

Request For Information

Biomarkers for prediction of response to obesity therapies and sustained weight loss

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Issued by: The Obesity Working Group, a subteam of the Metabolic Disorders Steering Committee of the Foundation for the National Institutes of Health (FNIH) Biomarker Consortium.

The mission of the FNIH Biomarkers Consortium is to conduct research into biomarkers in a pre-competitive manner in order to speed the development of medicines for the prevention, detection, diagnosis and treatment of disease. The mission of the Obesity Working Group (OWG) is to develop pre-competitive biomarkers specifically for establishing early signals of long-term efficacy in weight loss trials. The membership of the OWG is broad, reflecting many pharmaceutical companies, the NIH, FDA, and prominent academic institutions. The results of these efforts, which are under the auspices of the FNIH, will be made broadly available.

This Request for Information (RFI) is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the FNIH, the NIH, or Pharmaceutical Research Manufacturers Association (PhRMA). The FNIH does not intend to make any awards based on responses to this RFI or to otherwise pay for the preparation of any information submitted or for the use of such information.

Purpose:

The current medical therapies for the treatment of obesity are inadequate. There is a need for novel agents and combination therapies in order to achieve the levels of efficacy that patients and physicians are looking for. As new drugs and combinations progress through development, it will be important to optimize study designs to manage the cost and length of development. Having biomarkers

of response to therapy and having the ability to predict response in individuals would therefore be very useful advances.

The purpose of this RFI is to solicit preliminary ideas, resource estimates, and timelines regarding the creation and progressive validation of approaches to predict long-term (≥ 12 mo) weight loss response from short-term controlled weight loss clinical trials in adults. That is, which markers/measures after 1 and 3 months of an intervention predict the 12-month (or longer) response to a sustained intervention? It is also advantageous to distinguish early future responders from non-responders in order to make trial designs more efficient and improve benefit/risk/cost ratios in medical practice. The development of this approach would comprise part of a proposal by the OWG of the FNIH Biomarkers Consortium to improve the design and outcome of clinical trials of pharmacotherapy for use in conjunction with lifestyle (diet and physical activity) interventions.

Our objective is to improve the ability to predict weight loss response, thus aiding clinical trial design via improved patient selection, reducing drop-out rates in placebo groups, and reducing risk to subjects unlikely to benefit from a weight loss intervention. As trials commonly have placebo control (diet and exercise) and active treatment arms, it is important to consider how each of these could be optimized to achieve the goals of this project. Each specific response to the RFI will be kept confidential, but will be used as part of an overall process to plan for a request for proposals. The RFP will solicit a more detailed proposal.

Background:

In trials of weight loss interventions, the best predictor thus far of weight loss following 12 months of an intervention is the weight loss at 3 months. The 3-month intervention, however, is too long to be a practical means of comparing different therapies, which may include combinations of agents in different ratios, and identify responders to improve patient selection for longer term controlled clinical trials. It is highly desirable to be able to identify earlier in the treatment period individuals who are predicted to have a sustained weight loss with a particular intervention.

The explosion in science and technology in the last decade has yielded a number of promising exploratory biomarkers for assessing the potential for sustained weight loss in obese subjects. These can be grouped into three major classes: “traditional” soluble/circulating biomarkers, functional measures of energy balance and expenditure (e.g., RMR), and behavioral assessments (changes in hunger, satiety, or food intake and adherence to either drug prescription or lifestyle modification prescription). All of these measures can be considered biomarkers. Yet despite the variety of biomarkers from which to choose, there is a paucity of information as to how these measures, either at baseline or in response to an intervention, predict future events. Also unexplored is whether there is some combination of biomarkers in which the change(s) over time in the combined markers provide an earlier (e.g., at ≤ 1 month), reliable prediction of longer term weight loss (e.g., at 12 months or beyond)?

A significant complexity for predictive biomarkers of obesity is that these biomarkers are usually studied individually in different patient populations, effectively separating studies into univariate observations. Moreover, the timing of the measures often differs between studies. As a result, it is difficult to generalize biomarker findings from one study to other studies.

Although these different markers may show varied facets of the pathobiology or anatomy of obesity, it is not clear which measure(s) may be the best predictor(s) of future events. That is, how do these different measures/technologies compare to one another? By studying each biomarker separately, we effectively reduce the ability to contrast them. Moreover, the predictive power of any measure may depend on the number of measurements and/or intervals between measures after the introduction of the treatment or intervention. Finally, as obesity is a multifactorial process, it is unlikely that any single marker will robustly characterize the response to an intervention. How do we take the multifactorial process that leads to weight loss and better identify those components most predictive of long-term weight loss?

The complexity of this problem is heightened by the introduction of new technologies and science. These new markers or measures are being added to the panoply of markers with varying degrees of acceptance (validation). For the “consumer groups” of these markers, the menu of options becomes increasingly difficult to sort through. Given that the chances of successfully developing any new drug are very low (<8% overall), pharmaceutical

companies must rely on biomarkers in proof-of-concept or Phase II to help make go/no-go decisions on proceeding into Phase III, including cardiovascular events trials. Moreover, pharmaceutical companies must balance the relative risks of projects in their respective portfolios, and without good, well-qualified Phase II biomarkers with improved power to predict Phase III outcomes, it is expected that high-cost, high-risk indications such as weight loss will receive significantly less emphasis.

Information is sought from the following sources:

- Scientists with expertise in obesity and related disciplines;
- Members of the scientific community at large;
- Employees of the biotechnology and pharmaceutical industries;
- Health professionals; and
- Relevant professional societies or organizations

Key Questions:

It is the intention of this RFI to seek preliminary ideas for approaches to address the following key questions to support early decision making in controlled clinical trials for weight loss:

1. Can we predict long-term responders to a weight loss intervention
 - a. of diet and lifestyle, typically used in a placebo control group and during a run-in phase of a trial?
 - b. of a pharmacotherapy in addition to diet and lifestyle, typically used as the active treatment group?
2. Can we more accurately predict the long-term effects of an intervention based on short-term effects (less than 3 months)?
3. Are there predictors (biomarkers) that are more accurate at different points in a weight loss trial, i.e. more accurate when used early in an intervention, but less accurate later, e.g. 1 v. 3 v.12 months?

Approaches:

The possible approaches might include acquisition of existing data or prospective generation of new data. From existing data, one can consider integration and analysis of multiple biomarkers or types of measures (e.g.

biological plus behavioral) and the use of modeling. Alternatively, respondents can consider proposition of new experimental studies to address the objectives of the RFI.

For retrospective analyses, please address the following relative to your approach:

Accessing datasets: One of the strengths of the FNIH Biomarkers Consortium is the possibility that datasets, with or without stored clinical samples, may be accessible from pharmaceutical companies. That is, beyond group means and distributions, it is likely desirable to have individual subject data. If access to industry interventional studies were made available, what variables and parameters would be useful in your approach? For example, consider trials which were part of recent approvals for obesity treatments as well as trials of other drugs, including those that had negative results or have been withdrawn. Please provide a brief rationale as well as a preliminary idea of what data from these trials would be requested. These could be outcome studies or clinical trials which measured biomarkers on a schedule of regular intervals throughout the study length

Building a database: The management of diverse sets of knowledge is a fundamental need for this effort. It is expected that different datasets from varied sources will need to be incorporated into a larger database. Responding organizations should include thoughts on building this database. Moreover, as it is planned that the results of this effort would be available to many participating parties, data must be in a consistent format and be available to all team members/consortium participants.

Description of statistical methodology: Briefly describe how different data will be evaluated and/or combined.

For Prospective Studies: Please include sufficient description of study design and primary outcome variables to be measured to provide context for the estimates of timeline and budget.

Timeline and Budget: In addition to the above, it is requested that a preliminary estimate of timeline and budget are provided. Although it is recognized that these estimates are preliminary, the respondents need to know

that the information will be used for drafting a budget request to the potential sponsors of this effort.

How To Respond:

Responses will be accepted until **April 28, 2013**. Responses should be limited to five pages. Be sure to include enough information to judge the budget in context of the proposal. Responses are preferred in electronic format and can be e-mailed to Maria Vassileva, Ph.D. mvassileva@fnih.org

Due to the short timeframe and limited size of this proposal, it is recognized that full responses to the issues above may not be possible. Nonetheless, please try to respond to the above as best as you can.

Respondents will receive an email confirmation acknowledging receipt of their response, but will not receive individualized feedback.

Responses to this RFI are voluntary and may be anonymous. All individual responses will remain confidential. Any identifiers (e.g., names, institutions, e-mail addresses, etc) will be removed when responses are compiled. Only the processed, anonymized results will be shared internally with scientific working groups. Nonetheless, no proprietary information should be submitted.

Communications: For any questions or feedback, please contact:

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