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Algorithmic lifestyle optimization

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ABSTRACT

Objective: A hallmark of personalized medicine and nutrition is to identify effective treatment plans at the individual level. Lifestyle interventions (LIs), from diet to exercise, can have a significant effect over time, especially in the case of food intolerances and allergies. The large set of candidate interventions, make it difficult to evaluate which intervention plan would be more favorable for any given individual. In this study, we aimed to develop a method for rapid identification of favorable LIs for a given individual.
Materials and methods: We have developed a method, algorithmic lifestyle optimization (ALO), for rapid identification of effective LIs. At its core, a group testing algorithm identifies the effectiveness of each intervention efficiently, within the context of its pertinent group.
Results: Evaluations on synthetic and real data show that ALO is robust to noise, data size, and data heterogeneity. Compared to the standard of practice techniques, such as the standard elimination diet (SED), it identifies the effective LIs 58.9%–68.4% faster when used to discover an individual's food intolerances and allergies to 19–56 foods.
Discussion: ALO achieves its superior performance by: (1) grouping multiple LIs together optimally from prior statistics, and (2) adapting the groupings of LIs from the individual's subsequent responses. Future extensions to ALO should enable incorporating nutritional constraints.
Conclusion: ALO provides a new approach for the discovery of effective interventions in nutrition and medicine, leading to better intervention plans faster and with less inconvenience to the patient compared to SED.

Key words: irritable bowel syndrome, diet, N-of-1 trials, lifestyle, group testing

INTRODUCTION

The variance of responses to lifestyle interventions (LIs) has been a major challenge in the fields of nutrition and medicine throughout history.[1,2] Typical LI include changes in diet,[2] exercise,[3] administrating drugs,[4] stress management,[5] smoking cessation,[6] assisted sleep methods,[7] and fasting,[8] among others. Despite this variance in response to LIs, practical and effective LI guidelines have been developed for some prevalent conditions such as type 2 diabetes and cardiovascular disease.[9] In some conditions such as irritable bowel syndrome (IBS) and food allergies, trial-and-error approaches such as the standard elimination diet (SED) are used to pinpoint a person's response to individual LIs.[10,11] It has been shown that biomarkers can predict an individual's response to a given LI,[12–14] however, such biomarkers are often difficult to acquire and carry limited information when in isolation.[15,16]

A successful lifestyle modification depends on 2 main factors. First, is a set of candidate LIs, and second is a diagnostic tool that pinpoints the LIs that will be potent for a given individual based on their bio-state. Previous studies have proposed and measured the adoption of systematic diagnostic strategies for particular interven-

tions including diet and physical activity. The SED is used for identification of food allergies in serous otitis,[17] atopic dermatitis (eczema),[10] as well as food intolerances in IBS,[18] esophagitis,[19] and ADHD[20] among others. In SED, series of oral food challenges are used in which target symptoms are evaluated following dietary elimination and subsequent introduction of each food for 2–3 days at a time. More recently, N-of-1 trials have emerged for systematic personalization of medical treatments in cases were the individualized potency of alternative treatment strategies need to be determined.[21] They involve trial periods during which alternative treatments are followed one after the other and treatment outcomes are measured in order identify the treatment with the best statistical support. N-of-1 trials are used for dietary intervention in inflammatory bowel disease,[19] determining the impact of dietary macronutrients on postprandial glucose response,[20] and personalized goal setting strategies to increase physical activity[22] among others. These trial-and-error approaches commonly involve a single LI at a time, which is impractical and suboptimal when there is a large number of noninteracting candidate LIs. Therefore, the number of candidate LIs that can be evaluated by an individual will be limited given the time that they can spend for determining LI responses.

To address this issue in a faster, less invasive, and more efficient way, we propose a systematic approach that we call "algorithmic lifestyle optimization (ALO)," a heuristic approach for identifying the individualized binary labels (ie, potent or impotent) of the candidate LIs, based on heterogeneous data, including biomarker information. In ALO, the required time for discovering candidate LI potencies in an individual is minimized. In its core, ALO uses an adaptive group testing strategy and involves multiple rounds of LIs for each individual. In each round, a set of LIs are provided to the individual to follow. These LIs are chosen by ALO based on: (1) the individual's health score (0|1) in response to each set of LIs in prior rounds, and (2) the probability of a positive health score for each LI in a population. These probabilities may also be calibrated based on a biomarker when available. In ALO, we strive to identify the individual's response to each LI in minimal number of rounds and provide guarantees for both average and worst-case scenarios. The ALO methodology is fully described under the "Materials and Methods" section and illustrated in Figure 1.

ALO is based on adaptive group testing,[23] a category of algorithms used to improve efficiency in telecommunications,[24] quality control,[25] and biotechnology[26] among others. Briefly in adaptive group testing, groups of available objects are selected in sequential rounds for testing, with the goal of discovering the target objects (eg, defective light bulbs, SARS-CoV-2 positive nasal swabs, or the potent LIs that we discuss here) amongst many, in minimum number of rounds. Group testing is applicable in cases where objects are noninteracting. This means that if multiple objects are tested together in a group, a positive test result is indicative of one or more target objects in the group (eg, at least 1 defective light bulb in the group), while a negative test result indicates that the group is void of any target object (eg, no defective light bulbs in the group). Note that, in this article, a "potent LI" corresponds to a "target object" that is subject to group testing while in the literature the "defective lightbulb" terminology is commonly used.

MATERIALS AND METHODS

Main algorithm

ALO is applicable in cases where: (1) the individual is concerned about a single binary target health score such as having a symptom-free digestive state (0|1), (2) each LI is binary such as drinking coffee in the morning (yes/no), (3) it takes the same amount of time (eg, 3 days) to see the impact of each LI on health score, (4) multiple LIs are independent hence can be followed together simultaneously, and (5) multiple LIs are noninteracting. Noninteracting here means that if a set of LIs together are determined to be "impotent" (ie, not leading to a positive health score), we can conclude that each LI is also "impotent." However, when a given LI is "potent" (ie, leading to a positive health score), it will remain as "potent" when combined with other LIs.

Constrained adaptive group testing

ALO relies on the constrained adaptive group testing (CAGT) method that we have developed. The CAGT algorithm aims to identify the minimal number of adaptive group testing rounds needed to identify the set of potent LIs (V_1) amongst the set of candidate LIs (LI) for a given individual, by solving the optimization problem in Equation (1). Here $R_i \subseteq LI$ represents the group of LIs that will be followed simultaneously by the individual in round i during which the potency of R_i will be determined as represented by $r_i \in \{0: \text{ impotent}, 1: \text{ potent}\}$. V_1 and V_0 represent the sets of potent LIs and impotent LIs respectively which can be fully identified by a function f given LI, R, $\boldsymbol{r}$ as well as the l : low and h : high bounds for the number of potent LIs. This is a generalization of strict group testing in which only the maximum number of LIs (h) is known and its minimum (l) is always zero.[27]

$$\begin{aligned} \mathrm{R}^* = \quad & \operatorname{argmin}_R \quad |R| \\ & \text{subject to} \quad R = [R_1 \dots R_{|R|}],\ R_i \subseteq LI,\ i = 1, \dots, |R| \\ & \qquad\qquad \boldsymbol{r} = [r_1 \dots r_{|R|}],\ r_i \in \{0,\ 1\}, i = 1, \dots, |R| \\ & \qquad\qquad [V_0, V_1] = f(LI,\ R,\ \boldsymbol{r},\ l,\ h) \\ & \qquad\qquad V_0 \cup V_1 = LI \\ & \qquad\qquad l \le |V_1| \le h \end{aligned} \tag{1}$$

In CAGT, we solve Equation (1) following Algorithm 1 with 3 major steps in each round, using the *CAGTModel* that captures l and h bounds for subsets of LIs that are generated in each round. In step1, a nonnested subset of LIs (R_i) that is expected to minimize the final $|R|$ is identified given the *CAGTModel*. In step2, the potency r_i of R_i is determined by the individual based on their health score after following R_i. In step3, the model is updated (given R_i and r_i), and the sets of impotent and potent LIs (V_0 and V_1) that can be determined using the updated model are identified. These 3 steps are repeated until the potency of all LIs are identified. See Supplementary Information Section S1 that describes the *CAGTModel* and its relevant functions in detail.

ALO modules

ALO consists of 3 modules, all of which rely on CAGT. The first ALO module builds a lookup table named "CAGT catalog" that CAGT relies on for optimal performance. The second ALO module creates an optimal LI partition (disjoint sets of LIs) that leads to minimum total rounds when CAGT is followed on each set separately. The third ALO module involves LIs that are suggested by the CAGT algorithm given each LI set until the potency of all LIs are determined.

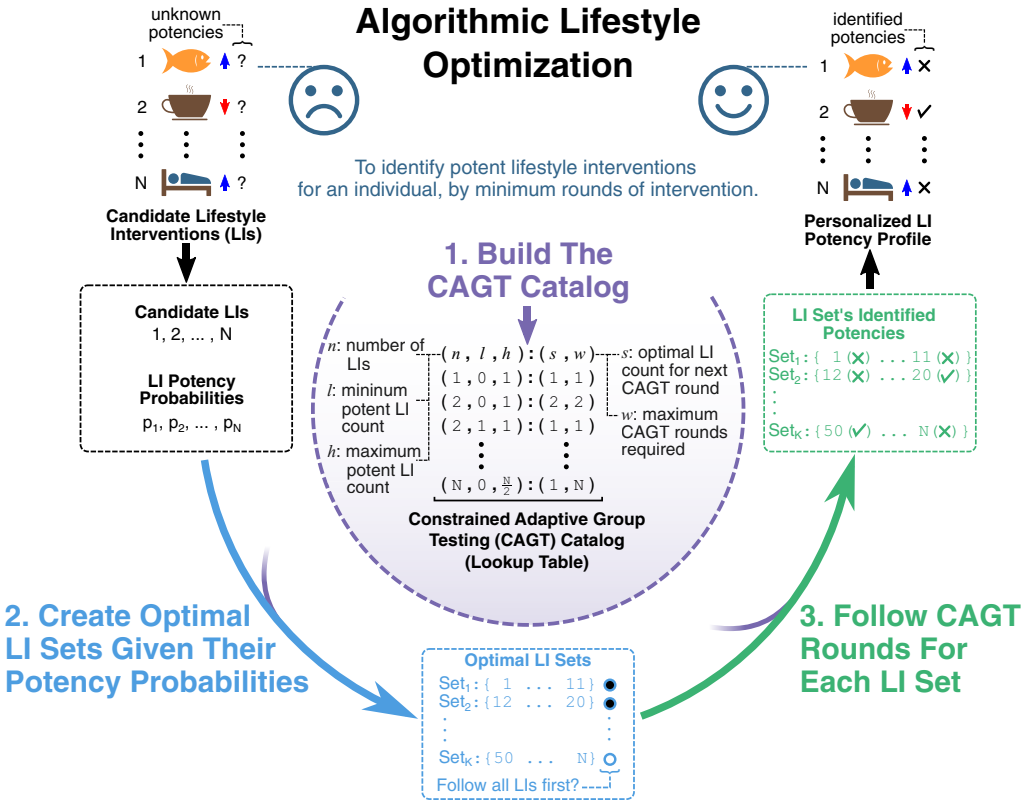

Figure 1. Algorithmic lifestyle optimization (ALO). ALO is designed to guide individuals in rapid discovery of lifestyle interventions (LIs) that are effective (potent) for them amongst many candidate LIs, for achieving a target health outcome. First, it builds the constrained adaptive group testing (CAGT) catalog, which is a lookup table for finding the maximum number of rounds needed by the CAGT algorithm for identifying between minimum l and maximum h number of potent LIs amongst n candidate LIs. Second, it partitions the LIs into disjoint sets given the potency probability of each LI, and determines whether the first step of the CAGT algorithm involves following all the LIs in a given set. These probabilities can be estimated from population wide studies that report the percentage of individuals that achieve the target health outcome following each LI. Third, the suggested LIs by the CAGT algorithm is followed by the individual in subsequent rounds. The CAGT algorithm stops once the potency of the LIs in each set is identified.

Algorithm 1. Solve the optimization problem in Equation (1) using the CAGT algorithm.

Inputs: The set of candidate LIs (LI). The low and high thresholds (l and h) that bound the number of potent LIs.
Outputs: The set of impotent LIs V_0 and potent LIs V_1 identified by the algorithm.

$V_0 \leftarrow \{\}$; $V_1 \leftarrow \{\}$
$model \leftarrow CAGTModel(LI,\ l,\ h)$
do:
  $R_i \leftarrow model.nextround()$ `//step1`
  $r_i \leftarrow getpotency(R_i)$ `//step2`
  $(V_0, V_1) \leftarrow model.f(R_i,\ r_i)$ `//step3`
while $|LI \setminus V_0 \setminus V_1| > 0$
return (V_0, V_1)

ALO module-1 (build the CAGT catalog). In the first module, we build the CAGT catalog which is a lookup table that the step1 of Algorithm 1 relies on. This lookup table determines the tuple (s, w) for a given tuple $(n,\ l,\ h)$ where w is the maximum number of rounds that the CAGT algorithm needs for identifying the potencies of n LIs when there are between l and h potent LIs amongst them. The value of s, determines the number of LIs to be used in the first round of Algorithm 1 in order to achieve w for the given $(n,\ l,\ h)$ tuple. A dynamic programming strategy is used for building the CAGT catalog based on the fact that in each round of Algorithm 1, the $CAGTModel$ gets updated and existing LI subsets within the model are split into smaller subsets. Therefore, in this module, we populate the catalog starting from tuples with $n = 1$ for which the optimal (s, w) are known, and iteratively populate the catalog by tuples with larger n values given the catalog itself. See Supplementary Information Section S2.1 for further details.

ALO module-2 (create optimal LI sets). In this module, we use the LI potency probabilities (estimated a priori) to create an optimal LI partition (ie, disjoint LI sets), such that the expected total number of rounds needed for identifying LI potencies is minimized while the maximum total number of rounds is kept at bay. This is done by: (1) ordering the LIs by their potency probabilities, (2) estimating "h" for a given LI set, from the corresponding potency probabilities, the Poisson binomial distribution, and a confidence threshold t, (3) using the CAGT catalog to determine "w" for a given set of LIs with their estimated "h," and (4) allowing "ex" more rounds compared to the maximum total rounds needed, for decreasing the expected total rounds needed by introducing rounds that involve all LIs in a set. This module, as described in Supplementary Information Section S2.2, provides the disjoint LI sets for separate runs of Algorithm 1 in Module-3, and identifies the disjoint LI sets that their associated run should start with all LIs in the set.

ALO module-3 (follow CAGT rounds for LI sets). Lastly for each individual, we perform independent runs of the Algorithm 1 where in each run a disjoint set of LIs (determined by Module-2) is used leading into identification of LI potencies after all runs are completed. See Supplementary Information Section S2.3 for further details.

Evaluation

Datasets

In our evaluations, we relied on synthetic data for robustness and sensitivity analysis, and on real data for food intolerance and allergy identification applications.

Synthetic data. We initiated the data generation from 3 sets of LI potency probabilities each with 50 values that follow beta distributions with 3 different shapes (Dataset-1: $\alpha = 0.5$, $\beta = 5.0$, Dataset-2: $\alpha = 2.0$, $\beta = 6.0$, and Dataset-3: $\alpha = 0.1$, $\beta = 0.1$). Next, we generated 200 values for each LI potency probability of the prior step following Bernoulli distributions parametrized by each probability value. This provided us with 3 datasets that each consists of a 200×50 matrix that represent the LI potencies for 200 individuals, along with the set of LI potency probabilities that were used to generate each. Finally, for each set of LI potency probabilities in a dataset, we generated 9 sets of noisy LI potency probabilities by adding different levels of white noise with standard deviation (SD) values that ranged from 0.05 to 0.5. These noisy LI potency probabilities were clamped in the 0–1 range (ie, set to 0 if less than 0, and set to 1 if greater than 1).

Real data. We defined 2 sets of LIs, one for management of food intolerances in IBS and another for management of allergic food reactions. In both LI sets, an LI corresponds to the elimination of a particular food from the patient's diet, and the LI's potency probability corresponds to the fraction of individuals in which a given food triggers adverse symptoms. First, we extracted the LIs and their potency probabilities from published studies of IBS[28] and food allergies[29] separately. Second, we used the Poisson distribution parametrized by the average number of potent LIs from each study (reported as 7 in the IBS study and estimated as 1.43 for the food allergy study given their reported statistics), in order to generate 1000 integers for each study, where each integer corresponds to the number potent LIs in a given individual. Finally, we randomly assigned individual potency values (0|1) for the LIs in each patient given the number of potent LIs in each, and the potency probability of each LI that was extracted from the corresponding study. This provided us with an IBS dataset with 56 LIs, and a food allergy dataset with 19 LIs, each with the corresponding potency probabilities, and 1000 LI potency profiles that adhere to the reported summary statistics.

Evaluation metrics

We used the average and median number of rounds needed for identifying the LI potencies of individuals for our method evaluations. For each dataset, we first identified the optimal hyperparameters using grid search on half of the dataset, then performed our evaluations on the remaining records. In each case, a maximum of 50 pair of hyperparameter values were examined for ex and t in the ALO method, while for the spatial inference vertex cover (SPIV) method, a maximum of hundred hyperparameter value pairs were examined for its epsilon, and t parameters including the default parameter values.

RESULTS

Robustness and sensitivity analysis

We generated 3 datasets with various levels of homogeneity (Figure 2A, D, and G), for evaluating the sensitivity of each method to the number of LIs (Figure 2B, E, and H), and to the noise in LI potency probabilities (Figure 2C, F, and I). In all cases the average rounds needed for identifying the LI potencies increased linearly while the ALO method had the lowest increase, followed by SPIV, and the baseline (Figure 2B, E, and H). The largest reduction in average rounds needed for ALO compared to the baseline was observed for Dataset-1 and Dataset-3 in which a large portion of LIs have low potency probabilities (Figure 2B and E). This reduction was much lower for Dataset-2 in which a lower proportion of LIs have low potency probabilities (Figure 2E). The addition of white noise to LI potency probabilities increased the average rounds needed by each method (see Figure 2C, F, and I, where methods were evaluated on all 50 LIs while white noise with varying SDs were added to the LI potency probabilities). For example, white noise with SD of 0.5 increased the average rounds needed in Dataset-1 by ALO from 18.2 to 26.5 (45.6%), and by SPIV from 26.9 to 34.7 (29.0%) (Figure 2C). Based on our simulations, 32% is a maximum threshold for individual LI potency probabilities after which the expected number of rounds following ALO is not better than the baseline. In other words, ALO would not be recommended if individual LI potency probabilities are above 32%.

Rapid food intolerance and allergy identification with ALO

The gold standard method used in the clinic for identifying foods that cause intolerance or allergic reactions, is the SED during which food challenges are performed. A food challenge is a LI during which target health symptoms are monitored while a given food item is introduced to the individual's diet for 3 days, then subsequently removed from the diet for another 3 days (the number of days may vary). We compared ALO with SED as well as a state of the art group testing method called SPIV[30] for identification of food intolerances and food allergies as described next.

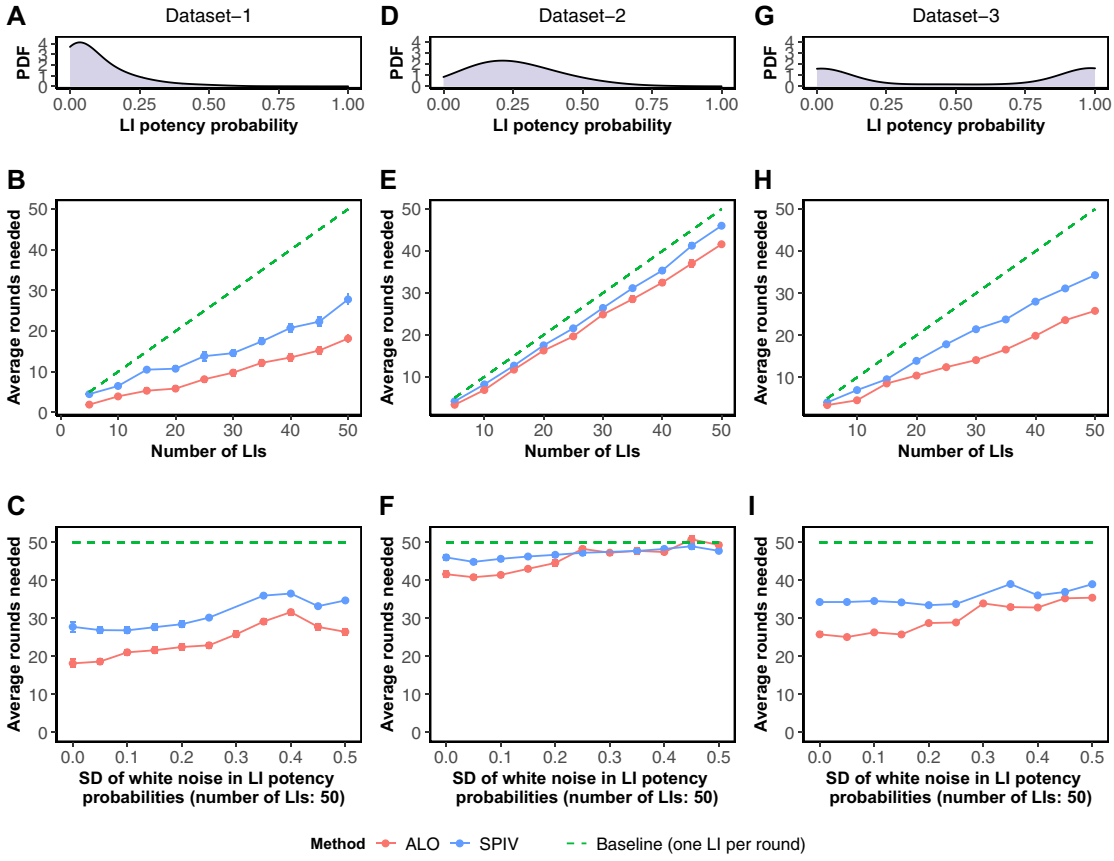

Figure 2. Robustness and sensitivity analysis. Three synthetic datasets of potency probabilities relating to 50 LIs were sampled independently from heterogeneous beta distributions A, D, and G as visualized using their probability density function (PDF), and subsequently used to generate synthetic Datasets 1–3 each representing the LI potencies (0|1) for a 100 individuals. B, E, and H (relating to Datasets 1–3) illustrate the average number of rounds needed by each method to identify the potent LIs in 100 individuals for LI subsets having 5–50 LIs each. C, F, and I (relating to Datasets 1–3) illustrate the method's robustness to the standard deviation (SD) of the added white noise that was added to LI potency probabilities. The error bars represent the standard error.

Food intolerance in IBS case study

IBS is a chronic gastrointestinal disease with 11% prevalence in adults.[31] One of the most effective symptom management strategies of IBS is to identify their food intolerances (ie, food items that exacerbate IBS symptoms such as bloating, constipation, diarrhea, and abdominal pain) and eliminate them from the patient's diet. We used ALO for discovery of food intolerances based on realistic synthetic data of 500 IBS patients given self-reported intolerance statistics of 56 food items[28] and compared the performance of ALO with the SED involving a constant 56 of LI rounds. The results are shown in Figure 3A, where ALO reduced the median number of LI rounds by 58.9% (33/56), while the SPIV method reduced the number of LI rounds by 32.1% (18/56). Our results suggest that both ALO and SPIV can replace the SED method in the clinic, however our novel ALO method showed 26.8% advantage compared to the SPIV.

Food allergy case study

Food allergy is an immune response from food exposure, and has a prevalence between 5.3% and 9.1% in the United States' adults.[29] Food allergy can be managed by strict avoidance of trigger foods that can be identified using SED. We simulated ALO for food trigger identification based on realistic synthetic data from 500 individuals given medical doctor diagnosed food trigger statistics of 19 foods,[29] and compared the performance of ALO with SED and SPIV. The results are illustrated in Figure 3B, where ALO reduced the median number of LI rounds by 68.4% (13/19), while the SPIV method resulted in 52.6% (10/19) reduction compared to SED. Both ALO and SPIV showed considerable performance advantage over SED while ALO method was 15.8% more efficient than SPIV.

DISCUSSION

We developed ALO for rapid identification of LIs that a given individual needs for achieving a target health goal such as a symptom-free digestive state. ALO relies on estimated LI potency probabilities that can come from population wide studies that report the percentage of population in which a given LI is potent for achieving the target health goal. ALO uses a group testing method that we have developed called CAGT for identifying the group of LIs that a given individual needs to include in their lifestyle in each round, given their health state (0|1) in response to LI groups followed in prior rounds, as well as the minimum and maximum number of potent LIs in the set of candidate LIs. ALO shines where most of the candidate interventions are impotent for most people, and the existing diagnostic tools cannot pinpoint the potent interventions amongst them accurately. In such cases, simultaneous evaluation of multiple LIs together at a time (as done by ALO) can rule out the impotent LIs rapidly.

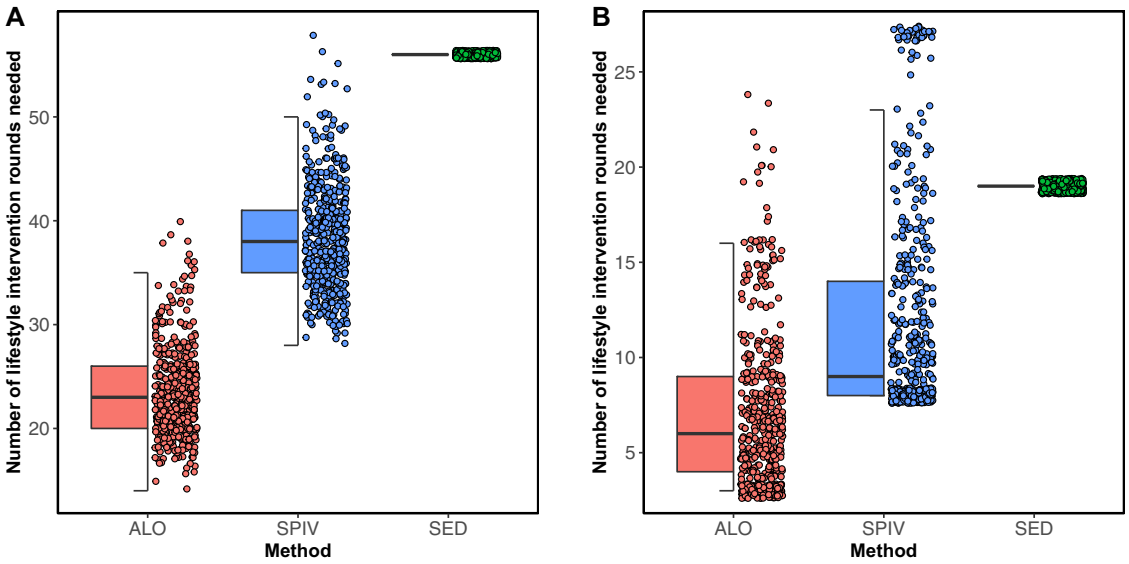

Figure 3. Rapid IBS food intolerance and allergy identification. Various methods were used for discovery of food intolerances in IBS and food allergies (A and B). (A) ALO and SPIV methods lead into 58.9% and 32.1% reduction in median number of lifestyle intervention (LI) rounds needed compared to SED, for discovering the foods that exacerbate IBS symptoms amongst 56 foods in 500 IBS patients. (B) The median number of LI rounds needed compared to SED was reduced by 68.4% using ALO, and by 52.6% using SPIV, for identifying the foods that trigger allergies amongst 19 foods in 500 patients.

Given that ALO is 58% faster than the best standard of practice for identification of 56 food intolerances in IBS, its adoption will mean that patients can know their food intolerances for management of IBS symptoms within 5 months vs. 12 months (considering 3 days of intervention and 3 days of washout for each round). This improvement grows to 68% for identification of food allergies. Such major improvements can have financial and life-changing benefits for patients and the healthcare system, determining the mere feasibility of dietary management of food intolerances and allergies in patients.[32,33] Average self-reported dietary adherence levels can drop by about 50% in a course of 12 months,[34] indicating the that time is of essence in personalized dietary treatments. The performance of ALO can be enhanced further when better estimations of LI potency probabilities are available through biomarker tests such as food allergy testing kits that are commonly used for eosinophilic esophagitis,[35] allergic rhinitis,[36] and asthma.[37]

Certain nutritional supplementations including B, C, and D vitamins, magnesium, folate, zinc, omega-3 fatty acids, probiotics, as well as physical activity, yoga, assisted sleep, and decreased screen time are amongst candidate LIs for management of chronic anxiety and depression.[38–40] ALO can be used to identify the potent LIs for a given individual amongst the candidate LIs.

We speculate that in the future, the potent LIs for an individual will be determined in 2 main steps. In step1, diagnostics tools such as blood assays or stool tests would be used for estimating the LI potency probabilities for a given individual. In step2, an algorithmic approach such as ALO would be used to determine the potency (0 or 1) of each LI. Potential extensions to ALO includes: (1) updating the estimated LI potencies based on the data and individual's responses in each round, (2) considering the potential constrains and interactions between LIs such as food interactions and nutritional limitations in the algorithm.

Machine learning (ML) approaches have shown considerable promise in precision nutrition and medicine.[41] Several ML models have been developed to predict individuals' cardiovascular and digestive health metrics in response to different dietary choices based on personal features such as genetic and gut microbiome biomarkers.[10,42,43] Despite their promise, such ML models typically come with 2 limitations. First, they rely on precise biomarker data that may not be readily available.[44–46] Second, they do not provide a recourse in cases where an individual's response to a given LI cannot be predicted accurately.[47] ALO is complementary to ML approaches and can be used when either accurate biomarker data is unavailable, or the ML models are not accurate.

Future research should focus on evaluating group testing methods such as ALO in practice for personalized LI, in order to improve the efficiency of existing methods such as SED and N-of-1 trials and identify application specific considerations that need to be made in the group testing method to minimize the associated risks and maximize its practical efficiency. We anticipate that future algorithmic improvements using active ML, and optimal experimental design that are shown to speedup biological discoveries,[48] will lead into further performance improvements, and guide us into a new era of personalized nutrition.

Limitations

The LI potency probabilities can vary in different populations, which can lead to algorithmic bias. Although ALO is resilient to errors in the estimated LI potency probabilities (see Figure 3C, F, and I), it achieves its best performance when such errors are low. Therefore, it is important to monitor and calibrate the LI potency probabilities, particularly for groups that are underreported in research.

The performance of ALO is highly dependent on whether the patient adheres to the suggested LIs in each around, and whether their responses are recorded accurately. Methods such as 24-h recall interviews or smart-phone food journaling and reminders should be used to maximize accuracy. This is particularly vital and potentially challenging in ALO since the recommended LIs in each round depend on the patient's prior responses and unknown in advance.

ALO is particularly vulnerable if LIs that are followed in the same round interact to cancel out the impact of each other. Such

interacting pairs of LIs should be determined beforehand and not used together in the same round.

CONCLUSION

The speed of trial-and-error approaches such as SED that are used for discovery of personalized LIs can be improved substantially using the proposed ALO method. ALO potential applications include rapid discovery of food intolerance and food allergies. We note some of the limitations of the current implementation, with the application of ALO being limited to cases where a binary health score can be identified, and the candidate LIs are noninteracting such that: (1) a potent LI remains effective when combined with other LIs, and (2) an impotent LI remains ineffective when combined with other impotent LIs.

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AUTHOR CONTRIBUTIONS

AE and IT conceived the project, designed the ALO algorithm, and wrote the manuscript. AE implemented the algorithm, performed all computational analysis, and generated the figures. IT supervised all aspects of the project.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

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