ENDOCRINE SOCIETY
Hormone Science to Health

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NIHBC 31 BG RM 9A52
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Dear Dr. Rodgers,

The Endocrine Society appreciates the opportunity to provide input on research strategies to address obesity heterogeneity. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. Our membership consists of over 18,000 basic and clinical scientists, physicians, educators, nurses, and students from more than 120 countries. Our members include basic and clinical scientists that receive funding from the National institutes of Health (NIH) to conduct research on obesity as well as health care professionals that treat patients with obesity. Obesity is one of our society's priority areas and our membership of scientists and physicians help us maintain our leadership and commitment to understanding and treating this disease. Our response below is informed by our Research Affairs Core Committee in collaboration with a group of our members with expertise treating patients with obesity.

1. How to best study obesity heterogeneity based on scientific opportunity and potential health impact.

Understanding the heterogeneity of obesity is a complex, scientific challenge that will require a combination of approaches to advance our knowledge of obesity. There are opportunities to learn from the research and management approaches for other chronic diseases like diabetes and hypertension to aid in the development of strategies to study obesity heterogeneity. We suggest that the NIH draw ideas from existing efforts in the European Union such as the SOPHIA (Stratification of Obesity Phenotypes to Optimize Future Therapy) project, which aims to optimize obesity treatments for patients by collecting patient information and managing a database that can be used to identify obesity phenotypes and model disease progression and

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treatment. A central repository of information maintained by the NIH can help identify the phenotypes and endotypes of obesity.

Insight into the development of obesity over the lifespan should be investigated by conducting large-scale, longitudinal studies in diverse patient populations. This would allow for the observation of the development of obesity in individuals at different ages and identify different endotypes of obesity, especially as individuals transition from being overweight to obese. Social determinants of health (SDoH) should be taken into consideration when conducting longitudinal cohort studies (as described further in the response for question 5).

Genetics and metabolism are two factors that the NIH should consider in studying obesity heterogeneity in which we have tools and techniques available to capture information from patients. Identification of the origins of obesity through genetics can reveal and possibly help predict obesity and its endotypes. Specifically, genetics and epigenetic factors from maternal and paternal sources and other ancestors should be considered in the development of obesity endotypes. As a disorder of the metabolic system, metabolic profiling using techniques such as single cell RNA seq and spatial transcriptomics can be used to further our understanding of obesity heterogeneity.

Sex differences are another important factor that should be considered in studying obesity heterogeneity. The prevalence of obesity in women is significantly higher than in men. The mechanisms underlying this increased susceptibility should be investigated when defining different obesity endotypes.

Some hormone therapies can affect weight gain or obesity. It is critical to investigate their mechanism of action to help identify and define obesity endotypes. For example, patients who take hormone contraceptives such as synthetic progestins and estrogens can experience significant weight gain. Additionally, patients who are prescribed hormone therapy may also see effects on body composition. Furthering our understanding of hormone therapies and their effects on weight and obesity should be a priority to enhance patient care.

Investigations underlying a patient's responses to obesity treatments can provide insightful information on distinct obesity endotypes. From the clinical perspective, the re-evaluation of the accuracy of bariatric trajectory prediction calculators compared

to patient treatment responses can help improve the accuracy of such calculators and ultimately improve patient care. Similarly, physicians have seen a range of patient responses to anti-obesity medications. Understanding the differences between non-responders and "super" responders of anti-obesity medications can help advance our knowledge of obesity heterogeneity.

In addition to specific factors, we also suggest several general strategies that could apply to the study of obesity heterogeneity. We appreciate the NIH's longstanding commitment to studying basic research on pathophysiology that leads to excess adiposity in animal models; however, translational research is needed to draw stronger relevance to humans. The NIH should also prioritize foundational research on the physiology of weight reduction and research on how excess adiposity leads to health complications should be conducted across institutes and will require advances in technologies in body imaging and composition and measures of cellular- and organ-level functions. Finally, we enthusiastically welcome the NICHD and NIA's participation in this effort; joint funding approaches with these institutes could investigate the genetic and epigenetic factors in the development of obesity endotypes such as race, ethnicity, age, physiological development (including neurodevelopment with gut-brain interactions, puberty, reproduction), physiological changes (such as the impact of stress, exposures that shape neurodevelopment), and lifestyles.

2. Promising strategies to reveal distinct mechanistic pathways [endotypes] underlying obesity subtypes, and their biomarkers.

We expect that understanding the biological underpinnings of different obesity subtypes will help us identify and develop novel treatments and therapeutics for treating obesity. We recommend using genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS) towards this objective. These approaches will help identify genetic, genomic, and epigenetic predispositions and inherited or *de novo* changes that contribute to obesity phenotypes. Another approach is to compare the endotypic variations observed throughout the lifespan in pediatric and adult obesity and establish the contribution and abnormalities of the endocrine system and how they define different endotypes and phenotypes presented. Artificial intelligence approaches including machine learning can be used to identify obesity endotypes through the analysis of large data sets. We elaborate our thoughts on artificial intelligence as both a strategy and tool in our response to question 3.

3. How advances in data science, including machine learning and artificial intelligence, can be leveraged to accelerate the development of precision approaches to prevention and treatment of obesity and its associated co-morbidities.

Advances in data science can help identify novel strategies for the prevention and treatment of obesity by accelerating data analysis to identify new pathways that underlie obesity subtypes. Applied to large patient datasets, machine learning and artificial intelligence technologies could:

- Define endotypic characteristics that would identify and allow for the precise targeting of therapeutics specific to the distinct signaling pathways of each obesity subtype.
- Analyze and predict unexpected co-morbidities or characteristics of endocrine system abnormalities once they are established.
- Identify potential correlations between BMI in different patient populations and associated comorbidities such as prediabetes, diabetes, hypertension, heart disease, and more.

While machine learning and other AI tools have the potential to advance data analysis and research, we caution that AI technologies could reinforce unintentional biases formed while attempting to identify factors that shape endotypes such as genetics, race, ethnicity, growth, development, lifestyles, and other sensitive factors. Funding strategies should therefore consider ways to mitigate unintentional bias.

5. Strategies that incorporate community factors, cultural, social, and economic factors, or social determinants of health into endotypes.
We applaud the NIH's effort to incorporate Social Determinants of Health (SDoH) into the development of research strategies for addressing obesity heterogeneity. Understanding the role of SDoH, including socioeconomic status, cultural and social norms on obesity, impacts of local policies on human health such as access to food, recreational spaces, and environmental changes or exposure to chemicals, is essential for investigating contributions to disease development and when developing individualized treatment plans for patients. To advance SDoH as part of strategies to address obesity heterogeneity, we recommend that the NIH collect and manage a central data repository of SDoH information for analysis by scientists, statisticians,

and other professionals in the field. Cultural agreements and other ethical concerns should be considered in collecting and maintaining patient information for this repository, for example through research strategies that engage community members as active participants at early stages.

6. The potential role of obesity endotypes in discerning susceptibility to or resilience from obesity co-morbidities.
Understanding how endotypes contribute to susceptibility and resiliency to obesity-related co-morbidities is an important step in identifying opportunities for personalized patient care. As a first step, NIH research can help establish different obesity endotypes based on biological, phenotypical, and clinical characteristics. Examples of biological factors that should be considered are hormonal regulation and the role of the immune system. Once obesity endotypes are clearly defined and established, precision medicine approaches can be developed by medical professionals to create prevention and treatment strategies based on those who are most at risk for obesity and specific co-morbidities.

7. Other comments, suggestions, or considerations relevant to this RFI and obesity heterogeneity.
There are several additional points that should be considered in the context of clinical care that could also inform research. Because obesity is a metabolic disorder, understanding energy consumption and expenditure of a patient with obesity will provide beneficial insights for developing precision treatment for the patient, while also generating data that could be useful for research. We therefore suggest that the NIH support the development of novel tools, particularly wearable technologies, to measure energy consumption and expenditure. We also recommend that the NIH work with WHO, CDC, and other agencies as appropriate to re-evaluate Body Mass Index (BMI) cutoffs for different groups with different racial or ethnic backgrounds according to factors that shape the patient's health risks. For example, patients of South Asian origin tend to have an increased risk for metabolic syndrome and coronary artery disease risks at a lower BMI.

We thank NIDDK for considering the Endocrine Society's recommendations and welcome opportunities to work together on the development of strategies to address obesity heterogeneity and on future projects and initiatives. If we can be of further

assistance, please contact Sophia Kaska, Ph.D., Manager of Science Policy and Research Affairs at skaska@endocrine.org.

Sincerely,

John Newell-Price, MD, PhD, FRCP
President
Endocrine Society