Draft

Strategic Plan for

NIH OBESITY RESEARCH

A Report of the NIH Obesity Research Task Force

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EXECUTIVE SUMMARY

NOTE: The executive summary will be finalized and inserted after the public comment period.

1 # DISCOVERIES AND NEW DIRECTIONS IN OBESITY
2 # RESEARCH

3   Obesity is a growing threat to health in the United States and around the world. Reducing the
4   prevalence, incidence, and health impact of obesity requires a broad-based effort by many—
5   government, the private and nonprofit sectors, healthcare professionals, community
6   organizations, schools, businesses, and families.

7   The foundation of such a comprehensive effort is research conducted by a diverse scientific
8   community to illuminate the causes and consequences of obesity, develop and test prevention
9   and treatment strategies, and inform policy making and community efforts. The NIH supports
10 such research with the aim of extending healthy life and reducing the burdens of illness and
11 disability. Consistent with this mission, the *Strategic Plan for NIH Obesity Research* aims to
12 serve as a guide to accelerate research that will lessen the personal and public health burdens
13 of obesity.

14 **Epidemiology and Health Consequences of Obesity**

15 Obesity is a common medical disorder with serious consequences. At a fundamental level,
16 obesity develops because of a mismatch in "energy balance": calories taken in from food and
17 beverage exceed those expended in activity and metabolic functions—including growth in
18 children, with resultant excess adipose tissue (body fat) storage. While obesity is defined as an
19 excess of body fat, it is frequently assessed with the proxy of body mass index (BMI), a
20 measure of weight relative to height that is practical to use in population-wide studies and in
21 clinical and community settings.

22 A majority of the US adult population is overweight as defined by a body mass index, or BMI, of
23 25 kg/m^2 or greater, and more than one-third of adults are obese (BMI of 30 kg/m^2 or greater).
24 More than 16 percent of children and adolescents are obese as defined as BMI at the 95th
25 percentile or greater for age and sex[*], a prevalence that has more than tripled over the past
26 three decades. Additionally, the prevalence of extreme obesity (BMI of 40 or greater in adults
27 and BMI ≥97th percentile for age and sex) in children has increased precipitously. Although
28 recent data suggest that US obesity rates may be stabilizing in many population subgroups, BMI
29 has increased in the population to such an extent that adults and children within the healthy
30 weight range are a minority. Obesity prevalence rates have substantially increased throughout
31 much of the developed and developing world. In developing countries in particular, obesity and
32 undernutrition often coexist in proximity, especially in urban areas. Once established, obesity is
33 difficult to reverse over the long term, so strategies to prevent its development are essential. In
34 addition, safer, more effective and durable treatments are needed for individuals who are
35 currently obese.

36 The rise in obesity prevalence has resulted in an increase in the myriad serious medical
37 problems associated with excess body fatness[†]. For example, type 2 diabetes has increased

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[*] For children and adolescents, the BMI percentiles are based on 2000 CDC growth charts. These revised growth charts incorporate smoothed BMI percentiles and are based on data from NHES II (1963 to 1965) and III (1966 to 1970), and NHANES I (1971 to 1974), II (1976 to 1980), and III (1988 to 1994). The CDC BMI growth charts specifically excluded NHANES III data for children older than 6 years.
[†] For the purpose of this document, examples of comorbid conditions are used to illustrate current or future research and are not intended to exclude the importance of other relevant comorbid conditions.

38   dramatically over the past decade: almost 13 percent of US adults aged 20 years and older
39   have diabetes and an additional 30 percent are estimated to have pre-diabetes. An alarming
40   recent development is the increasing number of children and adolescents, especially from racial
41   and ethnic minority populations, diagnosed with type 2 diabetes.

42   Obesity is an important risk factor for cardiovascular diseases such as stroke and heart attacks
43   and for other cardiovascular risk factors such as hypertension. Certain forms of cancer are
44   associated with obesity. Non-alcoholic fatty liver disease, a consequence of obesity that can
45   progress to cirrhosis, is increasingly diagnosed in both adults and children. Obesity increases
46   the risk of many other disorders, including osteoarthritis and other musculoskeletal disorders,
47   some autoimmune and allergic disorders, gastrointestinal diseases, gallbladder disease, kidney
48   disorders, infertility and other disorders of the reproductive system, urinary incontinence,
49   asthma, sleep apnea, and dementia. During pregnancy, maternal obesity has a deleterious
50   impact on both the mother and fetus, increasing the risk of certain birth defects, gestational
51   diabetes, and pre-eclampsia. Obesity is associated with psychiatric disorders, including
52   depression and some eating disorders. Obesity significantly affects quality of life in children and
53   adults, reducing their mobility and ability to carry out activities of daily living.

54   Obesity can have an adverse impact on access to healthcare, including preventive services and
55   some diagnostic and therapeutic procedures. These disparities may contribute to the greater
56   health risk conferred by excess body weight. Obesity also may affect the response to
57   medications and other therapeutic interventions.

58   Not all obese individuals are equally susceptible to these health problems. Recently, a
59   phenotype of apparently "metabolically healthy" obesity has been identified, in which individuals
60   have increased body fat but are resistant to the development of conditions such as insulin
61   resistance and other cardiovascular disease risk factors. Understanding not only which
62   individuals are most at risk for (or protected from) obesity-related health conditions but also the
63   mechanisms by which increased body fatness or body fat distribution does or does not
64   contribute to disease in specific individuals or sub-groups can help target prevention and
65   treatment strategies.

66   Obesity is more common in certain racial and ethnic minority populations, including African
67   American and Hispanic/Latina women, American Indians/Alaska Natives, and Pacific Islanders.
68   As a result, these populations also experience more obesity-related consequences and
69   comorbidities. In Asians, the BMI underestimates adiposity; diabetes and other complications of
70   obesity are seen at normal or minimally elevated BMI. The relationship between race and
71   ethnicity and obesity is complex and needs to be better understood through untangling
72   biological, environmental, and cultural pathways, as well as differential response to treatment.

73   Finally, obesity confers important social and economic costs. Weight stigma may contribute to
74   reduced educational and employment opportunities. Socioeconomic status also confers
75   disparate risk for obesity, as those who are poorer and/or less educated are more likely to be
76   obese. The increasing medical costs attributable to obesity-related disorders play a significant
77   role in burgeoning national healthcare costs, and obesity also contributes to lost work
78   productivity.

79 **New Scientific Opportunities, Renewed Commitment to Obesity Research**

80 The pace of discovery in diverse areas of obesity research is rapid and accelerating. .
81 Advances in areas ranging from basic biomedical and behavioral science through clinical and
82 community studies have opened the door to new opportunities for both better targeted and more
83 comprehensive approaches to obesity prevention and treatment. Just a few of the many
84 examples of these advances are highlighted here.

85 Basic research has led to the development of new animal models, including some in which gene
86 function is changed only in specific tissues, such as brain, liver, fat, or muscle. Using these
87 animal models, scientists are gaining new insights into how genes and the proteins they encode
88 may function and interact with each other in metabolism and weight regulation in people.
89 Results of this research may lead to new therapeutic targets.

90 Studies of the complex signaling pathways within the brain and between the brain and other
91 organs and tissues, such as the gut and fat tissue, are further elucidating appetite and energy
92 expenditure regulation. For example, recent human brain imaging studies have demonstrated
93 differences in brain structure and activity associated with obesity and weight loss. In genetics,
94 new technologies allowing genome-wide association studies (GWAS) in humans have led to the
95 identification of common genetic variants near or within genes previously unsuspected to be
96 related to body weight. Although such genetic variants may predict only a small degree of
97 variation in body weight, their identification provides new targets for investigations of gene
98 function at both a metabolic and behavioral level. The combination of GWAS with deep DNA
99 sequencing and high-throughput functional assays in areas such as gene expression or
100 metabolomics in humans will lead to a greater understanding of how genetic variation leads to
101 disease risk. Elucidation of the ways in which susceptibility or protective gene variants interact
102 with environmental factors or drugs will provide an opportunity for personalized prevention and
103 treatment strategies. Understanding epigenetic mechanisms regulating metabolic tissues and
104 the role of environmental factors in modifying epigenetic states may lead to important
105 discoveries about potentially preventable contributors to obesity.

106 Our understanding of environmental contributions to obesity is increasing at all levels, from the
107 individual through society. In studies of environmental influences on obesity, technologies such
108 as geographic information systems are now enabling targeted examination of the impact of the
109 built environment on weight or physical activity. In addition, innovative methods to measure
110 food intake and physical activity are allowing better measurement of energy balance in real-
111 world settings. Emerging data on unique aspects of the gut environment suggest that gut
112 microbes and their collective genomes, called the "microbiome," may play a role in the
113 development of obesity. Expanded knowledge about the microbiome's role may someday
114 permit prevention or treatment of obesity by manipulating the composition of this environment.
115 Other environmental factors, such as exposure to infectious agents or environmental toxicants
116 and the ambient temperature, have emerged as potential targets of interest in the study of
117 obesity and its complications. Information regarding the impact of the intrauterine or neonatal
118 environment is also leading to research aimed at modifying these environments to prevent later
119 obesity—for example, by preventing gestational diabetes in the mother or by targeting factors to
120 enhance optimal rates of weight gain in infancy and early childhood.

121 Research findings are yielding new and important insights about social and behavioral factors
122 that influence diet, physical activity, and sedentary behavior. Research regarding social
123 networks, decision making, behavioral economics, sensory input, and sleep patterns as they
124 relate to weight may yield novel targets for intervention.

125 Advances in statistical and computational methodologies are emerging to help capture and
126 illuminate the dynamic complexity of obesity and test the effects of intervention strategies on
127 individual and societal outcomes. Policies such as mandated BMI screenings of school-age
128 children, enhanced nutrition labeling of packaged foods and restaurant menu items, changes in
129 vending machine options in schools or worksites, and incentives to purchase healthy foods are
130 being implemented in communities across the country, and present a prime opportunity for
131 research to evaluate their effects.

132 **About** *The Strategic Plan for NIH Obesity Research*

133 Given the importance of obesity as a public health problem and its relevance to the mission of
134 most of the NIH Institutes, Centers, and Offices, NIH established an Obesity Research Task
135 Force in 2003 to accelerate progress in obesity research across the NIH. The Task Force is co-
136 chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases
137 the Director of the National Heart, Lung, and Blood Institute, and the Director of the *Eunice*
138 *Kennedy Shriver* National Institute of Child Health and Human Development. The members of
139 the Task Force represent these and many other NIH Institutes and Centers with relevant
140 expertise.

141 A key element of the initial charge to the Task Force was the development of a *Strategic Plan*
142 *for NIH Obesity Research,* published in 2004. In light of the rapid progress in obesity research
143 highlighted above and the opportunity to capitalize on emerging scientific discoveries, the Task
144 Force decided to update the *Strategic Plan*.

145 Like the 2004 *Strategic Plan for NIH Obesity Research,* the 2010 *Strategic Plan* provides a
146 guide for coordinating existing obesity research activities across the NIH. It also encourages
147 the development of new research efforts.

148 The 2010 *Strategic Plan* is meant not to be all-inclusive or limiting, but to highlight areas of
149 challenge and emerging opportunity. As new scientific opportunities arise from current research
150 investments and accomplishments, the research planning process will build on these areas,
151 thus accelerating research in the most promising directions.

152 As in the 2004 *Strategic Plan*, this revised *Strategic Plan* was informed by experts external to
153 the NIH, who provide ongoing invaluable research planning advice at scientific meetings and
154 workshops convened by NIH Institutes and Centers. In addition to this external advice, which
155 will continue to inform the obesity research planning process, an initial version of the *Strategic*
156 *Plan* has been circulated to individuals and organizations outside the NIH, including scientists
157 with expertise in obesity research and leaders of voluntary and professional health advocacy
158 organizations. Their comments have been incorporated into this revised draft. The draft is
159 now posted on the Internet for public comment. The final *Strategic Plan* therefore will reflect
160 the contributions of a wide range of individuals and groups.

161 Given the complex interaction between biology, behavior, and environment in contributing to the
162 rise in obesity, formidable barriers stand in the way of simple solutions for altering energy
163 balance toward a healthy body weight. Therefore, the *Strategic Plan* encompasses all levels of
164 research, from basic biological and behavioral research through community and population
165 research.

166 <u>Cross-cutting Issues for Obesity Research</u>

167 Integral to all areas of the *Strategic Plan* are cross-cutting issues including health disparities; the
168 influence of sex and gender on biological determinants of obesity, diet, and activity; variations in
169 response to treatment; developmental issues across the lifespan; and the needs of vulnerable
170 and at-risk populations, including understudied populations such as racial and ethnic minority
171 populations, older adults, populations with low literacy and numeracy, people with disabilities,
172 rural populations, and those with extreme obesity.

173 The *Strategic Plan* places special emphasis on the following three areas that are increasingly
174 recognized as essential to a vibrant and successful obesity research effort:

175 <u>Translational Research</u>

176 Translational research is a key element in meeting the public health challenge of obesity. Early
177 translational research, sometimes termed "bench to bedside" research (i.e., from test tubes,
178 mouse models, or basic behavioral studies to clinical studies), is crucial for identifying novel
179 behavioral, environmental, social, and biological targets for obesity prevention or treatment and
180 then translating these targets into approaches that can be tested for efficacy in controlled
181 clinical trials. Early interaction between basic scientists and clinicians in developing, planning,
182 and executing translational research may assist in consideration of important issues such as
183 feasibility and potential for uptake in clinical care. "Bedside to bench research," brings
184 knowledge gained in a clinical setting back to the laboratory for further mechanistic exploration
185 that may in turn spur new clinical approaches. Translational research that helps speed these
186 bidirectional and iterative knowledge transfers is important to ultimately improving the public
187 health.

188 When intervention approaches are proven efficacious in a clinical trial setting, later phases of
189 translational research (e.g., bedside to practice and the community) are needed to examine
190 their effectiveness more broadly—that is, exploring how the interventions could be implemented
191 cost-effectively in real-world populations, clinical practice, and community settings to achieve
192 positive impacts on health. Later translational research addresses issues of feasibility,
193 adaptation, generalizability, adoption, dissemination, implementation and sustainability in
194 environments such as schools, community health centers, and worksites. Community-based
195 translational research is one approach for addressing health disparities issues: for example,
196 through research on culturally competent prevention, early intervention, and disease
197 management strategies for diverse population groups. Community and population-based
198 research also informs new targets for clinical research and practice.

199 <u>Training</u>

200 Strengthening and diversifying the pool of researchers who are dedicated to understanding and
201 ameliorating obesity and its many adverse outcomes is a priority for NIH. This commitment
202 includes attracting and training a cadre of researchers with a wide range of knowledge and
203 skills, such as expertise in the basic, clinical, behavioral, and social sciences, epidemiology,
204 cultural competency, measures and methods, interventions, and translation and dissemination.
205 Training in innovative multidisciplinary areas, such as social networks and complex systems,
206 would be useful. As a part of its commitment to supporting diversity in research, NIH will also
207 continue to support and develop new ways to attract and train researchers from racially and
208 ethnically diverse backgrounds.

209   <u>Transdisciplinary Research</u>

210   Meeting the obesity research challenges of the future will require transdisciplinary research
211   teams that include the talents of many, such as basic and molecular scientists; geneticists;
212   behavioral, clinical, environmental, and policy scientists; community leaders; industry partners;
213   transportation scientists; and urban design experts. To foster this, NIH encourages integrated,
214   cross-disciplinary thinking and hypothesis generation across the spectrum of obesity research, a
215   commitment increasingly embraced by scientific, industry, academic and healthcare institutions
216   and communities. This type of thinking can inform the ways in which component elements of
217   multidisciplinary and multilevel approaches are integrated to determine best practices for
218   optimal effectiveness of evidence-based programs.

219   **A Multi-faceted Approach to a Multi-faceted Problem**

220   A complicated interplay of environmental, social, economic, and behavioral factors, acting on a
221   background of biologic mechanisms and genetic susceptibility, has fueled the increase in
222   obesity prevalence. An appropriate response must be equally multi-faceted. Although
223   prevention of obesity and its medical complications is the ultimate goal, the *Strategic Plan*
224   recognizes that the current high prevalence of obesity in both adults and children highlights the
225   need for research on treatment as well, including the comparative effectiveness of interventions
226   delivered in settings such as primary care, specialized treatment centers, schools, and
227   community settings.

228   Research leading to a better understanding of the many contributors to obesity in individuals
229   and populations, the link between obesity and its associated health risks, and development of
230   improved methods for prevention and treatment has the potential to help people to live longer
231   and healthier lives. It is our hope that the *Strategic Plan for NIH Obesity Research* will help
232   accelerate progress toward these goals.

233 ## OBESITY RESEARCH ADVANCES AND OPPORTUNITIES

234 *The scope of obesity research across the NIH is broad, encompassing diverse issues, a range of*
235 *scientific disciplines, and multiple levels, from the genetic and cellular to individuals, communities, and*
236 *populations. The following sections of the* Strategic Plan *include some examples of significant and recent*
237 *scientific advances and outline opportunities across the spectrum of obesity-related research areas.*

238 *The first two sections focus on research opportunities designed to uncover causes and mechanisms of*
239 *obesity and identify potential targets for intervention.* **Discover Biological Mechanisms Regulating**
240 **Energy Balance** *highlights opportunities in genetics, neuroscience, metabolism, cell biology, and other*
241 *areas that will improve our understanding of fundamental biologic pathways involved in weight regulation*
242 *and point the way to novel therapeutic targets.* **Understand the Correlates, Determinants, and**
243 **Consequences of Overweight and Obesity** *moves beyond biological mechanisms to address research*
244 *into factors that are associated with increases in body weight and the development of obesity as well as*
245 *the many adverse outcomes resulting from obesity.*

246 *Efforts to change behavior as well as clinical and public health practice and policy are often based on the*
247 *results of carefully designed and evaluated interventions. NIH currently supports many such obesity-*
248 *related interventions, and* **Design and Test Interventions to Promote Healthy Weight** *outlines an array*
249 *of new opportunities that can further advance obesity prevention and management.*

250 *An important area of research focuses on ways to hasten the translation of research evidence from*
251 *discovery to intervention and from efficacy to effectiveness and application in clinical or community*
252 *settings.* **Conduct Dissemination and Implementation Research** *addresses opportunities in the fields*
253 *of surveillance, health services, dissemination, implementation, policy, and evaluation research.*

254 *Advances across these areas depend on accurate tools and measurements to enhance understanding of*
255 *etiology and allow for evaluation of interventions.* **Improve Measurement Tools, Technology, and**
256 **Methods** *highlights new opportunities for research to improve measurement of energy intake and output.*
257 *These tools and measures cover a number of areas, including development of biomarkers; assessment of*
258 *food intake, fitness, functional status, and thermogenesis; improvements in imaging and body*
259 *composition technologies; and development of objective measurement systems to better evaluate*
260 *changes in policy and environments. This section also highlights the need to use emerging methods of*
261 *analysis and design, which allow researchers to better capture and model the complex relationships in*
262 *obesity.*

263 *Issues of health disparities, high-risk populations, and critical periods across the lifespan, although not*
264 *always explicitly mentioned, are viewed as important considerations in all of the research opportunities*
265 *outlined in the* Strategic Plan.

268   # Discover Biological Mechanisms Regulating Energy Balance

269   Research has elucidated a large number of pathways that participate in the biological basis of
270   weight regulation and the dysfunctions in these pathways that result in obesity. This has led to
271   the identification of potential therapeutic targets to treat obesity and prevent associated
272   comorbidities. Further advances in this fundamental understanding of basic biological
273   mechanisms will yield novel approaches to prevent, as well as treat, obesity and its
274   comorbidities   For example, understanding how genes, interacting with the environment, confer
275   risk for obesity should allow investigators to define better targets for drug development, and may
276   also inform other approaches, including lifestyle approaches, for obesity prevention and
277   treatment. Identifying mechanisms whereby obesity causes dysfunction in many organ systems
278   will help target therapies for prevention of comorbidities. The increasing prevalence of
279   overweight in early childhood and increasing evidence that obesity and diabetes during
280   pregnancy have adverse effects on the fetus highlight the need to understand the potential
281   impact of excess energy consumption in the mother on development not only *in utero*, but well
282   into adult life.

283   **Selected Research Advances and Challenges**

284   The decade preceding the first *NIH Strategic Plan for Obesity Research* was a remarkable
285   period in obesity research, and recent advances have continued that high rate of discovery.
286   Much of this is due to improved characterization of the multiple biologic systems that interact to
287   regulate body weight. New technologies, such as cellular and functional imaging, metabolomics
288   and proteomics, gene expression arrays, genome-scale gene knockdown studies in non-
289   mammalian organisms, and powerful transgenic strategies to create complex genetic mouse
290   models have accelerated targeted research with increasing potential for translation to human
291   health. The following observations provide examples of particular insights and define directions
292   for future research.

293   - The identification of molecules, tissues, genes, and pathways involved in weight
294   regulation continues, and now includes a wide range of gut-produced factors;
295   "tissuekine" hormones produced by fat, bone, and skeletal muscle; and myriad brain
296   regions and peripheral nerves.

297   - The importance of sleep and the circadian "clock" in obesity development is increasingly
298   recognized. Chronic reductions in sleep time and circadian rhythm disturbance (e.g.,
299   shift-work) are commonly experienced by millions of Americans and result in alterations
300   in metabolism-regulating molecular and physiological pathways associated with
301   increased risk of obesity, cardiovascular disease, and type 2 diabetes.

302   - *In utero* exposure to stress, environmental toxicants, poor maternal diet, obesity, or
303   diabetes confers increased risk of metabolic disease in offspring.

304   - Understanding of the fundamental role of the brain in controlling energy balance
305   continues to grow. The specific functions of the structures known to be involved, such
306   as the hypothalamus, continue to be elucidated. Human brain imaging studies
307   demonstrate changes in structure and activity associated with obesity and also provide
308   clues to explain failure of normal satiety signals that lead to disordered metabolic states
309   and obesity in an energy-rich environment. Similar functional imaging studies show that
310   the dopaminergic pathways associated with motivation and addictive behaviors also
311   participate in obesity development or maintenance.

312   •   Increasing evidence in animal studies demonstrates that environmental toxicants
313   commonly found in both the food and water supply may contribute to obesity and type 2
314   diabetes. Many of these toxicants can be found in tissues and blood in the US
315   population.

316   •   The gut secretes a large number of factors that facilitate insulin secretion and regulate
317   eating behavior. The observation that bariatric surgery often leads to resolution of
318   diabetes, before significant weight loss has occurred, provides a model to explore
319   potential mechanisms by which the gut communicates with pancreas, liver, fat, and the
320   central and peripheral nervous systems.

321   •   Gut microbiota, which aid normal nutrient absorption and metabolism, may play a role in
322   obesity. Obesity is associated with remarkable changes in the composition of gut flora,
323   and alterations in gut flora also may have an impact on obesity development.

324   •   Although excess fat is the very definition of obesity, adipose tissue has important
325   beneficial properties that seem designed to protect against adverse effects of excess
326   lipids elsewhere in the body. Fat molecules can be safely stored in adipose tissue, but
327   when the storage capacity of this tissue is exceeded, the resulting deposition of excess
328   fat into other tissues and organs is associated with morbidity. Adipokines, secreted as a
329   function of adipose tissue mass, regulate eating behavior and fat oxidation.

330   •   Brown adipose tissue, a tissue that plays an active role in many species to turn excess
331   nutrients into heat rather than stored fat, was thought to be present only in infancy in
332   humans. Recent work has demonstrated that human adults have significant depots of
333   brown fat, which appears to be metabolically active.

334   •   Obesity is associated with both systemic inflammatory cytokines and inflammatory cell
335   infiltration into fat, liver, and placenta and may activate inflammatory processes in the
336   brain.

337   •   Improvements in the ability to measure differential responses to diet and energy
338   expenditure are confirming that the same exposures do not lead to the same changes in
339   body composition and fat mass in all people.

340 **Research Opportunities**

341 A growing appreciation for the elegance with which the organism adapts to maintain its reserves
342 of energy is giving rise to important questions for future research. How do genes, biological
343 pathways, behavior, and the environment interact to maintain proper energy balance, and what
344 goes awry in an environment of excess calories and reduced energy expenditure to contribute
345 to obesity? The complexity of regulation of energy balance and the relative refractoriness of
346 these regulatory pathways to pharmacologic manipulation suggest the desirability of exploring
347 all possible avenues for sites sensitive to manipulation. Concomitant with support for basic
348 discoveries, NIH must develop paths to translate these discoveries into new diagnostics, new
349 therapeutics, and most important, new strategies for preventing obesity.

350 Specific opportunities for basic biological research that could provide new therapeutic
351 approaches to obesity include the following:

352   <u>Specific Roles of Organs, Tissues and Molecules in the Development of Obesity</u>

353   •   Determine the roles of gut microbiota in normal and pathological nutrient absorption and
354   metabolism, including how the disturbance of the biota by different factors might
355   contribute to obesity or weight loss, and explore novel therapeutic strategies to reduce
356   excess nutrient absorption associated with the gut flora or other pathways.

357   •   Determine whether human brown fat plays a major role in energy balance, and explore
358   pharmacologic or environmental (temperature) approaches to manipulate brown fat
359   activity to uncouple excess nutrient intake from energy storage in white fat tissue.

360   •   Elucidate the relationship between excess nutrient intake and physical inactivity on
361   adipose inflammatory processes, define the role of inflammation in obesity-related
362   complications, and explore therapeutic approaches targeting inflammatory pathways.;

363   •   Determine whether mitochondria, the cell's energy factories, are a primary site of
364   dysfunction in obesity or if obesity causes mitochondrial dysfunction resulting in
365   metabolic diseases associated with obesity.

366   •   Identify the brain pathways which integrate cognitive, endocrine, nutrient, and sensory
367   information and the links between these inputs and integrated behavioral, autonomic,
368   and neuroendocrine outputs to regulate energy balance.

369   •   Determine the mechanisms whereby food activates brain reward pathways and
370   association of activity in these pathways with obesity.

371   •   Explore how complex behaviors, such as sleep, patterns of sedentary behavior, and
372   exercise, can influence eating behavior, energy balance, and metabolic health.

373   •   Determine whether specific nutrients, non-nutrient additives, or other dietary
374   components (such as alcohol) have specific bioactivity that would modulate metabolic
375   processes associated with body fat storage and distribution, and thus contribute to the
376   development of obesity.

377   •   Explore the role of neuronal degeneration in brain regions regulating energy balance in
378   the development of obesity.

379   •   Examine potential deleterious effects of obesity on brain function, and define the
380   mechanisms and effects of weight loss and weight gain.

381   •   Study the mechanisms by which different bariatric surgical procedures accomplish
382   weight loss and improve health outcomes as targets for developing new pharmacologic
383   therapies. For example, study patients undergoing bariatric surgery and animal models
384   of bariatric surgery to expand the understanding of the role of gut signaling pathways
385   and secreted molecules in regulating eating behavior, nutrient handling, and energy
386   balance.

387   <u>Genes, Epigenetics, and Critical Periods in Human Development</u>

388   •   Identify genotypes that protect against development of obesity in the face of an obesity-
389   promoting environment.

390   •   Identify genetic variants that may contribute to circadian regulation of metabolism and, in
391   particular, those that are associated with variations in eating behavior.

392   •   Examine mechanisms whereby gene polymorphisms in defined loci confer risk of
393   developing obesity or influence development of associated morbidities.

394   •   Define the epigenetic mechanisms regulating metabolic tissues, such as brain, liver,
395   muscle, heart, and fat, and determine whether and when environmental factors (e.g.,
396   stress, toxicants, nutrient excess, bioactive nutrients, alcohol, and energy expenditure)
397   can perturb epigenetic states and lead to obesity; determine the plasticity in epigenetic
398   regulation of metabolic tissues.

399   •   Define the biological contribution of the critical periods of susceptibility to the
400   development of obesity during an individual's lifetime.

401   •   Define the contribution of intrauterine exposures related to maternal diet and physical
402   activity, obesity, and diabetes to the subsequent risk of obesity in the offspring.

403   •   Explore the impact of diet composition, obesity, and obesity-associated inflammation on
404   the developing brain and maturation of cognitive functions in children.

405   •   Determine the effect of excess adiposity on normal human development.

406 **Enabling Tools for Basic Research in Obesity and the Translation of Discoveries into Clinical**
407 **Utility**

408   •   Use global approaches (such as genome-wide association studies [GWAS], genomics,
409   metabolomics) to define all the molecules and pathways that participate in regulating
410   eating behavior, physical activity, sedentary behavior, nutrient absorption, muscular
411   response to exertion, and energy partitioning.

412   •   Devise approaches to measure and manipulate tissue- and organ-specific
413   thermogenesis and adaptations to diet, and weight gain or loss. In particular, new
414   means of monitoring brown adipose tissue mass and activity are needed.

415   •   Explore the use of imaging technology for obesity research, including new tools to probe
416   neuronal pathways controlling eating behavior, investigate lipid metabolism and
417   inflammation in tissues, and image energy expenditure.

418   •   Develop tools to monitor mitochondrial function *in vivo*.

419   •   Develop novel screens to identify small molecules that can modulate energy balance
420   pathways.

421   **Understand the Correlates, Determinants, and Consequences**
422   **of Obesity**

423   This section highlights two research areas critical to understanding obesity—factors associated
424   with the development of overweight and obesity, and the consequences of obesity.

425   A wide range of factors—biological, demographic, psychological, socio-cultural, organizational,
426   environmental, and regulatory—influence obesity-related lifestyle behaviors and weight gain.
427   These factors span multiple interacting levels, from the individual through societal.
428   Considerable evidence supports a growing list of physical, social, psychological, and economic
429   consequences associated with excessive weight gain. Research in the United States, as well
430   as in international settings which have recently experienced increases in obesity prevalence,
431   can help disentangle the various factors that promote obesity or protect against excess weight
432   gain.

433   Because obesity is not a single condition, increased knowledge about phenotypes and the
434   various influencing factors and consequences can be used to develop novel hypotheses to be
435   tested or to identify targets for intervention, surveillance, and translational research.

436   **Selected Research Advances and Challenges**

437   Knowledge about the correlates, determinants, and consequences of obesity has expanded
438   significantly in recent years, as illustrated by the following advances:

439   • Research has emerged suggesting links between obesity and the physical environment.
440   For example, the presence of sidewalks and more street connectivity in neighborhoods
441   is associated with more physical activity and less obesity.

442   • Several dietary behaviors have been strongly associated with weight gain, including
443   frequent consumption of fast foods, sugar-sweetened beverages, foods prepared
444   outside the home, and larger portion sizes. These behaviors occur in an environment
445   that favors inexpensive, highly palatable, energy-dense food that can be consumed with
446   minimal preparation.

447   • Sedentary behavior, which occurs in the context of an increasingly automated
448   environment, has been linked to weight gain, possibly independent of low levels of
449   physical activity. It is well-documented that large amounts of TV or video game use are
450   associated with increased risk of obesity in children and adults.

451   • Sociocultural factors have been associated with a higher risk of excess weight gain,
452   including race/ethnicity, education, low socioeconomic status, and acculturation. For
453   example, obesity co-occurs among persons connected through social networks,
454   although it is unclear how socio-cultural, environmental, and genetic pathways interact to
455   influence these associations.

456   • Several studies suggest that self-monitoring, such as frequent self-weighing and keeping
457   food and activity diaries, leads to better weight control.

458   • Excess weight gain during growth and maturation has been associated not only with
459   adverse outcomes during childhood but also with a higher risk of obesity and obesity-
460   related diseases in adulthood. Given that the prevalence of overweight has markedly
461   increased across pediatric age groups, premature onset of obesity-related diseases is

462   likely to rise. The prevalence of metabolic consequences of obesity, such as type 2
463   diabetes and metabolic syndrome, is increasing. This is especially true for adolescents
464   in some racial and ethnic groups.

465   **Research Opportunities in the Correlates and Determinants of Obesity**

466   Understanding the independent and interacting biological, behavioral, social, cultural, and
467   environmental correlates and determinants of obesity and how these differ among groups is
468   crucial to identifying new targets for intervention at the individual, community, and population
469   levels.

470   Several understudied and emerging areas provide opportunities for research:

471   • Disentangle the roles of and interactions among different aspects of the food- and
472   physical activity-related built, economic, policy, and natural environments in promoting or
473   preventing obesity. Research in this area would be enhanced by the application of
474   theories and approaches from diverse disciplines in longitudinal multilevel analyses.

475   • Encourage research that includes careful behavioral and biological phenotyping of
476   obese individuals at multiple time points. Because obesity does not have a single
477   phenotype, understanding the various causal pathways and characteristics that promote
478   or protect individuals from becoming obese will likely be important for the development
479   of more targeted and effective interventions.

480   • Enhance research that evaluates the effects of policy to better inform policy makers.
481   Several priority areas in policy research related to obesity include capacity development,
482   agriculture and food supply, economic research, built environment, and educational
483   policies.

484   • Identify how psychosocial factors and mental disorders influence weight gain, energy
485   intake, and energy expenditure. Identify factors, such as social support, that may
486   moderate these relationships. Identify how weight gain, energy intake, and energy
487   expenditure interact with high-risk behaviors such as smoking, drinking alcohol, and drug
488   use.

489   • Encourage research that identifies the reasons for increased risk of obesity in high-risk
490   populations, including racial and ethnic minorities, economically-disadvantaged groups,
491   and people with physical or developmental disabilities or comorbid mental disorders.

492   • Understand how developmental factors and learning influence the initiation and
493   maintenance of behaviors that promote weight loss or prevention of excess weight gain.

494   • Understand how individuals interpret and are influenced by messages related to diet and
495   physical activity (e.g., interpersonal, cultural, media, marketing, food labels) through
496   research on learning, cognition, information processing, persuasive communications,
497   and message framing. Explore how traditional and emerging communication channels,
498   such as social media and mobile technology, influence the adoption of these messages.

499   • Investigate factors related to excess weight gain associated with critical periods and life
500   events, such as fetal exposures *in utero*, infancy, childhood, puberty, adolescence,
501   young adulthood, pregnancy/ postpartum period, workforce entry, marriage, parenting,
502   menopause, and retirement. Identifying factors that may be unique to a specific point in
503   the lifespan could provide important insights for intervention development.

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- Clarify the temporal sequence and understand the biological and behavioral relationship between sleep and obesity across the lifespan. For example, conduct studies to clarify the role of chronic sleep time reduction and circadian rhythm disturbance in influencing adiposity or eating and activity behaviors.

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- Distinguish the intersecting roles of biological, behavioral, psychological, social, and environmental factors on obesity across the lifespan in longitudinal studies.

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- Study how the specific components and characteristics of diet, physical activity, and sedentary behavior interact in contributing to excess weight gain, weight cycling, and weight maintenance across the lifespan.

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- Increase the understanding of the role of common drugs/medications, including medications used for the treatment of mental illness, on obesity development.

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- Identify how environmental toxicants and other chemical exposures affect the development of obesity in children and adults.

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- Explore interactions between genetic and environmental factors related to weight stability, loss, or gain across the lifespan. These interactions, in which environment is broadly defined to include the individual, built, social, economic, policy, and natural environments may help identify new and more personalized targets for prevention and treatment.

522 **Research Opportunities in Understanding the Consequences of Obesity**

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Research is needed to continue to explicate the relative contributions of excess weight gain, body composition, and body fat distribution to risk factors and disease outcomes, and investigate how the consequences differ for population subgroups, such as those defined by age, sex, race/ethnicity, and life stage. Also important are explorations of the impact of age of onset, duration, and magnitude of weight gain and weight loss patterns on the development of adverse outcomes.

529 Several understudied and emerging areas provide opportunities for research:

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- Document the relationship between obesity and health conditions such as liver disease, osteoarthritis, obstructive sleep apnea, asthma, cancer initiation and progression, and Alzheimer's disease. Elucidate the causal pathways, mediators, and moderators of these associations.

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- Identify the mechanisms and behaviors across the lifespan of the "healthy obese" phenotype, as characterized by a favorable cardiovascular disease risk profile despite excess adipose tissue.

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- Clarify whether weight gain trajectory, overweight, and obesity lead to adverse consequences among older adults (65 years and older), and whether effects differ by functional status.

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541
- Explore how body composition and fat distribution predict adverse physical and mental health outcomes throughout the lifespan.

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543
- Investigate whether physical fitness can ameliorate specific adverse health consequences of obesity.

544   •   Determine the economic and societal effects of differing levels of obesity across the
545   lifespan and in different subgroups (e.g., by gender or socioeconomic status), including
546   healthcare costs, presenteeism/absenteeism, reduced productivity, earning potential,
547   quality and duration of life, stigma, and discrimination.

Design and Test Interventions to Promote Healthy Weight

This area of research includes interventions to prevent overweight or obesity, avoid additional weight gain or promote weight loss in those already overweight or obese, and reduce weight regain in overweight or obese persons who have successfully lost weight. It also encompasses interventions to examine effects of weight loss on various health outcomes.

It is unlikely that any one approach will address the needs of all individuals at risk for or living with overweight or obesity. As a result, this section includes interventions that address multiple levels (from the individual to societal), various modalities (e.g., medical, surgical, behavioral, environmental, and policy), and across critical or high risk periods throughout the lifespan. Given the tremendous public health burden of obesity, intervention research should, where possible, consider intervention benefits in relation to risk, cost, and feasibility.

Selected Research Advances and Challenges

Recent intervention studies have examined a wide variety of topics including, lifestyle interventions for weight loss, maintenance of weight loss, or preventing comorbidities; diets varying in macronutrient composition for weight loss; increasing physical activity in schools, site-based and community approaches to weight control; bariatric surgery outcomes; and efficacy of weight loss medications. Key conclusions have emerged:

- Both sides of energy balance—intake and expenditure—are important for obesity control.

- Macronutrient composition (i.e., percentage of fat, carbohydrate, and protein) is less important than calorie reduction for weight control after one year or more.

- Modest weight loss in overweight/obese adults (i.e., 5% to 10% loss of initial body weight) can result in significant and clinically important reductions in disease risk factors or morbidity, such as blood pressure level, incidence of type 2 diabetes, and osteoarthritis pain.

- Modest weight loss in adults is achievable with a set of standard behavioral counseling tools, such as goal-setting, feedback, self-monitoring, relapse prevention training, social support, and problem-solving. A "toolbox" approach that allows for multi-component individualized strategies—including lifestyle, meal replacements, and/or support for behavior change—has been effective in relatively long-term weight reduction for up to 4 to 5 years. However, these findings are with intensive interventions delivered in large, well-controlled clinical trials and will likely need adaptation to be used in real-world settings.

- Maintenance of successful weight loss remains a challenge and maintenance strategies are less than optimal. Strategies involving brief, monthly personal contact are modestly effective in maintaining weight over 2.5 years, and more effective than access to an unlimited Internet intervention.

- Environmental and community approaches seem promising, as they can reach large numbers of people, but their effectiveness has yet to be adequately demonstrated.

- In children, there is some evidence that interventions to reduce television/computer use (screen time) and to reduce sugar-sweetened beverage consumption have favorable impacts on overweight or obesity.

590 • Current weight-loss medications have modest efficacy, but the high drop-out rate in
591 medication studies often makes conclusions difficult and limits their generalizability.
592 Serious adverse effects remain a concern as well.

593 • Observational (non-randomized) studies suggest that bariatric surgery may have a
594 favorable impact on mortality in those with extreme obesity.

595 **Research Opportunities**

596 Intervention research should be informed by findings from multiple disciplines and approaches
597 including basic biological, behavioral, and social science research; early-phase translational
598 research; epidemiology, pilot, and feasibility studies; and prior intervention studies. In addition
599 to weight and body composition, other outcomes also are important to include in obesity
600 research, including dietary intake and composition, physical activity patterns, quality-of-life,
601 psychosocial and functional status, and health outcomes (e.g., morbidities, adverse effects, and
602 cause-specific or all-cause mortality).

603 Several understudied and emerging areas provide opportunities for intervention research:

604 • Examine the effects of diverse approaches (e.g., single- and multi-level, interventions
605 delivered in settings such as schools, primary care, or community settings) to achieving
606 long-term prevention of overweight and obesity across the lifespan.

607 • Determine the optimal content, dose, and delivery channel of prevention messages
608 delivered within interventions.

609 • Develop and test the effectiveness of obesity prevention strategies in children, including
610 approaches in the very young (infancy to age 6 years).

611 • Evaluate the effects of provision, in schools or pediatric primary care settings, of BMI
612 information and parental counseling on children's weight, health, and psychosocial
613 outcomes

614 • Examine long-term effects of targeted prevention or treatment strategies focused on
615 subpopulations at elevated risk of developing obesity, such as those in
616 disproportionately affected race-ethnic subgroups, of lower socioeconomic status, in
617 rural communities, with physical and mental disabilities, in smoking cessation programs,
618 and in individuals taking medications that can increase body weight.

619 • Study approaches to weight control associated with life events and critical periods where
620 excess weight gain often occurs (e.g., infancy/early childhood, young adulthood,
621 menarche, pregnancy, parenting, menopause). For example, develop and test
622 interventions to promote healthy weight gain during pregnancy and to facilitate/or return
623 to pre-pregnancy weight after delivery.

624 • Explore impact of interventions to promote breastfeeding on post-partum weight
625 retention in the mother and weight and body composition in the offspring.

626 • Test approaches that modify the built environment in ways that are designed to prevent
627 or reduce obesity.

628 • Examine the long-term effects of treatment modalities (e.g., behavioral, pharmacological,
629 and surgical) delivered in healthcare or community settings on weight loss and
630 maintenance.

631 • Study long-term effects of various treatment modalities in extremely obese children and
632   adults to determine which approaches are most efficacious, deliver the most
633   improvement in health status, and are safest in these populations.

634 • Examine effects of weight loss interventions in obese individuals who already have an
635   obesity-related illness to determine effects on long-term control or amelioration of the
636   illness (e.g. obstructive sleep apnea, type 2 diabetes, osteoarthritis, various cancers, or
637   cardiovascular diseases).

638 • Examine the efficacy of interventions to increase habitual sleep time on metabolic
639   regulation (e.g., reducing body weight, preventing weight gain, regulating appetite,
640   improving glucose tolerance and insulin sensitivity).

641 • Examine effects of diet composition, including nutrients and bioactive food components,
642   food additives, sensory and hedonic properties of food, and dietary supplements on
643   body weight and body composition.

644 • Test whether personalized dietary or physical activity approaches based on genotype or
645   phenotype are more effective than non-personalized approaches.

646 • Design and test novel weight control interventions based on basic behavioral and social
647   science findings. Explore how values, motives, and behaviors from non-health areas
648   may change obesity-related behaviors (e.g., how concerns about the environment may
649   increase active transportation).

650 • Study ways to enhance adherence to behaviors recommended in weight control
651   programs, such as self-monitoring behaviors, increased physical activity, and reduction
652   in caloric intake.

653 • Design and test novel weight control interventions that incorporate existing or emerging
654   technologies (e.g., mobile phones, interactive voice response, virtual reality mediums,
655   global positioning systems, social networking platforms).

656 • Study the effect of media (e.g., advertising, television programming, the Internet, digital
657   marketing) on obesity related decision making, energy intake, and physical activity, and
658   test child- and parent-friendly technologies to support behavior change or deliver
659   effective preventive messages.

660 • Explore approaches to improve the maintenance of successful weight loss over time in
661   diverse populations.

662 • Test the efficacy of economic strategies, alone or in concert with other strategies, to
663   promote weight loss or prevention of excess weight gain such as financial incentives,
664   subsidies, taxes, and pricing strategies.

665 • Develop and test the efficacy of weight management interventions that involve
666   collaborations between healthcare providers and non-clinical settings (such as
667   community centers or commercial weight-loss programs).

668 • Explore effects of existing and new obesity medications to determine which medications
669   and delivery methods, and what combinations of medication and lifestyle changes are
670   most effective in improving obesity and health outcomes in various population groups
671   over the long-term with an acceptable risk/benefit ratio.

672 • Determine the short and long-term effectiveness of bariatric surgery as compared to
673   behavioral and/or pharmacologic approaches in adolescents and adults with a variety of
674   comorbid conditions.

675   • Explore the short and long-term safety and effect on health of bariatric surgery in those
676   with a BMI <35 and significant co-morbid conditions.

677   • Test prevention or treatment approaches that are designed to better inform policy
678   decisions, including testing the effects of approaches that can reach large numbers of
679   people (e.g., communication strategies such as social marketing, environmental
680   changes, or food and activity related policy changes), as well as interventions in various
681   settings (e.g., home, school, worksite, healthcare, community) that are feasible for
682   broad-scale delivery and sustainability.

683   • Examine the interacting effects and complexity of multi-level and/or multi-component
684   intervention programs addressing behavior, environment, and policy issues, including
685   home/family, sociocultural, and built environments.

686   # Conduct Dissemination and Implementation Research

687   Dissemination and implementation research are key aspects of translational research and are
688   the focus of this section. These later phases of translational research encompass such fields as
689   surveillance, health services, dissemination, implementation, policy, and evaluation.

690   Traditionally, once targets for intervention were discovered and efficacy established for
691   individual or population-based approaches, a next step was to translate those results into real-
692   world practice and settings. In the past few decades, the need to build cyclical and externally
693   valid models of research, such as "rapid learning" clinical and public healthcare systems in
694   which research and evaluation infrastructures are built into these systems to allow evidence to
695   be gathered in the context of "real-world practice," has expanded the understanding of
696   translational research as an iterative process. In addition, research evidence documenting the
697   critical role of contextual, environmental, and policy forces on achieving sustained improvement
698   in human behavior has led to a focus on multi-level and systems studies that intervene not just
699   with individuals but also the environments in which they live and work.

700   Dissemination and implementation research are essential to meet the following aims: 1)
701   Quantify the extent of the problem in order to appropriately direct resources and interventions to
702   the populations with greatest needs; 2) Identify whether interventions proven to be efficacious
703   within the context of controlled randomized clinical trials have the same benefit when they are
704   applied in less controlled settings among populations with different characteristics; and 3)
705   Improve the effectiveness, efficiency, and sustainability of providing interventions so that a large
706   number of people can be reached with limited resources.

707   Emerging evidence indicates approaches that address multiple levels (e.g., individuals, their
708   families, and the environment in which people live) are likely needed for interventions to have
709   broad reach and for effects to be sustained. Therefore, research in surveillance, health
710   services, dissemination, implementation, policy, and evaluation is increasingly designed to
711   encompass data collected at multiple levels, including the individual, family, and community.

712   **Selected Research Advances and Challenges**

713   Key advances have occurred in recent years in dissemination and implementation research:

714   • Because surveillance of diet and physical activity has benefited by improved
715   measurement and analytic methods, the extent to which the population's behaviors align
716   with recommendations is now more accurately quantified. Improved methods are
717   illustrating that diets fall short of recommendations in many areas. A significant gap
718   exists between self-report (30% to 40% achieving recommended levels of physical
719   activity) and objective measures (3% to 5% achieving recommended levels) of
720   population prevalence of physical activity.

721   • Geographic information system (GIS) methodologies now enable linkage across levels
722   of data from individuals to family and community. GIS includes measures of the food
723   and physical activity environments, air and water quality, and access to health-promoting
724   environments, healthcare providers, healthcare access, and policies.

725   • Automated systems for data collection at multiple levels through electronic health
726   records in healthcare delivery systems, geospatial data on communities and
727   environments, and Internet-based survey methods allow integrated linkage of data on

728   individuals to their environments and examination of self-report and objective measures
729   of behaviors, biologic characteristics, social networks, medical conditions,
730   pharmaceuticals, and treatment that may influence obesity-related behaviors and body
731   weight or composition.

732   • The need for evidence to support and ensure high-quality obesity care has been
733   recognized. NIH led the first nationally representative physician survey, the *National*
734   *Survey of Energy Balance Related Care among Primary Care Physicians*, which
735   provides important national estimates of baseline data on knowledge and practices in
736   this area among providers treating adults and children.

737   • The establishment of health services and economics research consortia that work within
738   the context of healthcare delivery systems enables expanded collection of meaningful
739   use data on the process and cost of obesity-related healthcare. These consortia are
740   leading to an improved understanding of healthcare practice and outcomes, how they
741   relate to obesity and its comorbidities. They also provide opportunities for developing
742   electronic data and feedback systems that provide real-time clinically relevant
743   information to patients and providers.

744   • Emerging obesity policy research is developing rigorous approaches for evaluating the
745   influence of public policies to improve food and physical activity environments. Early
746   research suggests that approaches such as reducing sugar-sweetened beverages within
747   schools may have measurable benefits in reducing BMI in school-aged children.

748   • Methods to estimate the economic costs of obesity have evolved from cross-sectional to
749   longitudinal. This evolution is allowing researchers to examine relationships over time
750   and has improved the estimation of the long-term costs of obesity. Researchers can
751   now quantify the contribution of treatment for comorbid disease to increases in
752   healthcare costs.

753 **Research Opportunities**

754 A critical need in this field is to integrate theories and research approaches from multiple
755 disciplines to ensure appropriate research designs that address the complex and multifactorial
756 nature of successful obesity prevention and treatment in clinical and public health practice. In
757 addition, the development of valid measures appropriate to the specific research question and
758 populations and environments under study is a high priority. In some instances, these
759 measures may be objective, such as medical records data of medications or procedures or
760 coding of environmental variables. In other instances, appropriate and valid measures may be
761 based on self-report. Major advances in automated approaches to capturing both objective
762 (e.g., physical activity monitors) and self-reported (e.g., computerized dietary recall instruments)
763 measures of health behaviors and outcomes are being applied to this field. Advances in GIS-
764 labeled data, methodology, and application are essential to enable linkages across the socio-
765 ecological model of obesity.

766 A number of specific topics within dissemination and implementation research provide
767 opportunities for investigation:

768 Surveillance

769   • Develop infrastructure and methods to integrate surveillance research across individual,
770   family, community, and state and national levels, using valid measures of behaviors,

771   environments and policies to gain a better understanding of the interplay among
772   behaviors and influencing factors. It is critical that such systems include longitudinal
773   components to capture changes in health behaviors and weight over time, including
774   long-term maintenance of weight loss.

775   • Increase the use of sampling designs that allow for estimates of obesity and obesity-
776   related behaviors in local and/or underserved populations, such as at-risk populations
777   defined by race/ethnicity, income, age, geography, or other factors that influence
778   obesity. These improved estimations will enhance the relevance of obesity data for
779   public health action at the local, state, or national level.

780   • Encourage research that examines multi-level questions and promotes innovative
781   approaches to linking local, state, or national surveillance systems to monitor health
782   behaviors with GIS and other environmental-level data.

783   Health Services and Economics

784   • Conduct comparative effectiveness, cost, behavioral economic, and cost-effectiveness
785   research to identify effective interventions for obesity prevention and control in diverse
786   populations, for example, evaluating the effectiveness of targeted subsidies on
787   purchases of healthy food through nutrition assistance programs or evaluating the
788   impact of taxes on purchase of less healthful foods.

789   • Support multi-level research within the context of primary care, using advances in
790   eHealth technologies in combination with electronic medical records (EMRs). This
791   research will allow patients and providers to identify integrated and staged approaches
792   for addressing obesity, particularly among patients with multiple chronic diseases.

793   • Use research networks within healthcare systems to document obesity outcomes related
794   to implementing processes of care, such as screening for obesity and delivery of obesity
795   care within the healthcare setting.

796   • Enhance capacity to examine behavior and subsequent health outcomes and costs
797   related to factors such as agriculture, food supply, urban design, and transportation
798   policies. All these factors have an impact on physical activity and food choices.

799   • Determine economic, behavioral, and social costs and benefits, such as health
800   improvement, disability reduction, time use, convenience, perceived benefit, to
801   individuals of making behavior changes recommended for obesity prevention and
802   control.

803   Dissemination and Implementation

804   • Use approaches, such as community-based participatory research, that engage and
805   involve community members in designing, implementing, and interpreting large-scale
806   research in diverse communities to determine the acceptability of environmental and
807   societal changes that might be undertaken to promote healthy eating and activity
808   behaviors.

809   • Conduct research on appropriate terms, messages, media, and strategies to
810   communicate about weight control with attention to population-specific needs, such as in
811   children or adolescents and their families, women who are planning a pregnancy, or are
812   pregnant, ethnically diverse audiences and those of various cultural or socioeconomic
813   backgrounds, and different levels of general and health literacy.

814   • Conduct "best practices" research to enhance obesity screening, prevention and
815   treatment in primary care. Use these best practices and other resources to develop,
816   implement, and test messages, clinical guidelines, standardized lifestyle assessment
817   methods, and other tools, procedures, and organizational systems in various primary
818   care settings to increase the prevention, identification, and treatment of obesity in
819   children and adults.

820   • Test innovative adaptations of evidence-based obesity prevention and treatment
821   approaches that can be disseminated and sustained in families, clinical healthcare
822   practice, and child care, school, or community settings.

823   • Support research on how electronic applications, such as eHealth applications in mobile
824   phones or on the Internet, can expand reach, tailoring, and rapid dissemination of
825   interventions to large and diverse populations.

826   • Support research on education and outreach efforts to promote healthy weight gain
827   during pregnancy and to promote initiation and maintenance of breastfeeding through
828   creative approaches, including those that incorporate innovative technologies and
829   communications.

830   <u>Policy and Evaluation</u>

831   • Evaluate the influence of policy intervention "natural experiments" on diet and physical
832   activity practices at local, state and federal levels. Examples of this research include
833   examining the influence of price on food choices, the impact of school or worksite
834   policies to support physical activity, or the influence of safe environments on physical
835   activity.

836   • Develop improved methods for evaluation of natural experiments, such as cost effective,
837   practical, and valid approaches to determine the effect of grassroots initiatives to
838   implement community-wide or setting-specific (e.g., school, worksites) regulation
839   regarding diet or physical activity.

840   • Engage investigators and stakeholders from diverse disciplines to ensure that policies
841   under investigation have the potential for broad implementation.

842   **Improve Measurement Tools, Technology, and Methods**

843   At each step of the research continuum, appropriate measurement is essential for advancing
844   scientific knowledge and ensuring public health relevance. Accurate measures of body
845   composition, energy intake, and energy expenditure of individuals are essential for
846   understanding the etiology of obesity as well as the effectiveness of prevention and intervention
847   efforts. Many existing measures have limitations with regard to accuracy, reliability, and
848   sensitivity in free-living individuals. Measurement in children and adolescents is a particularly
849   challenging and important area for research.

850   Three types of self-reported diet and physical activity assessment instruments are widely used:
851   frequency questionnaires to assess nutrient intake, records (or diaries), and 24-hour recalls.
852   These approaches have limitations because individuals do not commonly attend to what they
853   eat or their activities levels, and often cannot accurately estimate usual dietary intake or bouts of
854   physical activity without error or bias.

855   Various objective measures also are used in diet and physical activity research. Direct
856   observation of dietary intake or physical activity is a useful objective measure but its use is
857   limited primarily to institutional settings. Research and clinical practice would be enhanced by
858   the development of new or improved objective measures that could be used in free-living
859   individuals to measure fitness and functional status. Most current biomarkers of diet cannot
860   capture amount of intake nor distinguish short-term versus long-term intake. For physical
861   activity, wearable monitors do not capture the full range of activities in which people engage,
862   and methods to convert monitor data into measures of energy expenditure are still evolving. For
863   both diet and physical activity, objective measures tend to be burdensome for research
864   participants and expensive.

865   Body composition measurement has advanced considerably in the past decade. However,
866   many of these measures are too costly, time consuming, and technically challenging to use in
867   clinical settings or in population studies. Although BMI is a good estimate of overall fatness in a
868   population, it is not ideal for understanding individual body composition status or changes and is
869   not sensitive to level of fitness, maturational stage, sex, and race. Thus, the same BMI may
870   represent very different body composition profiles. The capacity to measure body composition
871   accurately in all age groups in clinical settings would allow research studies of the relationship
872   between body composition and clinical features, potentially facilitating translation to medical
873   management in real-world situations.

874   High-quality environmental measures also are vital components of research on diet and physical
875   activity behavior and the prevention and treatment of obesity. Examples of environmental
876   measures of interest include access to nutritious and affordable food, quality and quantity of
877   sidewalks, and availability of bike lanes. Researchers use a variety of methods to measure food
878   and physical activity environments, including instruments—both self-reported and observed—
879   and methodologies such as geographic information system (GIS). Research that can place
880   individuals within the specific environments that they experience has been facilitated through
881   advances in micro-scale measurements, such as sidewalks, safety, and exact locations of food
882   vendors.

883   Finally, given the multiple feedback loops involved in the regulation of body weight, innovative
884   methods that reflect and encompass this complexity may provide the greatest opportunities for
885   moving forward. Systems methodologies may help uncover novel, and perhaps unanticipated,

886 strategies to combat obesity. They may also reveal unanticipated adverse consequences of
887 potential interventions and policies. A transdisciplinary systems approach can be used in a host
888 of research areas, from biological to population systems modeling and the integration of the two.
889 Advances in novel statistical approaches can also be applied to the design and analysis of
890 research studies, as well as to technological innovations for genetics and bioinformatics. All of
891 these applications present new and exciting opportunities for future obesity research.

892 **Selected Research Advances and Challenges**

893 Diet and physical activity tools and measures have improved markedly in recent years, as
894 shown by the following advances:

895 • Doubly-labeled water, an accurate measure of total energy expenditure over a 2-week
896 period, recently has been used to assess and correct for error in self-reported diet and
897 activity assessment instruments in free-living individuals.

898 • Recent advances have occurred in the use of relatively inexpensive, automated systems
899 for use in self-reported dietary intake and activity. These include Internet, personal
900 digital assistant (PDA), and mobile phone-based methods to collect data for frequency,
901 recall, and record questionnaires.

902 • Small-molecule metabolite profiles (serum metabolomic profiles) assessed by HPLC
903 MS-separations, coupled with colorimetric array detection, have been found to
904 accurately identify *ad libitum* fed and energy-restricted rats. These profiles are being
905 adapted for human epidemiology studies to provide insight about energy balance and
906 cancer.

907 • Accurate measurements of body movements and positions, combined with physiological
908 responses (e.g., heart rate, core temperature, oxygen saturation, and glucose) using
909 accelerometers and other advanced biosensors have improved the capacity of wearable
910 monitors to measure physical activity. Associated technological advances in sensor
911 miniaturization, data acquisition and processing, low power consumption, wireless
912 communication, large data storage, and advanced algorithms have placed objective
913 monitoring within the reach of a growing field of researchers.

914 • Over the past decade, researchers have developed "first generation" measures of the
915 food and physical activity environments using a variety of methods, including self-
916 reported measures, observation systems, and geospatial data mapping technology (e.g.,
917 GIS). Advances in mobile phone technology with integrated global positioning systems
918 (GPS) facilitate collection of data about individual physical activity behavior and context
919 in real-time.

920 • Advances in transdisciplinary research have brought together public health and medicine
921 with other fields, such as computer science and engineering, to apply systems thinking
922 to obesity research. These collaborations have capitalized on new, high-throughput
923 computing power to integrate complex concepts and data that range from genetics to
924 policy.

925 **Research Opportunities**

926 New diet and physical activity measures with improved accuracy, precision, reliability, usability,
927 and flexibility are needed. Measures with improved sensitivity to change are also needed,

928 especially in the areas of biomarkers, fitness and functional status, thermogenesis, imaging,
929 body composition, objective measurement systems, and environment. Given the complexity of
930 factors that influence obesity, new systems methodologies also need to be employed in
931 conducting next-generation obesity research.

932 Biomarkers

933 • Develop genomic, proteomic, and metabolomic approaches for use in identifying
934   biomarkers of energy balance as well as to assist with understanding specific genes,
935   proteins, and small molecules involved in energy balance that influence the tendency to
936   gain or lose weight.

937 • Develop nanosensors for quantifying circulating and tissue concentrations of macro- and
938   micronutrients and their metabolites to help improve accuracy and precision of dietary
939   assessment.

940 • Develop high-throughput, low-cost metabolomic profiling approaches in bio-fluids and
941   tissues to characterize and identify biomarkers involved in the progression of weight gain
942   and loss in animal models and humans.

943 • Develop mathematical models using metabolic profiles to predict energy intake or
944   energy expenditure.

945 • Encourage systems biology efforts to harness computing power in a way that can bring
946   together information on proteins, genes, metabolites, and human or animal phenotypes
947   related to metabolism and weight.

948 • Develop technologies for novel ways to noninvasively assess biochemical indicators of
949   fitness. Also develop assays to monitor measures such as nutritional status,
950   cardiovascular/cardiorespiratory tone, serum biochemistry, metabolic enzyme activity,
951   and epigenetic changes. Combinations of these metrics could provide an overall
952   biochemical measure of fitness.

953 • Refine existing measures and develop new methods to assess biochemical and
954   physiological indicators related to body composition, particularly adiposity and its type
955   and distribution, muscle mass, and bone health.

956 Fitness and Functional Status

957 • Clarify the optimal methods for assessing fitness and functional status in people who are
958   overweight or obese. Improve instruments and equipment to have higher dynamic
959   ranges as well as higher sensitivity to measure acute and intermediate changes due to
960   specific interventions.

961 • Develop practical and cost efficient methods to assess fitness in the context of a medical
962   visit.

963 Thermogenesis

964 • Develop technologies that can be used in free-living populations to measure resting
965   energy utilization of the various body tissues or to evaluate efficiency and heat
966   production to better understand energy utilization under various normal conditions.
967   These technologies might include 3-D imaging of heat production deep within tissues,
968   clothing with wireless sensors to capture body temperature and degree of sweating in

969 addition to movement, and new methods to non-invasively monitor mitochondrial
970 membrane potential and ATP production.

971 <u>Imaging</u>

972 • Use brain imaging approaches combined with neuropsychological and neuro-cognitive
973 assessment to characterize the many interacting roles of the brain in obesity. For
974 example, to improve understanding of the role and response of the brain in hunger and
975 satiety, taste, preference and reward with food and physical activity, the sensory and
976 emotional response associated with eating, food craving in the absence of hunger,
977 decisions surrounding food and physical activity, altered response to food and hormone
978 signals after weight loss or gain, and the central control of peripheral nutrient storage,
979 metabolism and heat generation.

980 <u>Body Composition</u>

981 • Develop improved technologies to determine body composition. Although dual-energy
982 x-ray absorptiometry is readily available, easily performed in children and adults, and
983 provides an estimate of fat distribution, it involves radiation exposure and generally has
984 body size limitations. Techniques that could minimize variability, yield site- and tissue-
985 specific fat content, eliminate size limitations, and minimize radiation exposure are
986 needed.

987 • Develop accurate and reliable tools to measure total and regional body composition
988 across the lifespan that are applicable to clinical and population study settings. For
989 example, develop tools to allow improved and safe measurement of body composition in
990 pregnancy, infancy, and early childhood.

991 <u>Objective Diet and Physical Activity Behavior Measurement Systems</u>

992 • Encourage development of improved mobile phone or camera devices that can use
993 digital pictures and image recognition technology to accurately identify foods and portion
994 sizes for purposes of advancing food record dietary assessment methods.

995 • Develop statistical methods for analyzing data obtained from wearable physical activity
996 monitors. These methods can be used to improve modeling of measurement error and
997 correct misclassification of physical activity, as well as model patterns of physical activity
998 behavior so as to better characterize "usual" activity.

999 • Develop accurate, reliable, and effective devices to be used in monitoring changes over
1000 time and in treating obesity and overweight across the life span, including low-cost field
1001 measures that are sensitive to change in different age and BMI groups. This includes
1002 engineering tools that integrate self-reported information with biologic and/or sensor
1003 measures of physical activity, diet/nutrition, and energy balance/obesity in real time.

1004 • Develop energy balance indicators, such as "smart" clothing, household, or office
1005 furnishings, that incorporate sensors, bar codes, or other identifying technologies to
1006 calculate energy expenditure, detect motion, identify food characteristics, and assess
1007 portion sizes.

1008 • Develop mathematical and computational models for predicting interrelationships
1009 between energy balance and weight control or obesity.

1010 • Explore how advances in the application of item response theory methodology can be
1011 applied to social and behavioral measurement.

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- Develop interactive technologies (e.g., virtual reality) to assist individuals in changing their behavior and affective response when making food and physical activity decisions.

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- Incorporate measurement approaches for family history and social networks in studies of obesity and health behaviors.

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Environment

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- Create measures of the initiation, support, and reinforcement of food and beverage consumption and physical activity practices and factors associated with decreasing sedentary behaviors. Measures should assess determinants of behaviors in multiple settings (e.g., home, daycare, preschool, or other community venues) facilitated by a variety of care providers (e.g., healthcare providers or teachers).

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- Develop wearable devices to combine GPS with physical activity and physiologic sensors.

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- Develop valid and reliable measures of community food and physical activity environment variables that are applicable to communities at highest risk for obesity.

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Systems Methodologies in Design and Analysis

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- Employ quantitative approaches, such as mathematical and computational modeling, to provide an infrastructure for systematically linking data and knowledge obtained from different biological scales and regulatory mechanisms in obesity. Computational models can be used to drive hypotheses and experimental design (e.g., inclusion of relevant risk regulators). They also can be useful in reformulating hypotheses to optimally address specific questions or predictions. Systems models may provide insights into the mechanisms underlying the success (or failure) of interventions in a particular context. Virtual (*in silico*) drug trials, for example, would save a tremendous amount of time and cost in obesity research.

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- Encourage systems science computational techniques to integrate individual and socio-environmental factors over time to investigate the etiology of obesity and to test intervention strategies in a virtual environment. Applying systems science methods in obesity research has the potential to explain how small changes at the individual level accumulate at the population level to reveal significant shifts in the root causes of disease. Examples of these integrative computational techniques include system dynamics modeling, agent-based modeling, network analysis, Markov modeling, dynamic microsimulation modeling, and discrete-event simulation.

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Advanced Statistical Approaches in Design and Analysis

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- Incorporate approaches to statistical modeling, such as non-linear quantitative statistics, non-parametric approaches, Bayesian and small n-statistics, dynamic modeling, and time-continuous methodology into obesity research.

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- Employ intervention designs that can be adaptive, account for multiple active components, and better balance internal and external validity.

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- Enhance innovation in the application of simulation modeling that integrates biologic, genomic, behavioral, contextual, policy, and economic data to identify the best candidates for large-scale interventions among diverse populations.

1053 <u>New Genetics Technology</u>

1054 • Encourage the development and use of next-generation sequencing, which holds the
1055   promise of identifying rare variants with large effect sizes. These variants are
1056   systematically missed in GWAS and may theoretically account for much of the currently
1057   unidentified heritability of obesity. Rare variants may be identified in samples of tens or
1058   hundreds of individuals (as opposed to the tens of thousands required to identify
1059   common polymorphisms with very small effect sizes).

1060 <u>Bioinformatics and Data Standardization</u>

1061 • Encourage advances in data storage, compression, and transmission technology to
1062   ensure that the storage infrastructure continues to support the ever-growing data output
1063   of scientific and diagnostic instruments. The scientific data storage infrastructure of the
1064   future will need to not only accommodate the enormous amounts of data derived from
1065   modern experimental techniques but also have the throughput necessary to make the
1066   data available for analysis. It also needs to be secure enough to ensure the long-term
1067   integrity of the scientific knowledge stored there.

1068 • Encourage the use of core measures across the individual, family, and community level
1069   to enable the results of similar studies to be directly compared.

1070 ## INTEGRATION OF RESEARCH INTO PRACTICE

1071 On the surface, it may seem that the solution to the obesity epidemic is obvious: help people
1072 to eat less and move more. The reality is that this change is very difficult to accomplish and
1073 research is critical to address the issue successfully.

1074 Research supported and conducted by the NIH will be a key contributor to the efforts to
1075 prevent and treat obesity and associated health consequences. The challenges of today's
1076 obesity landscape are daunting, yet the discoveries emanating from research investments
1077 offer unprecedented opportunities to help meet these challenges. NIH is committed to
1078 supporting basic research, clinical discovery, and translational research to inform practice
1079 and public policy. Much of this research is directly relevant to providing the scientific
1080 evidence base for developing and implementing national public health campaigns, such as
1081 the *Let's Move!* Campaign (http://www.LetsMove.gov), launched by the First Lady.

1082 The NIH, in collaboration with other governmental and nongovernmental organizations, helps
1083 to disseminate important research findings to the public, policy makers, and healthcare
1084 professionals.

1085 The opportunities for applying research findings in practice are many and diverse. As
1086 research opportunities identified in the *Strategic Plan for NIH Obesity Research* lead to
1087 effective interventions for prevention and treatment, NIH can serve a critical role in helping
1088 ensure that these advances reach the appropriate audiences to promote their rapid
1089 implementation.

1090 **Examples of NIH Efforts to Apply Research Findings in Practice**

1091 - The NIH has taken steps to translate obesity research into "best or promising
1092 practices" related to prevention and treatment for community leaders, practicing
1093 clinicians, patients, and the general public. Population-based strategies that include
1094 national education programs have been an important approach to engage numerous
1095 partners and organizations around a common message and evidence-based
1096 strategies. **We Can!**[TM] (Ways to Enhance Children's Activity and Nutrition) is one
1097 example of an evidence-informed national education program. This campaign
1098 provides flexible resources and strategies that can be implemented in diverse settings
1099 to help families, schools, communities, organizations, and national partners and
1100 corporations in their efforts to help children maintain a healthy weight. **We Can!**[TM]
1101 has an extensive website at http://wecan.nhlbi.nih.gov.

1102 - The NIH develops evidence-based clinical guidelines for overweight and obesity as a
1103 way to translate the science into practical recommendations for clinical care.
1104 Currently, the NIH *Clinical Guidelines on the Identification, Evaluation, and Treatment*
1105 *of Overweight and Obesity in Adults*
1106 (http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm) are being updated using a
1107 rigorous evidence-based approach that involves a systematic review of the literature.
1108 The updated guidelines will provide recommendations about measuring overweight
1109 and obesity in adults using BMI and/or waist circumference measures, information
1110 about the role of additional risk factors in defining the risk status of individuals, and
1111 recommendations on various treatment options. The expert panel is taking into
1112 account the needs of primary care clinicians and patients, and working to be sure that

1113   the guidelines are clear and focused, without ambiguity as to what providers and
1114   patients should do as based on the scientific evidence. Upon the release of the
1115   guidelines, the NIH will share tools and resources with key national and international
1116   audiences through Web Based communities of practice, where clinicians in primary
1117   care or patients themselves can also share ideas and strategies. The update to the
1118   obesity guidelines, along with updates to guidelines on blood pressure and
1119   cholesterol, will ultimately feed into an integrated Cardiovascular Risk Reduction
1120   Guideline for Adults.

1121   • The NIH has developed several obesity-related web-based resources. These
1122   include: the Aim for a Healthy Weight website that includes the BMI calculator
1123   (http://www.nhlbisupport.com/bmi/) and the Portion Distortion website
1124   (http://hp2010.nhlbihin.net/portion), the Automated Self-Administered 24-hour Recall
1125   System (ASA24: https://asa24.westat.com/index.htm), Measures of the Food
1126   Environment (https://riskfactor.cancer.gov/mfe), Cancer Control P.L.A.N.E.T
1127   (http://cancercontrolplanet.cancer.gov), and the Weight-control Information Network
1128   (http://win.niddk.nih.gov/). The uptake and dissemination of research advances have
1129   been accelerated by collaboration among research funders and national
1130   organizations. One example of such collaboration is the National Collaborative on
1131   Childhood Obesity Research (NCCOR: (http://www.nccor.org/). The NIH has joined
1132   with the Centers for Disease Control and Prevention, the Robert Wood Johnson
1133   Foundation, and the United States Department of Agriculture to establish NCCOR in
1134   an effort to improve the efficiency, effectiveness and application of childhood obesity
1135   research and to halt—and reverse—the increase in childhood obesity.

1136   **Opportunities for Fostering the Uptake of Research Findings**

1137   Enhanced adoption and uptake of outreach and education programs will maximize the public
1138   health benefit of research. The NIH can support opportunities for applying research findings
1139   in practice in several ways:

1140   • Support communication and collaboration between researchers and other sectors of
1141   the community to foster translation and uptake of evidence-based strategies.

1142   • Support population-based strategies, public education outreach programs, and media
1143   campaigns aimed at preventing overweight in at-risk groups, such as children and
1144   youth, young adults, low income, and racial and ethnically diverse populations.
1145   These strategies should draw on research findings to help direct key messages,
1146   promote evidence-based strategies, guide social marketing techniques and policy
1147   interventions, and develop the role of new technologies and social media.

1148   • Foster communication strategies that are tailored to diverse audiences, including
1149   individuals who are overweight and obese, healthcare and public health
1150   professionals.

1151   • Convey research evidence about the causes of obesity and its prevention and
1152   treatment in a respectful, appropriate and user-friendly way to the public, healthcare
1153   professionals and organizations/practices, and policy makers.

1154   • Encourage healthcare systems to apply evidence-informed obesity screening,
1155   prevention, and treatment interventions for both children and adults in ways that
1156   minimize barriers to uptake for both individuals and healthcare professionals.

1157
CONCLUSION

1158   Meeting the challenges of obesity and its health consequences in the U.S. and worldwide will
1159   require the efforts of many. The NIH is committed to moving research forward to build the
1160   scientific evidence base for action at multiple levels. This research will address the multi-
1161   faceted contributors to obesity, helping to identify novel therapeutic targets and develop more
1162   effective approaches to prevent and treat obesity in children and adults, with steps that can
1163   be taken by individuals, families, healthcare providers, schools, worksites, and communities.
1164   As the NIH pursues promising avenues and exciting new scientific opportunities, this updated
1165   *Strategic Plan for NIH Obesity Research* will serve as a guide to accelerate progress in
1166   obesity research, from basic discovery to application and integration of prevention and
1167   treatment strategies in clinical practice and community settings, with the goal of extending
1168   healthy life and reducing the burdens of illness and disability.