Editorial

See corresponding article on page 449.

Predicting therapeutic weight loss[1,2]

Nicholas Finer

Although personalized medicine is now well established in fields such as oncology, most therapeutics, including obesity treatment, still rely on starting a treatment and then evaluating the individual's response (e.g., weight loss or decrease in blood pressure or blood glucose) to make a decision about the benefit, risk, or cost-efficacy of continued intervention. In the case of weight-loss treatment, the biological response of a decrease in body mass shows marked variability and is usually slow or gradual. Thus, this requires prolonged exposure to establish therapeutic efficacy and to allow a decision to continue or switch to an alternative, potentially better, treatment. In trials, the use of mean weight loss as an outcome may mask or conflate "responder" and "nonresponder" populations, thus underestimating benefit in a responsive population. Categorical weight-loss endpoints (e.g., a 5% or 10% loss at 1 y) are increasingly used as a more practical way of defining efficacy and are now required by regulatory authorities (1, 2). Such data can be converted into a "number needed to treat" and can serve to ease the perpetual problem of how, statistically, to deal with patients who drop out of treatment. Developing tools to predict weight-loss responders, or nonresponders, can clearly provide clinical benefit. Knowledge of response-determining markers may also increase understanding of underlying biological mechanisms involved in the pathophysiology of overweight and obesity.

In this issue of the Journal, Thomas et al. (3) have derived various regression models for weight loss, based on age, sex, initial weight, energy intake, and month-by-month measured vs. predicted loss in participants in the POUNDS Lost (Preventing Obesity Using Novel Dietary Strategies) study. This study was predominantly a "heart-healthy" dietary intervention. Receiver operating characteristic curve (ROC) analyses were then used to evaluate which model best predicted a 5% loss at 1 y. A very similar approach was used to explore predictors of weight loss in participants with diabetes in the Look AHEAD (Action for Health in Diabetes) trial (4). The ROC, which was first developed during World War II for distinguishing false-positive radar signals of flocks of birds from German airplanes, has since been applied to many other fields, including medicine. The technique plots the true-positive rate against the false-positive rate at various threshold settings, and the area under the ROC curve quantifies the overall ability of a "test" to discriminate between individuals with a disease and those without the disease or, in this case, weight-loss responders and nonresponders. The first published use of ROC analysis for defining weight-loss response was related to the use of now-withdrawn sibutramine (5) and has been used widely for other antiobesity pharmacotherapy to drive "stopping rules," which enhance the estimation of cost-efficacy (6). Thus, the newly approved antiobesity drugs phentermine/extended-release topiramate (7), lorcaserin (8), and naltrexone/bupropion (9) have all been approved with explicit stopping rules based on responder analyses. The use of ROC curves with weight loss as both the response and outcome variable is of course statistically flawed. Taken ad absurdum, it is clear that the weight lost at 364 d is likely to be the best predictor of loss at 1 y. Both Thomas et al. (3) and Unick et al. (4) have advanced this field of prediction by applying ROC analysis to more complex derived models using additional phenotype and response variables (age, sex, ethnicity, and initial loss) that outperformed analyses based solely on percentage of weight loss.

So how useful are these predictive techniques? Although both the POUNDS Lost intervention and Look AHEAD identified early weight loss as a predictor for loss at 1 y, the sensitivity and specificity were far from precise. Would one withdraw treatment after 2 mo in a "nonresponder," or is the value in identifying patients who may need intensified support? The predictive algorithms are complex and would require desktop or other "apps" to be provided. Both studies were selective in their inclusion and exclusion criteria, so the data generated are unlikely to be generalizable to other populations, ethnicities, or cultures.

Would genetics-based prediction be better? Although numerous genes have been identified through genome-wide association studies that are associated, either directly or indirectly, with the regulation of body weight, they account for a small part of the incidence of overweight or obesity or variance between individuals (10). Two studies explored gene-diet interactions in relation to weight loss: the Nutrient-Gene Interactions in Human Obesity (11) and the DIOGENES (Diet, Obesity, and Genes) trial (12), which focused on weight-loss maintenance. Both studies found that single nucleotide polymorphisms (SNPs) of the transcription factor AP-2 β (activating enhancer binding protein 2 β) (*TFAP2B*) gene, encoding a transcription factor that is mainly expressed in adipose tissue, showed statistically significant, but clinically small interaction effects with response to different

[1] From the National Centre for Cardiovascular Prevention and Outcomes, UCL Institute of Cardiovascular Science, London, UK.

[2] Address correspondence to N Finer, National Centre for Cardiovascular Prevention and Outcomes, UCL Institute of Cardiovascular Science, 170 Tottenham Court Road, London, UK W1T 7HA. E-mail: n.finer@ucl.ac.uk.

First published online January 28, 2015; doi: 10.3945/ajcn.114.106195.

macronutrient diets. Recently, Whole Genome Prediction (a statistical method incorporating thousands of SNPs into a regression model to yield estimates for the contribution of all markers to the overall variance in a particular phenotype) has been applied to weight-loss surgery in a simulation of remission of type 2 diabetes (13). The authors suggested that treating only those patients predicted to lose at least 80% of their excess body weight would prevent 41 more future cases of type 2 diabetes compared with not using the tool and treating everyone. Pharmacogenomics in the field of obesity is poorly developed, in part because there has been a dearth of pharmacologic agents. However, several SNPs influenced weight-loss response to sibutramine. Thus, those patients who were homozygous for a C for T substitution of the guanine nucleotide binding protein (G protein), β polypeptide 3 (*GNB3*) gene (encoding the Gb3 subunit of heterotrimeric G proteins) lost only half the weight of those with at least one T allele (14).

It would seem that in the field of therapeutic weight loss, prediction remains in its infancy and the Danish aphorism "Prediction is very difficult, especially if it's about the future" (15) holds true.

The author reported no conflicts of interest in relation to this editorial.

REFERENCES

1. US Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research. Guidance for industry developing products for weight management. February 2007 [cited 2015 Jan 10]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071612.pdf.
2. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on clinical evaluation of medicinal products used 14 in weight control [cited 2015 Jan 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170278.pdf.
3. Thomas DM, Ivanescu AE, Martin CK, Heymsfield SB, Marshall K, Bodrato VE, Williamson DA, Anton SD, Sacks FM, Ryan D, et al. Predicting successful long-term weight loss from short-term weight-loss outcomes: new insights from a dynamic energy balance model (the POUNDS Lost study). Am J Clin Nutr 2015;101:449–54.
4. Unick JL, Hogan PE, Neiberg RH, Cheskin LJ, Dutton GR, Evans-Hudnall G, Jeffery R, Kitabchi AE, Nelson JA, Pi-Sunyer FX, et al; Look AHEAD Research Group. Evaluation of early weight loss thresholds for identifying nonresponders to an intensive lifestyle intervention. Obesity (Silver Spring) 2014;22:1608–16.
5. Finer N, Ryan DH, Renz CL, Hewkin AC. Prediction of response to sibutramine therapy in obese non-diabetic and diabetic patients. Diabetes Obes Metab 2006;8:206–13.
6. Neovius M, Narbro K. Cost-effectiveness of pharmacological anti-obesity treatments: a systematic review. Int J Obes (Lond) 2008;32:1752–63.
7. MedLine Plus. Phentermine and topiramate [cited 2015 Jan 10]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a612037.html.
8. MedLine Plus. Lorcaserin [cited 2015 Jan 10]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a613014.html.
9. European Medicines Agency. Mysimba recommended for approval in weight management in adults [press release; cited 2015 Jan 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/12/WC500179334.pdf.
10. Blakemore AI, Froguel P. Investigation of Mendelian forms of obesity holds out the prospect of personalized medicine. Ann N Y Acad Sci 2010;1214:180–9.
11. Stocks T, Angquist L, Banasik K, Harder MN, Taylor MA, Hager J, Arner P, Oppert JM, Martinez JA, Polak J, et al. TFAP2B influences the effect of dietary fat on weight loss under energy restriction. PLoS ONE 2012;7:e43212.
12. Stocks T, Ängquist L, Hager J, Charon C, Holst C, Martinez JA, Saris WH, Astrup A, Sørensen TI, Larsen LH. TFAP2B -dietary protein and glycemic index interactions and weight maintenance after weight loss in the DiOGenes trial. Hum Hered 2013;75:213–9.
13. Dhurandhar EJ, Vazquez AI, Argyropoulos GA, Allison DB. Even modest prediction accuracy of genomic models can have large clinical utility. Front Genet 2014;5:417.
14. O'Connor A, Swick AG. Interface between pharmacotherapy and genes in human obesity. Hum Hered 2013;75:116–26.
15. Moore WJ. Schrödinger, life and thought. Cambridge (UK): Cambridge University Press; 1989.