genetic risk reports were retroactively reviewed with respect to intolerances/sensitivities towards lactose, gluten, caffeine, salt intake and assessed risk for weight gain based on fat intake, insulin sensitivity and cholesterol level response to exercise. Each participants' Digbi Health treatment plan was personalized based on his/her individual genetic propensities for each of these factors.

Statistical analysis

Summary statistics and graphs were generated using R. Our data consists of both discrete and continuous variables. To check the normality of continuous variables Shapiro-Wilk test was used. Besides that summary statistics for continuous variables were obtained using summary SE within R package.

Results and Discussion

Overall response

All the continuous variables such as weight loss amount in pounds, fasting blood glucose levels, Hemoglobin A1c levels exhibited normal distribution. Participants in this survey (all of whom had lost at least 5% of their starting body weight within the first 100 days of the program) lost 8.75% (95% confidence interval from 7.49 - 10.02%) of their body weight, on average (Figure 2).

Sufferers of all three comorbidities lost significant amounts of weight. Those with insulin- dependent disorders lost 7.95% (95% confidence interval from 5.50-10.39%) of their body weight, those with gastrointestinal symptoms lost 8% (95% confidence interval from 6.67-9.34%) of their body weight, and those with hypertension lost 10.24% of their body weight (95% confidence interval from 7.16-13.33%) (Figure 3).

A major personalized dietary intervention for all subjects was adjusting dietary fat consumption based upon predicted inflammatory risk, specifically advocating cooking with ghee and coconut oil for those low risk for saturated fats, cooking with olive oil for those low risk for monounsaturated fats, and cooking with grape seed and flaxseed oil for those low risk for polyunsaturated fats. This intervention was deployed without a specific comorbidity

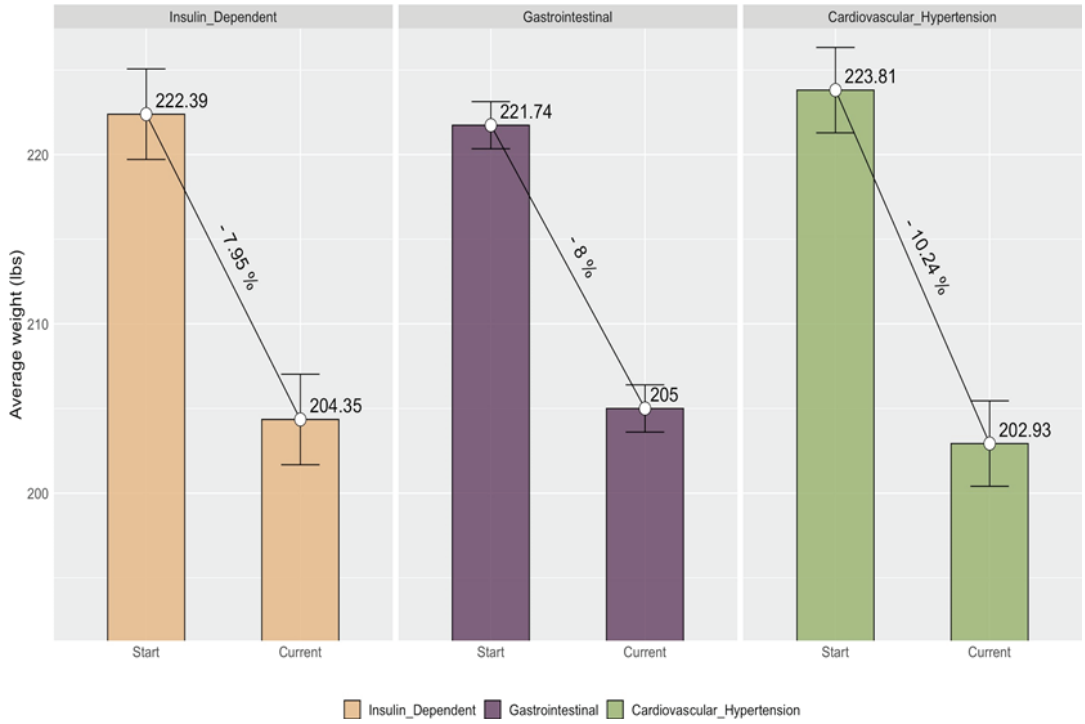


Figure 3: Average Weight Loss of Survey Participants by Insulin-Dependent Illness, Gastrointestinal Disorders and Cardiovascular Hypertension

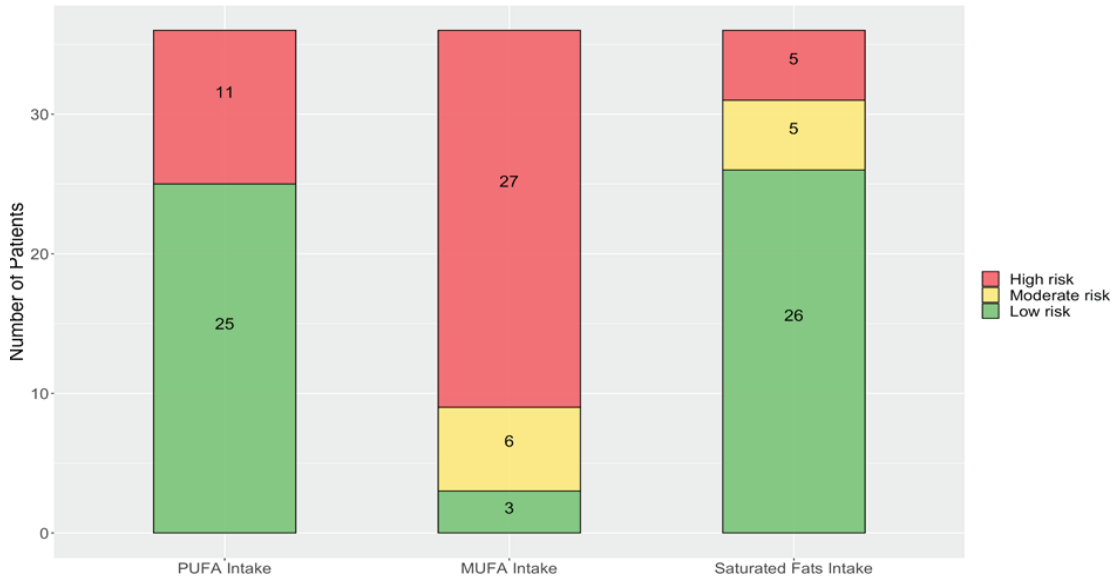


Figure 4: Breakdown of Survey Participants' Genetic Risk for Weight Gain by Type of Dietary Fat Consumed

in mind, but instead geared towards reducing systemic inflammation that may be refractory to weight loss (Figure 4). A notable feature of this cohort is that a vast majority of respondents are high risk for elevated MUFA intake, but low risk for saturated fat intake - a contradiction to the conventional wisdom of the Mediterranean diet (high in monounsaturated fats such as olive oil, almonds, etc.) [49]. This finding could potentially be tied to why these respondents have struggled with weight gain in the first place. Commonly held nutritional advice like avoiding saturated fats in deference to cardiovascular health may be more nuanced in light of findings elucidating genetic contributions to adiposity [50].

Insulin-related disorders

Participants with self-reported insulin-related illness (pre-diabetes or Type 2 Diabetes) experienced significant alleviation of diabetic symptoms. Of the participants who reported their blood markers before and during program participation, 100% experienced improved blood sugar (Figures 5a and 5b). The vast majority of subjects with insulin-related disorders (35 out of 37) were found to have a genotype that indicated insulin sensitivity would improve with

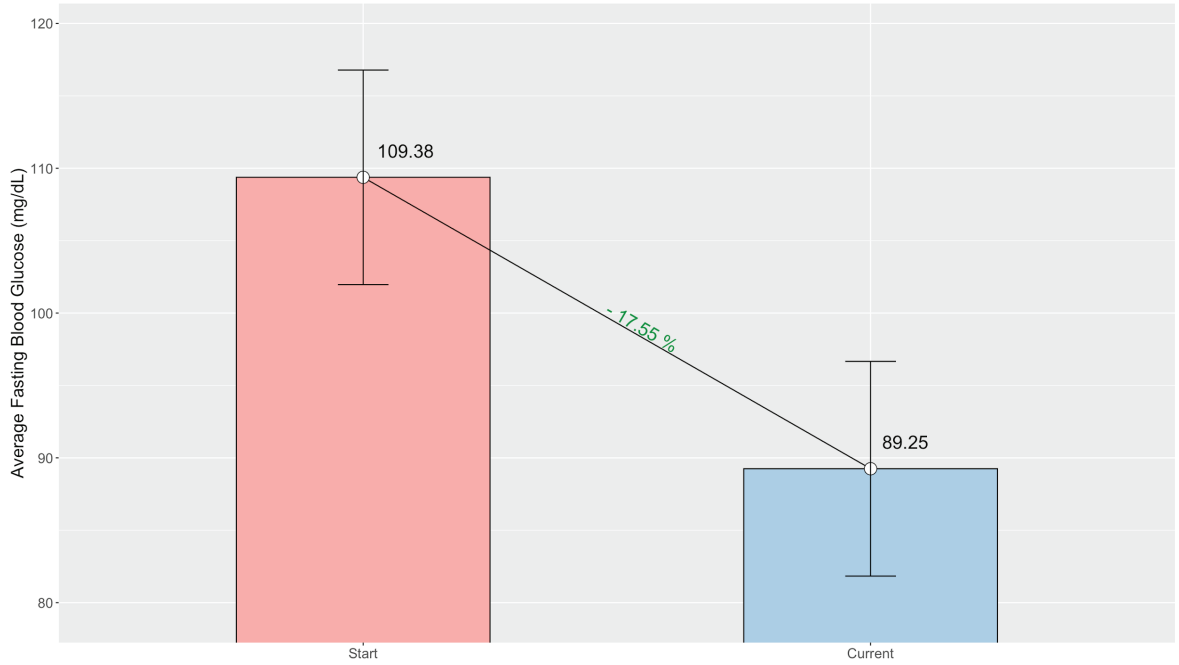


Figure 5a: Survey Participants' Changes in Fasting Blood Glucose

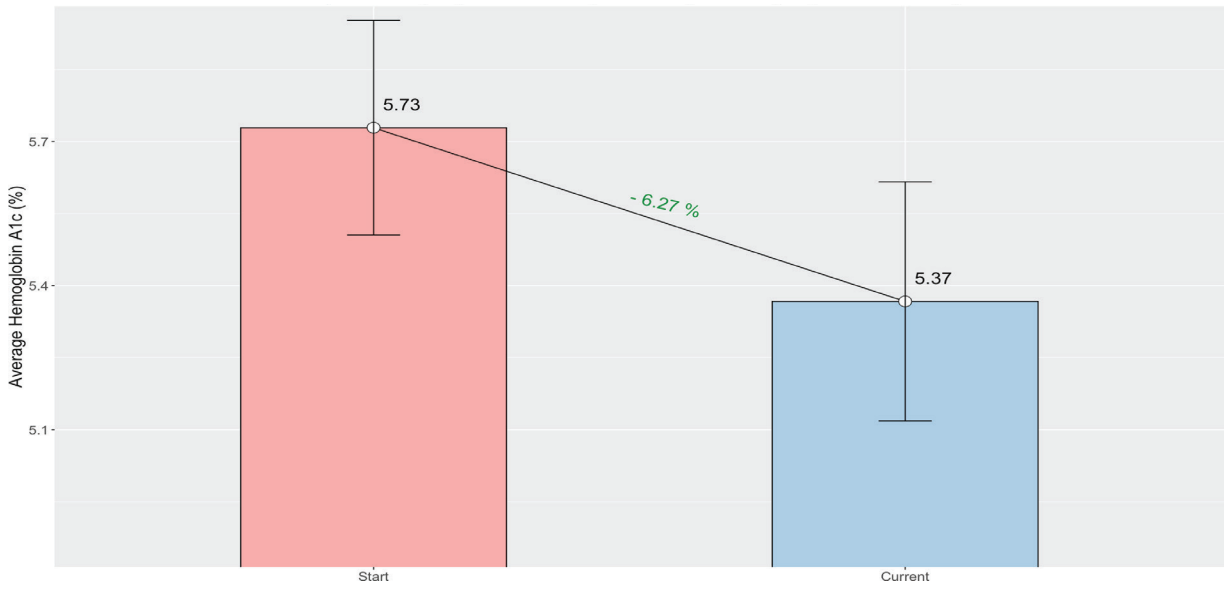


Figure 5b: Survey Participants' Changes in average Hemoglobin A1c

exercise and were coached into becoming physically active for at least 20 min per day (Figure 6). At the start of the program, participants had a mean fasting blood glucose level of 109.38 mg/dL and a mean HbA1c percentage of 5.73. At the time of survey completion, the same cohort had a mean fasting blood glucose level of 89.25 mg/dL (average 17.55% reduction per participant: 95% confidence interval: 10.09%-25.02%) and a mean HbA1c percentage of 5.34 (average 6.27% reduction per participant: 95% confidence interval: 0.89%-11.65%).

Gastrointestinal distress

The 20 participants experiencing various forms of gastrointestinal distress lost more than 8% of their total body weight (Figure 2). In the survey, participants were asked to rank their experience of a variety of gastrointestinal symptoms on a scale of 0 to 5 (5 indicating maximal discomfort). Irritable Bowel Syndrome and gastric pain, in particular, both experienced more than 80% reduction in symptoms. Overall, gastrointestinal symptoms decreased by 7.5%, and specific symptoms were alleviated by 40-70% on average.

A majority of survey participants self-reported significant improvement of gastrointestinal symptoms upon participating in the Digbi Health program. More than 60% reported some improvement in symptoms, and 75% of those reported significant improvement (Figure 7a).

When looking at the various subtypes of gastrointestinal

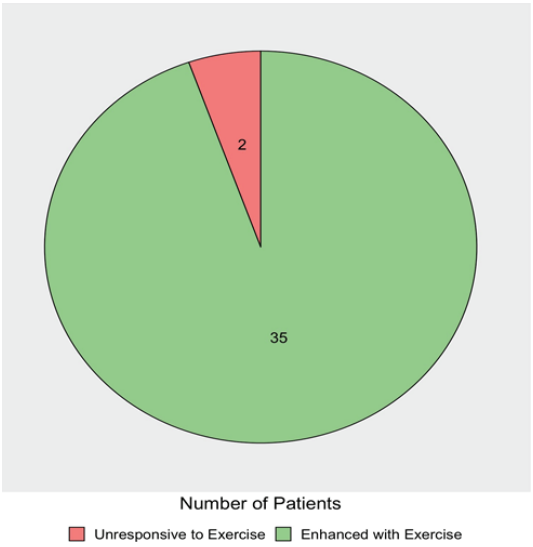
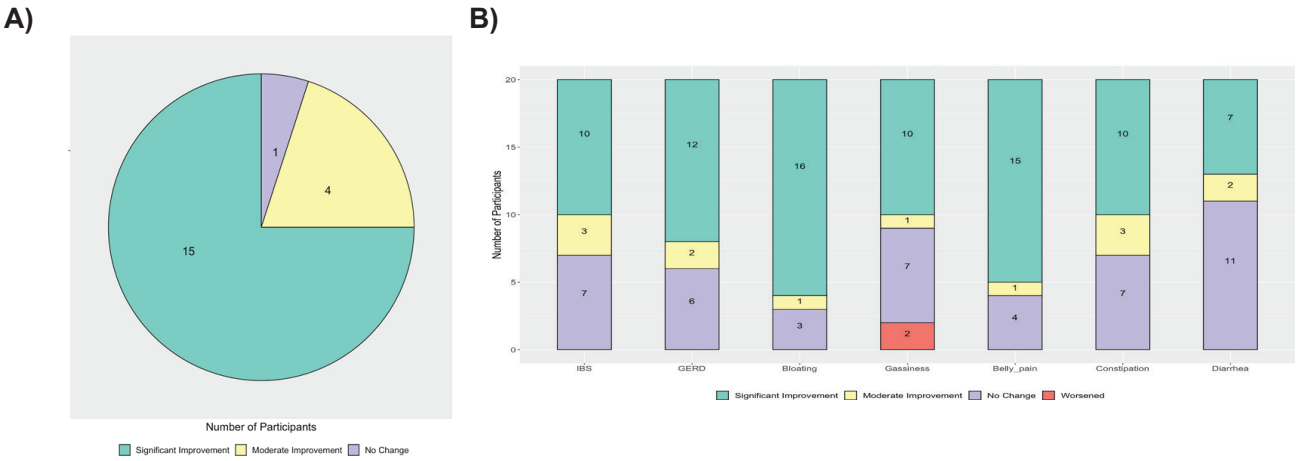


Figure 6: Survey Participant's Genetic Predispositions to Modulating Insulin via Exercise



Figures 7a and 7b: Survey Participants' Changes in Self-Reported Gastrointestinal Symptoms. Fig 7b Survey Participants' Changes in Self-Reported Gastrointestinal Symptoms by Condition/Symptom

symptoms, the greatest improvements were seen in gastric pain - 75% of respondents experienced significant reduction in pain whereas only 20% experienced no change (and none experienced an increase) (Figure 7b). In fact, of the various measures of gastrointestinal distress, only sufferers of gassiness experienced an increase in symptoms - 45% experienced more gas during the program than before it (although the same percentage experienced some relief). With regard to gassiness, these symptoms are likely a function of significantly increased dietary vegetable/fiber intake, which increases transit time through the gut and results in longer fermentation by microbes and resultant gas release, symptoms that could be relieved with better hydration. Irritable Bowel Syndrome, gastroesophageal reflux, gastric pain, and constipations all had more respondents reporting symptom improvement compared with symptoms remaining the same. 50% of respondents suffering from abdominal bloating experienced improvement (80% of them experiencing significant improvement). The majority of diarrhea sufferers saw no change in symptoms, but almost 45% did improve (78% of them significantly). The targeted interventions for alleviated symptoms of gastric distress were focused on reducing potential inflammatory agents from the diet, primarily eliminating gluten and lactose for those who were likely sensitive/intolerant, and reducing/eliminating caffeine for those likely moderately slow to slow metabolizers; a majority of respondents were high risk for at least one sensitivity (most were likely gluten-sensitive) (Figure 8).

Hypertension

The 8 participants with hypertension lost more than 9% of their weight (Figure 2). Participants suffering from hypertension reported both their systolic and diastolic blood pressures before and after commencing the Digbi Health Program. Subjects who were high or moderate risk with regard to salt intake were strongly advised to reduce sodium consumption in order to better control hypertension. Similarly, subjects who were sensitive to riboflavin and blood pressure response were advised to increase vitamin B2 consumption to better control hypertension (Figure 9).

Of the 44 survey respondents, only 8 reported current blood pressure data, and although their results look promising, larger scale review of hypertensive subjects and their outcomes will have to wait for a subsequent analysis and publication with larger sample sizes.

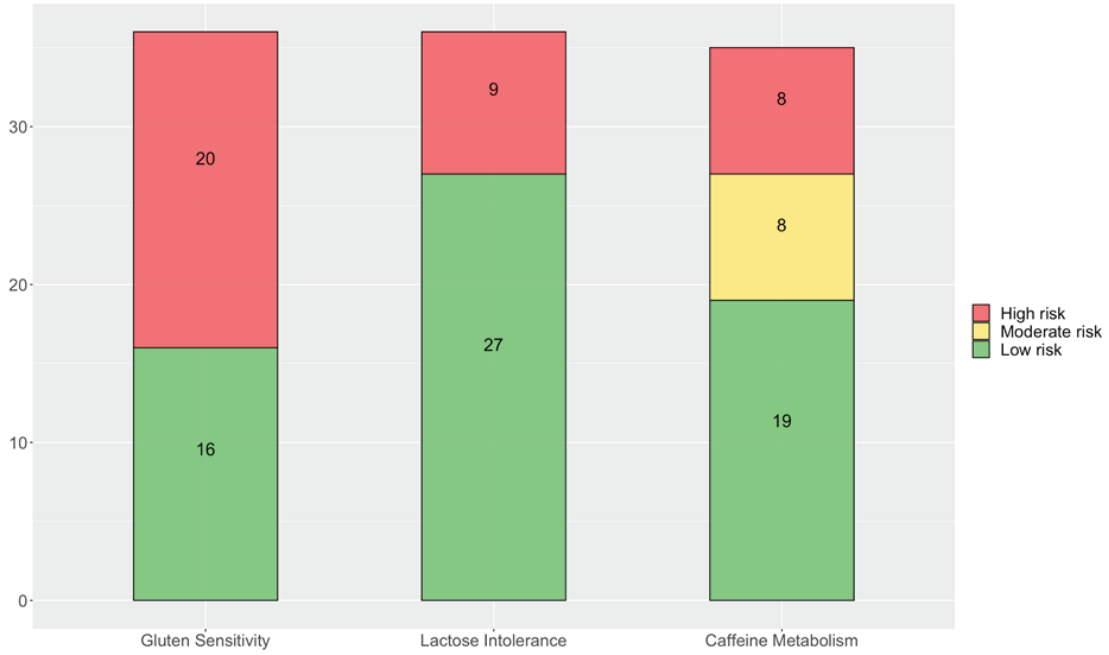


Figure 8: Survey Participants' Genetic Predispositions to Gluten Sensitivity, Lactose Intolerance and Caffeine Metabolism

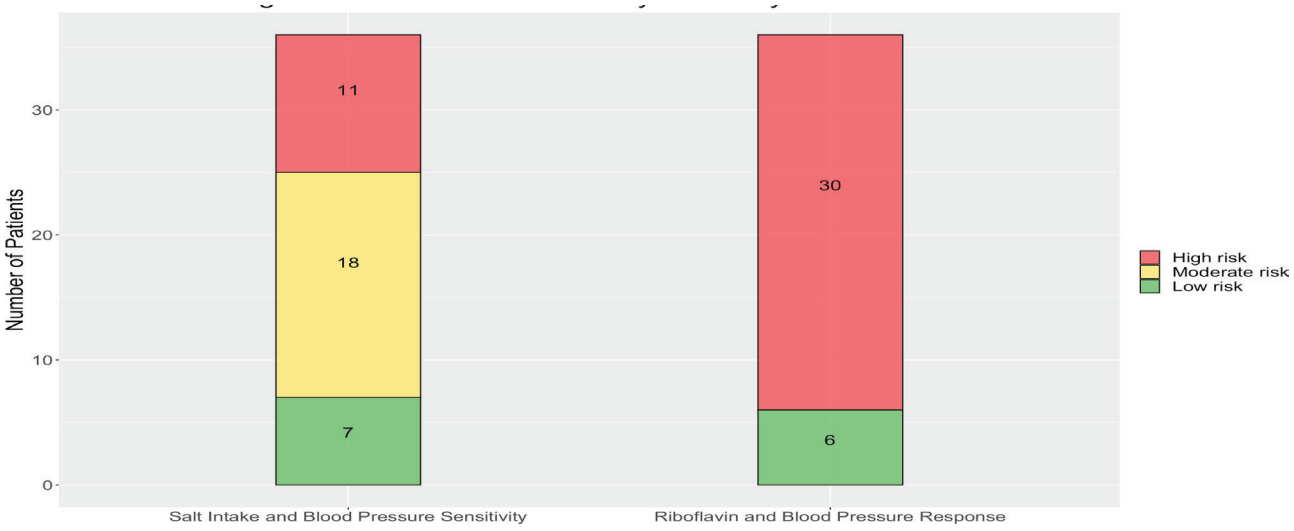


Figure 9: Survey Participants' Genetic Predisposition to Blood Pressure Sensitivity via Dietary Intervention

Conclusion

Combating obesity-associated comorbidities is a notoriously difficult clinical undertaking that is largely complicated by the heterogeneity of the underlying causes of obesity. Obesity is polygenic, and the expression of many of the involved genes is contingent upon epigenetic regulation modulated by environmental factors such as lifestyle [51]. Many current clinical interventions target these environmental lifestyle factors of patients without access to information regarding underlying genetic predispositions. Moreover, a "precision medicine"-based clinical intervention is one that optimizes course of treatment not only for an individuals' environmental and cultural constraints and individual biology (genetic and microbiomic factors), but it is also based upon individual patients' behavioral requirements and responses (eg, different individuals will require varying degrees of support and interaction from a healthcare provider via various media or utilizing varying tools to reach a target weight loss goal) [9]. Each of these factors - biological constraints, lifestyle constraints, and behavioral constraints - allows for myriad permutations when optimizing precision care-based clinical courses of action, and elucidates, atleast in part, the heterogeneity in outcomes of individuals following any given clinical weight loss intervention [9,10].

A precision digital care based approach to nutrition and health, especially when related to weight- management, shows great potential in improving patient outcomes [52]. Leveraging genomic and microbiomic data, the way the Digbi health approach does, allows for personalizing care tailored toward an individual's specific disease etiology. Obesity is a multifactorial disease arising from an at-risk genetic profile, and environmental risk factors, such as physical inactivity, insufficient sleep, excessive caloric intake, medications, socioeconomic status, endocrine disruptors and the gastrointestinal microbiome [51] and affects more than 40% of Americans. The healthcare costs associated with obesity and its comorbidities are vast and rapidly increasing. Insulin-related illnesses cost $250 billion annually, gastric diseases cost $150 billion annually, hypertension cost $113 billion annually [17,24,31]. These three comorbidities account for almost 15% of the U.S. $3.6 trillion annual healthcare costs [53]. Based on a study using a microsimulation on the obese population of the U.S., it was determined each pound of weight lost was translated to $62.50 per pound saved in annual healthcare costs [54].

Digbi Health (Mountain View, CA) is a precision care digital provider designed to combat obesity by leveraging participants' genomic and gut microbiomic data along with incremental behavioral modification mediated by app usage and individualized health coaching. Either clinicians prescribe the program or members self-enroll through their health insurance. In a cohort of 44 survey participants who had lost at least 5% of their bodyweight, a total of 671.9 lbs were lost within these individuals' first 100 days using the Digbi Health program - a result that translates to more than $40,000 in annual healthcare savings [54]. Greater distribution and availability of genetic and gut microbiome-based precision weight loss intervention may be able to produce significant improvement of obesity related comorbidities and ultimately result in drastic healthcare savings in the population at large [48]. The sample size of the analyzed cohort in this study is admittedly small, and interpretations of the data are limited as the study is restricted to individuals who were able to rapidly lose 5% of their starting bodyweight, but even so, many of the results are of statistical significance, especially when viewed in conjunction with qualitative self-reported data such as a majority of respondents reporting improved symptoms.

To date, the most successful non-invasive interventions have been in lifestyle and dietary changes, but substantial gaps exist in understanding how behavioral, psychosocial, and biological mechanisms both drive the development of obesity and influence treatment response [55]. Improving that understanding is imperative to tailoring treatment strategies that leverage individuality amongst disease etiologies and result in successful outcomes. Further large-scale studies are needed on various obese cohorts to provide key insights and improve clinical guidelines for the monitoring and treatment of obesity and associated comorbidities.

Conflicts of Interest

This study was funded by Digbi Health and co-authors, Roshni Ray Ricchetti; Karthik Muthukumar; Ranjan; Simitha Singh-Rambiritch; Imran Junaid; Chandana Reddy-Sinha; Jessica Kotini; Carmel Irudayanathan, of this manuscript are also salary-funded and share ownership stake in Digbi Health. Dr. Bruce Underwood, reviewed and contributed to the manuscript as an external consultant. He is not salary funded nor does he own any shares in Digbi Health. The Digbi Health authors had full access to all data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis. Independent peer review of this manuscript would serve as further safeguard against conflict of interest in this instance.

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