LEARNING & OUTCOMES FROM OUR FIRST DIGITAL THERAPEUTIC PILOT

MARK BERMAN, MD FACLM

Lifestyle as medicine. It's the *how* that's hard.

For decades we have known that a small number of lifestyle changes can have a big impact in preventing, treating and in some cases even reversing common chronic diseases.[1-4] The what - like a dietary pattern with an abundance of fruits, vegetables, whole grains, legumes, nut and seeds, regular exercise and not smoking - has been established, but the how has remained elusive. *How* do we apply what we know in a cost-effective, scalable and widely accessible manner to fight disease and enable healthier, more vibrant living?

At FareWell, our answer to the *how* is to pioneer novel digital therapeutics targeting lifestyle-related cardiometabolic diseases. In the long run, we believe we can create a new class of therapies at lower cost to existing ones, with equal or greater effectiveness and considerably fewer side-effects. It is an ambitious aim but to be fair, we are standing on the shoulders of giants -- not just those who pioneered the use of lifestyle as medicine and behavioral science but also those who developed the social networks and high-powered computing that enables a new platform for the delivery of lifestyle medicine.

Last year, we built a rudimentary version of our first therapeutic and studied it in a real-world implementation. Our goal was to assess user engagement and demonstrate efficacy in weight loss. Target weight loss at 16 weeks was 5% of initial body weight, a clinically meaningful threshold known to impart reductions in cardiometabolic risk factors.

Our first pilot study

We recruited participants online for a pragmatic, non-randomized pilot study. Then we preferentially screened for women, in any US state, aged 45-54, with a BMI of 30-35 kg/m2 (i.e. Class 1 Obesity), who also reported a willingness to prepare meals at home and eat mostly whole, plant-based foods.

We offered each participant who volunteered a 16 week intervention, comprised of an early version of our digital therapeutic. It included meal planning tools, smart shopping lists, recipes curated by a physician, dietitian and chef-educator, a daily self-monitoring feature with variable weekly goals, and a short weekly curriculum delivered by email. Each participant received a free digital scale that automatically logged weights on a simple dashboard, accessible by both participant and their health coach.

Each participant was randomly assigned to work with a health coach; a physician-led lifestyle medicine team provided oversight and support of the coaches. Coaching calls were scheduled every two weeks at the participant's convenience. Health coaching provided participants behavioral support while also enabling a degree of personalization or, as our coaches would say, "meeting our participants where they are at..."

The principle aim of the intervention was to achieve, in those that engaged, clinically meaningful weight loss in a manner consistent with long-lived lifestyle changes and long-term improvements in health and vitality. Our hypothesis is that facilitating lasting lifestyle change requires the development of a core skill set in a manner that is meaningful to that individual and fosters a growth-oriented mindset. Internally, we describe this skill set as culinary health literacy ("CHL") and use that term to be inclusive of specific components of food literacy, health literacy and behavioral skills like planning and self-monitoring. Our program is intended to enable a basic proficiency in CHL.

The nutritional features and exercise recommendations were all derived from evidenced-based interventions and findings.[1-8] Additionally, we incorporated key principles established by our advisory board. For instance, Dr. David Eisenberg's work has demonstrated the importance of meals prepared at home[9] and the mandate for teaching kitchens. Dr. David Katz has studied and written extensively on the need for skillpower and the power of lifestyle *as* medicine.[6] Margaret Moore pioneered the field of health coaching, and Master Chef Mark Erickson and the Culinary Institute of America are international leaders in culinary education.

Here's what we found

Baseline characteristics

We defined "starters" (n=95) as participants who completed two or more coaching calls and at least one digital engagement (e.g. logging a daily target) in four weeks. Of our 95 participants, 94 were female with an average age of 51 (range of 45.6 - 55.1 years old). Average starting BMI was 32.8 kg/m^2 (range of 25.9 - 38.4 kg/m^2). **Our participants came from 37 different US states,** demonstrating one compelling feature of digital interventions -- reach.

Retention

We defined "completers" (n=71) as participants who had at least 2 digital engagements in week 16 of the Program. **Therefore, our retention rate was 74.7%.**

Weight loss

Weight loss among completers was **5.1%** and, in those in the top tertile of engagement (i.e. recorded digital events) was **7.1%.**

WEIGHT LOSS IN COMPLETERS & HIGHEST ENGAGERS

	Completers (n = 71)	Top Tertile of Engagement (n = 24)
average % weight change	- 5.1%	- 7.1%
average weight change	- 10.1 lbs	- 13.6 lbs
average BMI change	- 1.57 kg/m^2	- 2.32 kg/m^2
% achieving 5% body weight lost or more	47.9%	70.8%
% achieving 7.5% body weight lost of more	28.2%	50.0%

Source: Mark Berman, MD FACLM / www.farewell.io

farewell

These results are consistent with those found in published lifestyle medicine interventions using in-person programs[1,2] and were achieved without prescribing caloric deficits or calorie counting.

Physical Activity

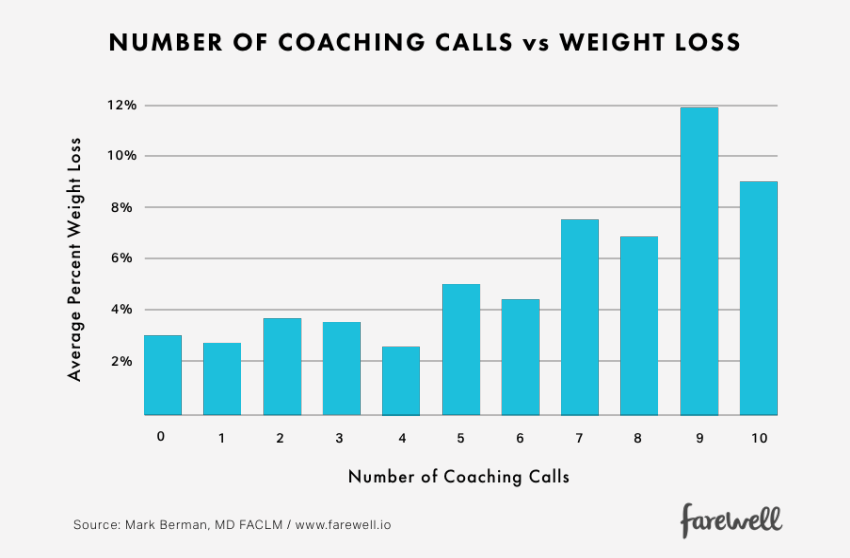
Average frequency of physical activity was logged as 4 times per week for completers. Physical activity was logged by self-report as a daily target. By default, the program set a goal of 20 minutes per day of moderately-intense activity as a goal for the first four weeks, increasing to a minimum of 30 minutes per day in week five. Participants logged whether they met or did not meet this minimum.

What else did we learn?

Engagement is predictive of success.

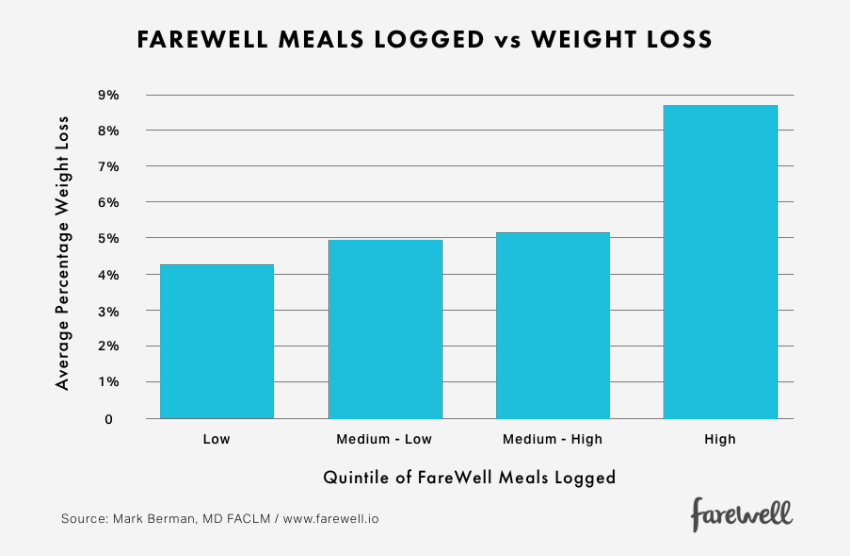
We hypothesized that participants who engaged more with our program would do better. Many explanations could account for this: it could be because the program facilitates behavior change (but only if a person engages); it could also be because those who are doing well, or feel more capable, stay engaged and engage more often. Either way, we discovered that we can clearly see this engagement response in our data. Here are some examples in our completers. Since our definition of completer mandates a continued minimal engagement at 16 weeks, this decreases the likelihood that the weight change was due to a greater ability to observe those who are more engaged.

Example 1: Coaching Calls



We see a strong relationship between participation in health coaching and weight loss.

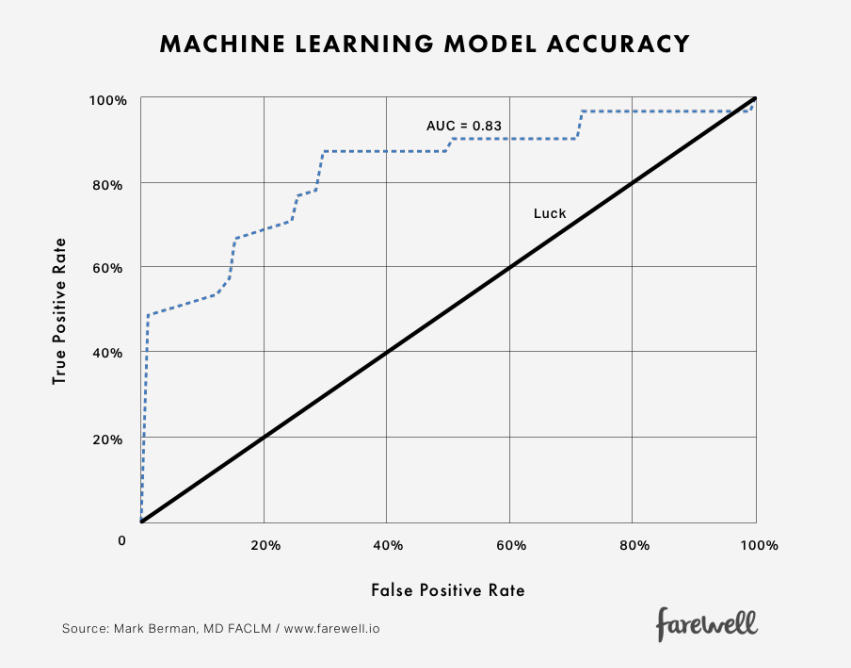
Example 2: FareWell Meals Logged



While both activity and dietary pattern impact weight, the consensus is that dietary pattern is a more powerful variable in today's environment.[10,11] Thus, we anticipate that measures reflecting changes in dietary pattern correlate with weight change. The data show that those who reported assembling the most FareWell meals had the greatest change in weight.

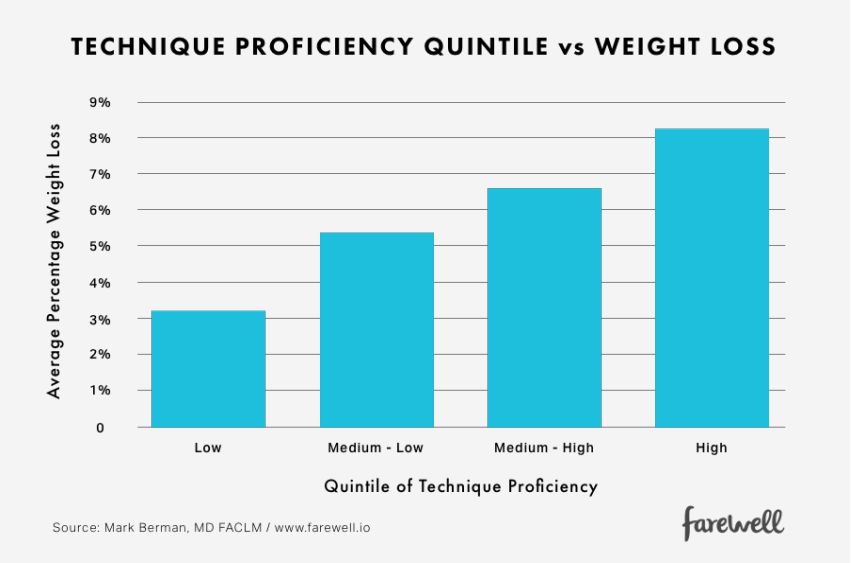
Machine learning offers predictive power

There will always be a distribution of outcomes in any given population receiving the same intervention. While it's important to understand the average impact, it's even more important to be able to predict who will be the most and least positively impacted. In our first foray into the world of machine learning, we examined the predictive power of each core feature in our product. We learned that all features showed some meaningful predictive power, but some more than others, and that our machine learning model could predict our main outcome with sufficient accuracy.



Skillpower also predicts weight loss

Informed by our advisors at the Harvard School of Public Health and the Culinary Institute of America, we created a technique-driven framework for categorizing meals by type and then loosely ordered their appearance in a given week's meal plan based on an estimated level of difficulty. In turn, when members logged meals they made, we could quantify which categories were made and how often. We chose an estimate of proficiency as making a given meal-type at least 7 times. Below we summarize change in weight based on quintile of categories made 7 or more times.



This finding supports our hypothesis that progressive repetition of core techniques (a method for gaining proficiency) is associated with a dietary pattern shift that affords progressive weight loss.

This relationship persists if we normalize this data by number of meals made. We can also use machine learning to see if a better threshold of proficiency can be made. As it turned out, 7 was was within the range discovered by our model.

Laboratory findings generate hypotheses

Weight loss alone is well established as a mediator of metabolic improvements in those who are overweight or obese. Similarly, healthy lifestyle changes can also mediate improvements that are independent of weight change. Therefore, to understand the full impact of a digital lifestyle therapeutic it's important to study other markers of cardiometabolic health. In parallel with this pilot, we began collecting laboratory data to inform our future studies.

Pilot participants in our last three enrolled cohorts were invited to participate in a laboratory study of before and after program labs. We screened participants who expressed interest to decrease likelihood of confounding factors, e.g. recent medication adjustments, and offered follow-up labs to those who had baseline metabolic abnormalities and completed the 16 week program.

At present, we have a small sample of before-after labs and our findings are consistent with those found in the plant-based nutrition and lifestyle medicine literature.[2,12] For example, among 7 participants with impaired glycemic responses at baseline, all 7 showed improvement in a1c (5 participants, with 3 returning to normal) or insulin sensitivity (7 participants) at 16 weeks. Glycemic measures assessed include fasting blood glucose and insulin, hemoglobin A1c, and calculated HOMA2 measures of beta-cell function and insulin sensitivity.

Ongoing data collection and future studies will enable us to determine the consistency of these findings.

Outliers and Anecdotal learnings

In clinical research, the average is a helpful statistic, especially when it comes to evaluating cost-efficacy or comparative effectiveness. However, it is the range that tells more of the full story, especially when paired with qualitative learnings on the human experience. A member of our team, usually a health coach, had contact with

every member that completed the program - this means that on a daily basis our team received anonymized feedback about the human experience of participating in our program. While we have not done a formal qualitative analysis of that data, two clear themes emerged:

The process of health coaching regularly provokes surprising insights in members that they consider to be transformative.

I've written elsewhere about the distinction between dieting and lifestyle change. Dieting involves no real transformation. It is a temporary obsessive state characterized by following a strict (and often arbitrary) set of dietary and exercise rules, routinely followed by a return to default patterns of behavior that inspired the dieting in the first place. Lifestyle change is something different. One characteristic of lifestyle change is the generation of insights. A well-structured coaching process repeatedly produces these insights. However, the nature of the insights is often experienced as surprising to both coach and member. This is rather delightful to observe. And I'd venture to say it's one of the most inspiring parts of working with people in this way.

Our approach to facilitating lifestyle change is different than what members have previously experienced.

For the vast majority of our members, this is not their first attempt to lose weight and improve their health. Most have tried countless fad diets and commercial weight loss programs. While we did our best to communicate what our program was all about, we often received feedback that members expected a small variation of programs they've done many times over -- count your calories, shrink your portions, do vigorous exercise 3x a week, etc. They were surprised that there was a different way to approach the same problem.

What's next?

This is just a beginning for us. The year ahead offers us the opportunity to apply the learnings from our pilot and gather more robust data.

More specifically, we intend to gather data from a broader demographic and attempt to reproduce our results with a more complete version of our product. While a focus on weight loss and health promotion was a natural starting point, our real interest lies in the management of lifestyle related chronic disease and to that end, we are beginning trials in people with more advanced metabolic disease.

Finally, we know there is more potential in digital therapeutics beyond a scalable operational method for lifestyle interventions. The application of machine learning and AI allows us to explore uncharted territories in lifestyle medicine and population health. In the year ahead, we will further develop our machine learning models and continue our journey from predictive to prescriptive analytics.

Final Thoughts

We've completed our first pilot trial and in doing so established a methodology for capturing and analysing data that will enable us evolve our digital therapeutics. While we are encouraged by our early results and inspired by the journey we've shared with our members to date, we also know there is much work ahead. One of the biggest mistakes a healthcare start-up can make is to underestimate the power of the disease-causing environment it sets out to address. It is not a simple matter to transform lives in a way that makes them resilient to this so-called toxic environment. But doing so mandates a belief that we can change the way people experience life for the better and can use data to continuously evaluate how well we are achieving our collective objectives.

REFERENCES

1. Ornish, D., Scherwitz, L.W., Billings, J.H., Gould, K.L., Merritt, T.A., Sparler, S., Armstrong, W.T., Ports, T.A., Kirkeeide, R.L., Hogeboom, C. and Brand, R.J., 1998. Intensive lifestyle changes for reversal of coronary heart disease. *Jama, 280*(23), pp.2001-2007.

2. Barnard, N.D., Cohen, J., Jenkins, D.J., Turner-McGrievy, G., Gloede, L., Jaster, B., Seidl, K., Green, A.A. and Talpers, S., 2006. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes care, 29*(8), pp. 1777-1783.

3. Jenkins, D.J., Kendall, C.W., Marchie, A., Faulkner, D.A., Wong, J.M., de Souza, R., Emam, A., Parker, T.L., Vidgen, E., Lapsley, K.G. and Trautwein, E.A., 2003. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *Jama, 290*(4), pp.502-510.

4. Ornish, D., Lin, J., Chan, J.M., Epel, E., Kemp, C., Weidner, G., Marlin, R., Frenda, S.J., Magbanua, M.J.M., Daubenmier, J. and Estay, I., 2013. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *The lancet oncology, 14*(11), pp.1112-1120.

5. Office of Disease Prevention and Health Promotion. 2008 Physical Activity Guidelines for Americans. *U.S. Department of Health and Human Services.* Available at https://health.gov/paguidelines/guidelines/summary.aspx

6. Katz, D.L. and Colino, S., 2013. Disease-proof: the remarkable truth about what makes us well.

7. Loef, M. and Walach, H., 2012. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. *Preventive medicine, 55*(3), pp.163-170.

8. Butryn, M.L., Webb, V. and Wadden, T.A., 2011. Behavioral treatment of obesity. *The Psychiatric clinics of North America, 34*(4), p.841.

9. Zong, G., Eisenberg, D.M., Hu, F.B. and Sun, Q., 2016. Consumption of Meals Prepared at Home and Risk of Type 2 Diabetes: An Analysis of Two Prospective Cohort Studies. *PLoS Med, 13*(7), p.e1002052.

10. Verheggen, R.J.H.M., Maessen, M.F.H., Green, D.J., Hermus, A.R.M.M., Hopman, M.T.E. and Thijssen, D.H.T., 2016. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. *Obesity Reviews, 17*(8), pp. 664-690.

11. Dugas, L.R., Harders, R., Merrill, S., Ebersole, K., Shoham, D.A., Rush, E.C., Assah, F.K., Forrester, T., Durazo-Arvizu, R.A. and Luke, A., 2010. Energy expenditure in adults living in developing compared with industrialized countries: a meta-analysis of doubly labeled water studies. *The American journal of clinical nutrition*, pp.ajcn-007278.

12. Trapp, C., Barnard, N. and Katcher, H., 2010. A Plant-Based Diet for Type 2 Diabetes Scientific Support and Practical Strategies. *The Diabetes Educator, 36*(1), pp.33-48.