

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The CardioMetabolic Health Alliance



Working Toward a New Care Model for the Metabolic Syndrome



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ABSTRACT

The Cardiometabolic Think Tank was convened on June 20, 2014, in Washington, DC, as a “call to action” activity focused on defining new patient care models and approaches to address contemporary issues of cardiometabolic risk and disease. Individual experts representing >20 professional organizations participated in this roundtable discussion. The Think Tank consensus was that the metabolic syndrome (MetS) is a complex pathophysiological state comprised of a cluster of clinically measured and typically unmeasured risk factors, is progressive in its course, and is associated with serious and extensive comorbidity, but tends to be clinically under-recognized. The ideal patient care model for MetS must accurately identify those at risk before MetS develops and must recognize subtypes and stages of MetS to more effectively direct prevention and therapies. This new MetS care model introduces both affirmed and emerging concepts that will require consensus development, validation, and optimization in the future. (J Am Coll Cardiol 2015;66:1050–67) © 2015 by the American College of Cardiology Foundation.

EXECUTIVE SUMMARY

AFFIRMED CONCEPTS. Think Tank (TT) participants reviewed concepts accepted by the medical

community and supported in previous recommendations. Those affirmed concepts (ACs) presented here constitute a consensus, are consistent with the evidence base established at the TT, and are deemed to

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have sufficient potential benefit to warrant actionable recommendations.

AC.1. Metabolic syndrome (MetS) is a progressive pathophysiological state associated with substantially increased risk for development of type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD).

AC.2. MetS is clinically manifested by a cluster of risk factors that are causally inter-related (not aggregating by chance alone).

AC.3. Risk for adverse health outcomes increases substantially with accumulation of component MetS risk factors, in addition to unmeasured (“residual risk”) factors. Timely recognition of MetS risk factors helps to identify individuals at high risk for ASCVD and T2D and to initiate preventive strategies before end-organ damage occurs.

AC.4. Obesity is a MetS risk factor that is imperfectly gauged by body mass index and/or waist circumference, and is modulated by adipocyte distribution, size, and function, as well as race, behavior, and lifestyle. Excess ectopic and/or visceral adiposity is fundamental to the pathophysiology of MetS.

AC.5. Treatment of MetS should prioritize therapeutic lifestyle changes, including a healthy diet and regular physical activity, to address all risk factors. Treatment should also continue to be focused on specific interventions for component MetS risk factors.

AC.6. The term “Metabolic Syndrome” will be used to designate a portfolio of descriptors that have previously included the terms *cardiometabolic syndrome*, *insulin resistance syndrome*, *syndrome X*, and others. TT participants concluded that MetS was the term most often used in the scientific published data and by health care professionals. Although arguments can be made for use of the other terms, the TT felt that trying to replace MetS would distract from its primary tasks.

EMERGENT CONCEPTS. New concepts emerged during the interdisciplinary discussions of the evidence base at the TT. These emergent concepts (ECs) require validation, but may have sufficient potential to generate actionable recommendations.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ACO = accountable care organization

ASCVD = atherosclerotic cardiovascular disease

BMI = body mass index

CMHA = CardioMetabolic Health Alliance

MetS = metabolic syndrome

PCMH = patient-centered medical home

T2D = type 2 diabetes

TT = think tank

VAT = visceral adipose tissue

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- EC.1.** MetS should be classified by subtype and stage, which translate to specific evidence-based management algorithms to improve clinical outcomes.
- EC.2.** Improved metrics to define high-risk obesity are needed and may be characterized by evidence-based assessments including, but not limited to, waist circumference, body composition, and imaging-based assessments of ectopic fat and/or visceral adipose tissue.
- EC.3.** Structured lifestyle interventions for residual risk reduction are required. Focused research and improved education on lifestyle medicine are also needed.
- EC.4.** Health care disparities need to be addressed with respect to: 1) access to structured lifestyle interventions; 2) integrated care delivery systems with enhanced provider awareness, accountability, and communication, along with tools to appropriately identify and treat those at risk; and 3) community engagement.
- EC.5.** New care models, such as the patient-centered medical home (PCMH) and Accountable Care Organizations (ACOs), are needed that incorporate new technology, electronic health records, and novel reimbursement paradigms.

KEY FINDINGS. After reviewing the affirmed and emergent concepts, the writing committee formulated 5 key findings (KFs).

- KF.1.** MetS is a cluster of risk factors, both formally defined and less well recognized, that increase the risk of certain diseases.
- KF.2.** The presence of ectopic fat and/or visceral adipose tissue is critical to the pathogenesis of MetS and may explain some of the variability in phenotypic presentation across racial groups.
- KF.3.** A new care model for patients with MetS is essential and should include screening, risk stratification, and algorithmic management of patients according to the specific subtype and stage.
- KF.4.** Structured lifestyle interventions are required to adequately treat MetS and reduce residual ASCVD risk.
- KF.5.** Implementation of a new patient care model should focus on integrated care delivery, alternative reimbursement strategies (perhaps utilizing the emerging constructs of the PCMH and ACO), and education that uses structured lifestyle intervention; optimal use of pharmaceuticals, including combination therapies; and appropriate consideration of surgery.

INTRODUCTION

MetS recognizes a group of risk factors underlying cardiovascular and metabolic disease. The most accepted clinical definition, established by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) in 2001, recognizes multiple components of the syndrome related to atherosclerotic cardiovascular disease (ASCVD) risk: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, proinflammatory state, and prothrombotic state. The criteria for clinical diagnosis of MetS are 3 or more of the following: 1) waist circumference >102 cm (40 in) in men and 88 cm (35 in) in women; 2) triglycerides \geq 150 mg/dl; 3) high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women; 4) blood pressure \geq 130/85 mm Hg; and 5) fasting glucose \geq 100 mg/dl (1). In 2005, the NCEP-ATP III criteria were modified to suggest lower waist circumference cutpoints for Asian Americans (\geq 90 cm [35 inches] in men and \geq 80 cm [31 inches] in women) (2). However, these criteria do not fully encompass the pathophysiological complexity of the syndrome, recognize predisposition to different types of end-organ damage, or account for health disparities according to race, sex, or socioeconomic status, in screening for or treating the syndrome.

MetS is typically under-recognized in the clinical setting, even just on the basis of the 5 standard criteria. Additional elements of MetS include high apolipoprotein B, small low-density lipoprotein (LDL) particle size, endothelial dysfunction, insulin resistance, and prothrombotic and proinflammatory states. Not only are these less widely appreciated as components of MetS, but they are also not typically measured in a clinical setting. MetS consists of elements that do not aggregate by chance alone and are causally inter-related, and each element contributes independently to an increased risk for ASCVD (3). Factor analysis in epidemiological studies in different populations, including adolescents and ethnic minorities, demonstrates clustering of risk in the domains of adiposity and/or dyslipidemia, hyperglycemia or insulin resistance, and hypertension that explain 37% to 70% of variation and vary by sex and race (4-7). For example, Malay women with MetS had different factor patterns with greater importance of hypertension, insulin resistance, and triglycerides when compared with other South Asian women (7). These findings highlight the racial phenotypic variability of MetS that is not well captured by standard MetS paradigms.

Additionally, ASCVD risk rises exponentially as the number of MetS elements increases. In the Hoorn study in the Netherlands, the risk of cardiovascular outcomes rose rapidly with an increasing number of MetS components, becoming statistically significant at ≥ 3 factors for men and ≥ 2 factors for women (8). Other studies have demonstrated that MetS compounds the risk for ASCVD when other known risk factors, such as T2D, are present. A meta-analysis, including 87 studies with 951,083 patients, demonstrated that MetS was associated with a >2 -fold increased risk for ASCVD and cardiovascular mortality (9). MetS is present in $\sim 50\%$ of patients with diagnosed vascular disease and may be even more prevalent among women with ASCVD (10,11). In the Framingham Offspring Study, both MetS and T2D increased the risk of stroke by approximately 2-fold, and those patients with both had an even higher risk (12). ASCVD risk is higher with MetS in the absence of T2D compared with T2D without MetS (13.9% vs. 7.5%, respectively) (13).

The prevalence of MetS increases dramatically with increasing obesity. In men in the NHANES (National Health and Nutrition Examination Survey) from 2003 to 2006, MetS was present in 6.8% of normal weight, 29.8% of overweight, and 65% of obese individuals (14). Similarly, among women, 9.3% of normal weight, 33.1% of overweight, and 56.1% of obese individuals had MetS (14). Susceptibility to MetS transcends obesity, however, as there are obese individuals without MetS and nonobese individuals with MetS. Several factors modulate the prevalence of MetS in the presence of obesity, including lifestyle factors such as poor nutritional quality and lack of physical activity. Age, race, and sex also contribute to metabolic susceptibility, in part mediated by differences in adipose tissue distribution and adipocyte size and function. For example, South Asians have higher body fat content, waist to hip ratio, visceral fat to subcutaneous fat ratio, and adipocyte area than Caucasians matched for age, sex, and body mass index (BMI) (15,16). Similarly, Filipina women may have higher waist circumference and truncal fat and 3- to 4-fold higher rates of type 2 diabetes (T2D) and MetS compared with Caucasian women, controlling for other factors (17).

In the Dallas Heart Study, total body fat correlated with multiple metabolic risk factors, including insulin resistance. Excess truncal fat further increased risk after adjusting for total body fat. Conversely, lower body subcutaneous fat was protective, and waist circumference appeared to be a better predictor of total body fat than BMI (18). Visceral adipose tissue (VAT) appears to be associated with dyslipidemia and atherosclerosis, regardless of sex or race (19). Finally,

adipocyte size and lack of hyperplasia is associated with adipose tissue dysfunction, inflammatory markers, and insulin resistance (20,21). Given these findings, using a combination of BMI and waist circumference in MetS risk assessment may prove better than either measure alone (22). There may also need to be thresholds for waist circumference and BMI that differ by race (23).

The challenge presented to the TT was 3-fold. First, the current definition of MetS identifies a population at increased ASCVD risk, but does not accurately assess that risk, nor does it account for susceptibility for a given degree of adiposity, as noted earlier. Second, there is no targeted comprehensive care approach to address the needs of MetS patients. Third, assuming there was such an approach, there is no system to implement risk reduction and disease prevention. In the sections that follow, each of these issues is addressed, culminating in the formulation of affirmed concepts, emergent concepts, and key findings relevant to MetS care.

METHODS

The Cardiometabolic TT was convened on June 20, 2014, in Washington, DC, at the American College of Cardiology (ACC) Heart House as a “call to action” activity focused on defining new patient care models and approaches to address contemporary issues of cardiometabolic risk and disease. The purpose of this event was for stakeholders to discuss how to best coordinate care for patients with cardiometabolic risk factors and MetS. Findings from the PINNACLE registry (24) prompted ACC leadership to initiate the TT concept and approach its partners in the Cardio-Metabolic Health Alliance (CMHA) to participate in the discussion. The CMHA includes 4 organizations: the ACC, the American Association of Clinical Endocrinologists (AACE), the Association of Black Cardiologists, and the National Minority Quality Forum, with a mission to improve cardiometabolic risk factor control in diverse and high-risk populations and provide more effective coordinated care for patients with established cardiometabolic disease. CMHA leadership identified and extended invitations to individual experts and representatives of other organizations beyond the core CMHA members; all participants are listed in Table 1.

The goal of the TT was to establish and organize an evidence base to address the following 3 key questions:

1. What is MetS?
2. What is the optimal care model for patients with MetS?

TABLE 1 Cardiometabolic Think Tank Representatives and Participant Organizations

Laurence S. Sperling, MD, Co-Chair	American College of Cardiology American Society for Preventive Cardiology
Jeffrey I. Mechanick, MD, Co-Chair	American Association of Clinical Endocrinologists
Maria Rosario G. Araneta, PhD	National Minority Quality Forum
Quie K. Blum, PhD, NP	American Association of Nurse Practitioners
Eliot A. Brinton, MD	American Heart Association
Karen K. Collins, MS, RDN, CDN	Academy of Nutrition and Dietetics
Stephen Cook, MD, MPH	American Academy of Pediatrics
Jean-Pierre Després, PhD	International Chair on Cardiometabolic Risk
Nikhil V. Dhurandhar, PhD	The Obesity Society
Dave L. Dixon, PharmD	Virginia Commonwealth University School of Pharmacy
Brent M. Egan, MD	Care Coordination Institute
Daphne P. Ferdinand, PhD, RN	Association of Black Cardiologists Patient/Community Advocate
Alan D. Forker, MD*	American College of Physicians
Scott M. Grundy, MD, PhD	Keynote Speaker
Yehuda Handelsman, MD	American Association of Clinical Endocrinologists
Lawrence M. Herman, MPA, PA-C	American Academy of Physician Assistants
Cynthia J. Herrick, MD	American Association of Clinical Endocrinologists (Fellow Representative)
Scott E. Hessen, MD	Health Information and Management Systems Society
Terry A. Jacobson, MD	National Lipid Association
Chiadi E. Ndumele, MD, MHS	Association of Black Cardiologists
Ian J. Neeland, MD	American College of Cardiology (Fellow Representative)
Russell R. Pate, PhD	National Physical Activity Plan Alliance
Gary A. Puckrein, PhD	National Minority Quality Forum
Robert E. Ratner, MD	American Diabetes Association
Krishnaswami Vijayaraghavan (Kris Vijay), MBBS, MD, MS	American College of Cardiology

*Dr. Forker was unable to attend the Think Tank, but contributed to this document.

3. What is the optimal strategy to implement this model?

To accomplish this, the TT was charged with formulating a paradigm to create and implement a new care model of patients with cardiometabolic risk factors and MetS. CMHA leadership organized the proceedings around 3 core topics:

1. Deconstructing MetS into its components;
2. Constructing a new care model through an interdisciplinary approach; and
3. Implementing a new care model in the real world.

The conference began with introductory remarks from the TT co-chairs (L.S.S. and J.I.M.) and a keynote address by Dr. Scott Grundy, followed by 3 discussion sessions organized around the core topics. Each topic session began with a brief presentation by the topic co-chairs, followed by general discussion and debate moderated by the co-chairs. An effort was made to establish points of consensus and identify alternative viewpoints and knowledge gaps requiring additional research. The proceedings were recorded and transcribed. At the end of the

day-long session, the TT was directed to develop a message patterned around affirmed concepts, emergent concepts, and key findings to document the current approach to cardiometabolic care (modeled after the 2013 AACE/ACE Consensus Conference on Obesity) (25).

WHAT IS MetS AND WHY DOES IT MATTER?

DEFINITION: SYNDROME VERSUS DISEASE. A unifying definition is needed to facilitate communication within the scientific community and between providers and patients, and to underscore the importance of incorporating MetS into a comprehensive preventive care assessment. There is significant heterogeneity of expert opinion as to what constitutes MetS, to what degree it represents a syndrome or a disease, and whether it has any health-related effects beyond that of its component disorders (26,27). The importance of MetS in cardiometabolic risk remains widely under-recognized, as highlighted by the fact that several of the most recent professional society guidelines on heart disease and stroke prevention give little or no attention to its role in disease prevention (28-31). Furthermore, noncardiovascular conditions promoted by MetS, such as endocrine, respiratory, and renal disorders, remain under-emphasized in clinical practice. Last, the current approach to MetS diagnosis does not take into account that a greater number of MetS components translate to a higher risk for adverse outcomes.

The past 2 decades have seen great debate over what term most precisely articulates the adverse cardiovascular and metabolic effects of MetS (Table 2). In 1988, Reaven noted that hypertension, insulin resistance, atherogenic dyslipidemia, and obesity tended to cluster to form a complex syndrome, *syndrome X*, defined by a unifying pathophysiology leading to multiplicative risk for ASCVD (32). A decade later, the World Health Organization introduced the term *metabolic syndrome*, with a primary focus on insulin resistance and hyperglycemia, creating controversy about whether the prime driver of MetS was insulin resistance or obesity (33). In 1999, the European Group for the Study of Insulin Resistance (EGIR) modified the World Health Organization definition, replacing it with *insulin resistance syndrome* (34). Later, the NCEP-ATP III report codified the term *metabolic syndrome*, highlighting abdominal obesity—specifically increased waist circumference—and an inflammatory/prothrombotic state as major components of the syndrome (35). Terms for MetS have continued to evolve, each focused around varying aspects of its pathophysiology, and have

TABLE 2 Previous Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

Organization (Year) (Ref. #)	MetS Definition	Insulin Resistance or Hyperglycemia	Body Weight	Dyslipidemia	Elevated Blood Pressure	Other
WHO (1998) (33)	Insulin resistance + any other 2 criteria	Impaired glucose tolerance, impaired fasting glucose, or lowered insulin sensitivity	Men: waist to hip ratio >0.90 Women: waist to hip ratio >0.85 and/or BMI >30 kg/m ²	TG ≥150 mg/dl and/or HDL-C <35 mg/dl in men or <39 mg/dl in women	≥140/90 mm Hg	Microalbuminuria
EGIR (1999) (34)	Insulin resistance + any other 2 criteria	Plasma insulin >75th percentile, impaired glucose tolerance, or impaired fasting glucose (but not diabetes)	WC ≥94 cm in men or ≥80 cm in women	TG ≥150 mg/dl and/or HDL-C <39 mg/dl in men or women	≥140/90 mm Hg or on hypertension therapy	None
ATP III (2001) (35)	Any 3 of 5 criteria	>110 mg/dl (modified in 2004 to >100 mg/dl), diabetes	WC ≥102 cm in men or ≥88 cm in women	TG ≥150 mg/dl, HDL-C <40 mg/dl in men or <50 mg/dl in women	≥130/85 mm Hg	None
AACE (2003) (36)	Insulin resistance + any of the other criteria	Impaired glucose tolerance or impaired fasting glucose (but not diabetes)	BMI ≥25 kg/m ²	TG ≥150 mg/dl and HDL-C <40 mg/dl in men or <50 mg/dl in women	≥130/85 mm Hg	Other features of insulin resistance including family history of diabetes, polycystic ovary syndrome, sedentary lifestyle, and so on
IDF (2005) (49)	Body weight + any other 2 criteria	>100 mg/dl, diabetes	Increased WC (population specific)	TG ≥150 mg/dl or on therapy, HDL-C <40 mg/dl in men or <50 mg/dl in women or on therapy	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on therapy	None
AHA/NHLBI (2005) (2)	Any 3 of 5 criteria	>100 mg/dl or on therapy	WC ≥102 cm in men or ≥88 cm in women	TG ≥150 mg/dl or on therapy, HDL-C <40 mg/dl in men or <50 mg/dl in women or on therapy	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on therapy	None

Adapted from Grundy et al. (2).

AACE = American Association of Clinical Endocrinologists; AHA = American Heart Association; ATP III = National Cholesterol Education Program's Adult Treatment Panel III; BMI = body mass index; EGIR = European Group for the Study of Insulin Resistance; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; MetS = metabolic syndrome; NHLBI = National Heart, Lung, and Blood Institute; TG = triglycerides; WC = waist circumference; WHO = World Health Organization.

included the dysmetabolic syndrome (36), insulin resistance syndrome (36), and cardiometabolic syndrome, originally introduced by the pharmaceutical industry. The position of others, such as the International Chair on Cardiometabolic Risk, has been to identify excess visceral/ectopic fat as the most prevalent form of MetS (37). In 2009, several major organizations released a statement harmonizing the criteria for MetS, which is in use today (38). Until recently, medical billing codes experienced a lack of uniform terminology as well, with the descriptor *dysmetabolic syndrome X* (277.7) chosen to represent a diagnosis of MetS. The more recent International Classification of Diseases-10 coding terminology, however, has shifted to the more accepted term, metabolic syndrome (E88.81).

These definitions are organized around the concepts that MetS: 1) is a chronic and progressive pathophysiological state; 2) represents a clustering of risk factors that form a complex syndrome defined

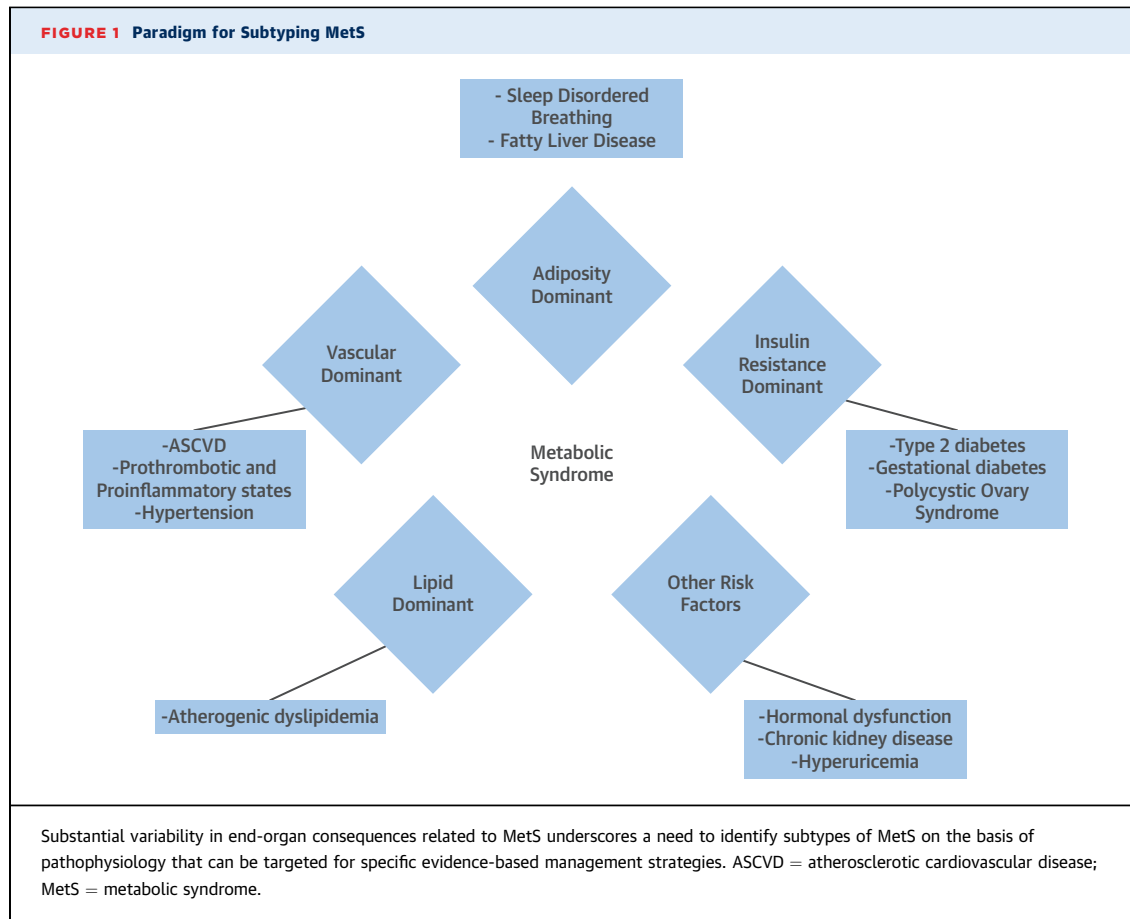
by a unifying pathophysiology; and 3) is associated with increased risk for ASCVD, T2D, and other related disorders. It is imperative to recognize that MetS is not just a repackaging of its individual risk components, but, as demonstrated in at least 1 analysis, is a clinical entity associated with an increased risk of ASCVD or death, even after controlling for its component risk factors (risk ratio: 1.54; 95% confidence interval: 1.32 to 1.79) (39). Furthermore, MetS incorporates so-called residual risk markers that associate with cardiovascular and metabolic disease risk, but are not universally agreed upon as criteria for MetS diagnosis. These include elevated levels of apolipoprotein B and small, dense LDL particles; a prothrombotic and proinflammatory state signified by high levels of circulating inflammatory markers, such as C-reactive protein and fibrinogen; and microalbuminuria (2). It is important to recognize this construct because it provides an opportunity to identify and treat residual risk

markers beyond the standard management of established risk factors.

Another concept essential to the MetS definition is that people with MetS have or are at risk for multi-end-organ damage. This includes, but is not limited to, cardiovascular (atherosclerosis and non-atherosclerosis types), metabolic (e.g., T2D and dyslipidemia), hormonal (e.g., polycystic ovarian syndrome), sleep-disordered breathing, certain malignancies, psychological distress (e.g., depression), chronic kidney disease, orthopedic/joint diseases, and nonalcoholic fatty liver disease (NAFLD). Substantial variability in end-organ consequences emphasizes a need to identify subtypes of MetS on the basis of their underlying pathophysiology and predisposition to adverse consequences, which can then be targeted for specific preventive and therapeutic management strategies (Figure 1).

FOCUS ON PATHOPHYSIOLOGY. Obesity. Recently, the AACE and the American College of Endocrinology developed an advanced framework for defining obesity as a chronic disease characterized by pathophysiological processes that result in increased adipose tissue mass and can result in increased

morbidity and mortality (40), with MetS as 1 such important consequence. MetS is strongly linked to the obesity epidemic in the United States (41). The latest prevalence estimates of MetS in men and women are 35% and 33%, respectively (42). Because forecasts suggest that over one-half of the U.S. population will be obese by the year 2030, rates of MetS will almost certainly increase over the next decade. However, there is a growing appreciation that obesity *per se*, as defined by simple anthropometric measures, such as BMI or waist circumference, is neither a necessary nor a sufficient descriptor of MetS and its consequences. Rather, it appears that risk for MetS varies substantially by distribution of both adipocyte and non-adipocyte (ectopic) fat, as well as by adipocyte size and function. Excess intra-abdominal (i.e., visceral) adipose tissue may be a primary driver of the cardiometabolic complications of obesity (43), and ectopic fat may be linked to VAT and may itself play a key contributory role. An increase in VAT is thought to reflect the relative inability of the subcutaneous adipose tissue depot to sufficiently expand its clearance and storage capacity in response to caloric excess (44). Defects in adipocyte maturation and



differentiation (21) cause adipocyte dysfunction, resulting in spillover of excess triglycerides and promotion of ectopic fat deposition in the viscera, liver, heart, and skeletal muscle. The ensuing milieu of overactive lipolysis, altered glucose homeostasis, proinflammatory adipocytokine release, and endothelial dysfunction appears to be a primary cause of the pathophysiological alterations observed in MetS. The several ectopic fat depots associated with increased cardiometabolic risk include excess liver, pericardial and epicardial, retroperitoneal, and intramuscular fat (45). Further evidence for the role of adipocyte dysfunction in adverse metabolic changes comes from the lipodystrophies, a group of rare genetic disorders that result in severe, generalized loss of adipose tissue. Although obesity and lipodystrophy represent 2 extremes of the physiological spectrum, the underlying mechanisms causing insulin resistance and MetS in both sets of patients may be similar; specifically, limited storage capacity in adipose tissue results in diversion of excess triglycerides to ectopic sites, with adverse metabolic sequelae (46,47). Notably, ectopic fat-associated cardiometabolic risk in MetS may be further modulated by race (e.g., South Asians are predisposed), nutritional factors, and lifestyle behaviors.

Although an increased waist circumference is central to the current clinical diagnosis of MetS and identifies individuals at increased risk for atherosclerosis (48) and mortality across different levels of BMI (22), it is an imprecise surrogate for the VAT phenotype. First, the correlation among BMI, waist circumference, and VAT is highly variable among different racial groups, prompting the American Diabetes Association and the International Diabetes Federation to define different cutoffs for abnormal BMI and waist circumference, respectively, in Asian populations (49,50). Second, waist circumference measurement includes both VAT and abdominal subcutaneous adipose tissue compartments. These 2 depots are anatomically and physiologically distinct, especially within the obese population, and are differentially associated with markers of cardiometabolic risk (19). VAT, but not abdominal subcutaneous fat, has been shown to associate with incident T2D and pre-T2D (51), incident hypertension (52), and alterations in left ventricular structure and function (53), and has also been linked to increased risk of developing CVD and cancer (54). Therefore, the TT recognized the central role of ectopic fat and/or visceral adipose tissue in the pathophysiology of MetS and endorsed evidence-based strategies to identify and treat these dangerous fat depots in individuals with or at risk for MetS.

Insulin resistance. Insulin resistance tracks very closely with MetS, playing a key role in MetS pathogenesis and relation to ASCVD risk (55). Although insulin resistance may be associated with impairment of fasting glucose, insulin resistance itself seems to worsen in severity across added components of the syndrome, suggesting an independent association with MetS beyond glycemic effects (56) and strengthening the evidence for a pathogenic role of insulin resistance. Moreover, insulin resistance has been associated with atherogenic dyslipidemia, including elevated levels of triglycerides and low concentrations of HDL-C (2); prothrombotic and proinflammatory markers, such as plasminogen activator inhibitor-1, fibrinogen (57), and C-reactive protein (58); increased sympathetic nerve activity and sodium retention predisposing to hypertension (59); androgen excess and polycystic ovarian syndrome (60); sleep-disordered breathing (60); chronic kidney disease (61); and some cancers (62,63). It remains unclear whether the insulin resistance seen in MetS is a purely independent etiological factor, or mostly a downstream consequence of ectopic/dysfunctional adiposity, or a combination of both.

RESIDUAL RISK. TT participants affirmed the concept of *residual MetS risk indicators*. This concept recognizes that there are additional markers/factors not incorporated within the traditional diagnostic framework of MetS that nonetheless relate to MetS and are associated with adverse health outcomes. These may vary by individual or group, may be modifiable or nonmodifiable, and may have genetic or environmental determinants. This is critical because differences in risk factor burden early in life translate into marked differences in the risk of adverse health outcomes later in life (64). One element of this has been highlighted in the “ticking-clock” hypothesis, which recognizes the detrimental effects of long-term exposure to MetS on future development of end-organ damage. For example, multiple factors that begin before birth and continue through delivery, such as low birth weight, small head circumference, gestational diabetes, and lack of breastfeeding, place children at risk for MetS in adolescence and adulthood (65). It is important for practitioners to recognize these and other social determinants of MetS susceptibility, such as low socioeconomic status and parental history of MetS; to consider providing “primordial prevention” (66) when possible; and to move toward identification and treatment of vulnerable families and communities to improve public health.

LIFESTYLE. The TT recognized lifestyle, referring to physical activity and nutrition, as being a modifiable

factor crucial to prevent and treat MetS and its consequences. Many observational studies show an association between higher levels of physical activity and lower rates of chronic diseases and increased longevity (67). Even in the presence of MetS, increased physical activity is associated with a substantially lower risk of ASCVD (68). The proposed mechanisms include beneficial effects on blood pressure and lipids, key components of MetS (28). Appropriate nutritional choices can also modify the risk of cardiometabolic disease. The Strong Heart Study identified specific dietary patterns associated with improved health outcomes (69). Several dietary patterns, such as the DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets, may reduce blood pressure, improve lipids, reduce inflammation, and reduce risk for ASCVD (28,70). Emphasis should be placed on dietary patterns, rather than specific macronutrients, given inconclusive evidence to date for an independent effect of macronutrient composition on outcomes (71). Emerging from these recent data is the belief that focused research and improved education on lifestyle interventions should be prioritized.

DISPARITIES. The TT identified disparity in care of patients with MetS to be a critical area for improvement. Disparity can manifest as decreased accessibility to health care and failure to recognize or appropriately treat at-risk populations. For example, current guidelines do not recognize racial-specific differences in lipid levels between Caucasian and African-American populations (30). On average, African-Americans have higher HDL-C and lower triglyceride levels (72). This paradox may translate to underdiagnosis of MetS in African-Americans using current diagnostic criteria, which would likely result in lack of treatment of MetS in this population. In addition to this and other race-specific issues, however, TT participants recognized that well-intentioned alteration of existing diagnostic criteria around racial differences could stigmatize minority populations and lead to undesirable consequences. Other nonracial, high-risk, under-represented populations likely requiring more intensive consideration include patients with human immunodeficiency virus/acquired immunodeficiency syndrome, cancer survivors, individuals with severe mental illness, and children with developmental disabilities.

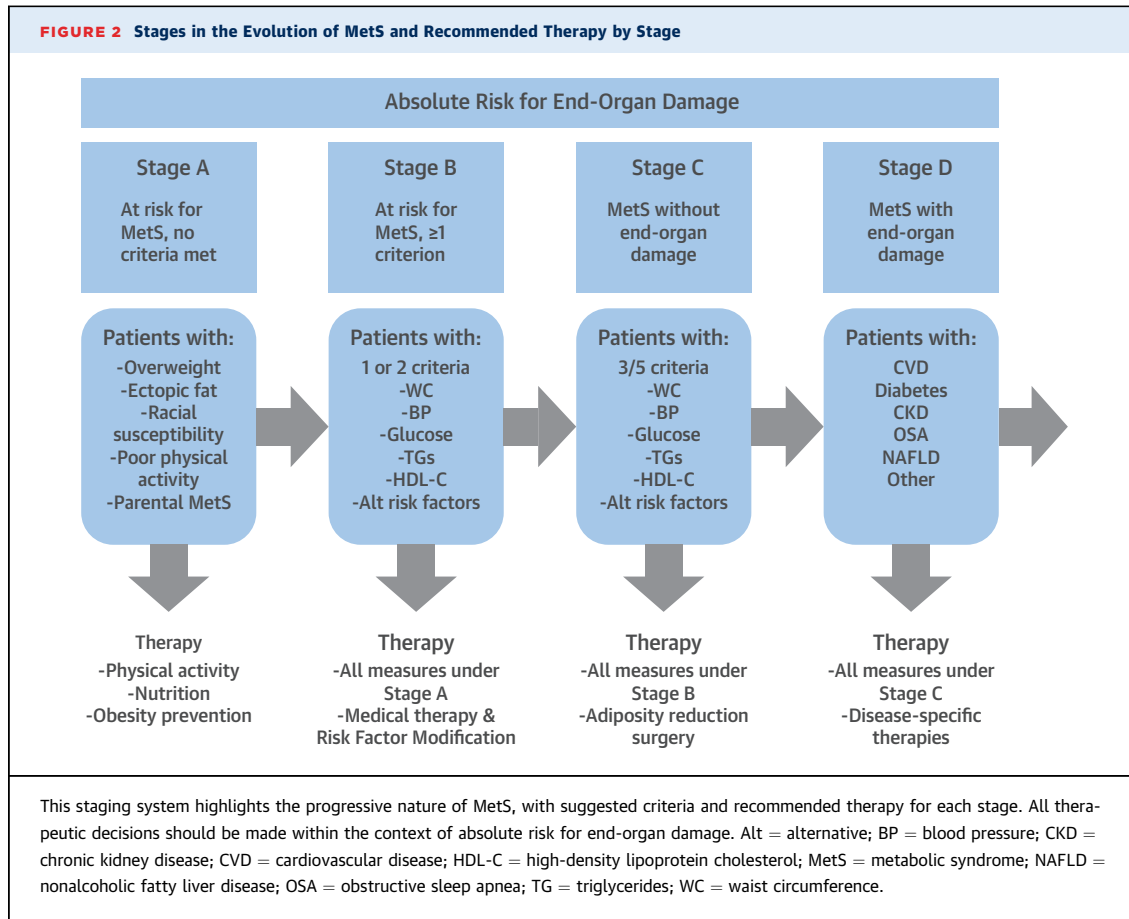
WHAT IS THE OPTIMAL INTERDISCIPLINARY CARE MODEL FOR PATIENTS WITH MetS?

Defining and deconstructing MetS laid the groundwork for the TT to begin discussing what they agreed

was an emergent need for a new care model for patients with or at risk for MetS. Participants identified several essential considerations in response to the dynamic health care environment of the 21st century. These included: focusing on comprehensive screening/case-finding strategies; considering varying MetS phenotypes; formulating a staging system to facilitate communication between patients and providers; and building a paradigm of care involving individual, community, and public/global health that emphasizes lifestyle choices.

STAGING SYSTEM FOR THE METABOLIC SYNDROME—A FRAMEWORK. The TT recognized that providers need a more comprehensive, but simply communicated, framework through which they can identify and risk-stratify patients with or at risk for MetS. Such a framework can be used to apply evidence-based, targeted therapeutic interventions. By highlighting the progressive nature of MetS in stages, participants proceeded to devise a theoretical system with suggested criteria and recommended therapy for each stage (Figure 2). The system starts by recognizing persons who are at risk for MetS, but without *any* of the 5 criteria required to meet a MetS diagnosis. Factors to consider at this stage include overweight (incorporating the recent ACE framework [40]), evidence for ectopic fat deposition by imaging, racial, or parental susceptibility to MetS, and adverse lifestyle choices. Therapeutic interventions would be implemented to address specific health behaviors or markers of susceptibility to prevent progression (primary prevention). The model then moves toward increasingly severe stages of MetS on the basis of established risk factors/diagnostic criteria and residual risk markers. Each stage, considered secondary prevention, proposes more intensive therapeutic strategies to treat MetS and its risk factors. It should be noted that although risk for adverse outcomes generally increases with each subsequent stage, the absolute risk for developing MetS consequences varies substantially within populations. Thus, it is imperative that treatment decisions be incorporated within the context of *absolute* risk.

In summary, this model categorizes patients first on the basis of the stage of their disease progression and second by underlying MetS pathophysiology. The strengths of this model are that it: 1) recognizes the heterogeneity of MetS and the need for individualized care strategies; 2) highlights the importance of disease-specific pathophysiology in the evolution of MetS; 3) acknowledges that many patients with MetS have overlapping subtypes requiring a multidisciplinary approach to their care; and 4) maps MetS stages with specific management strategies. The TT



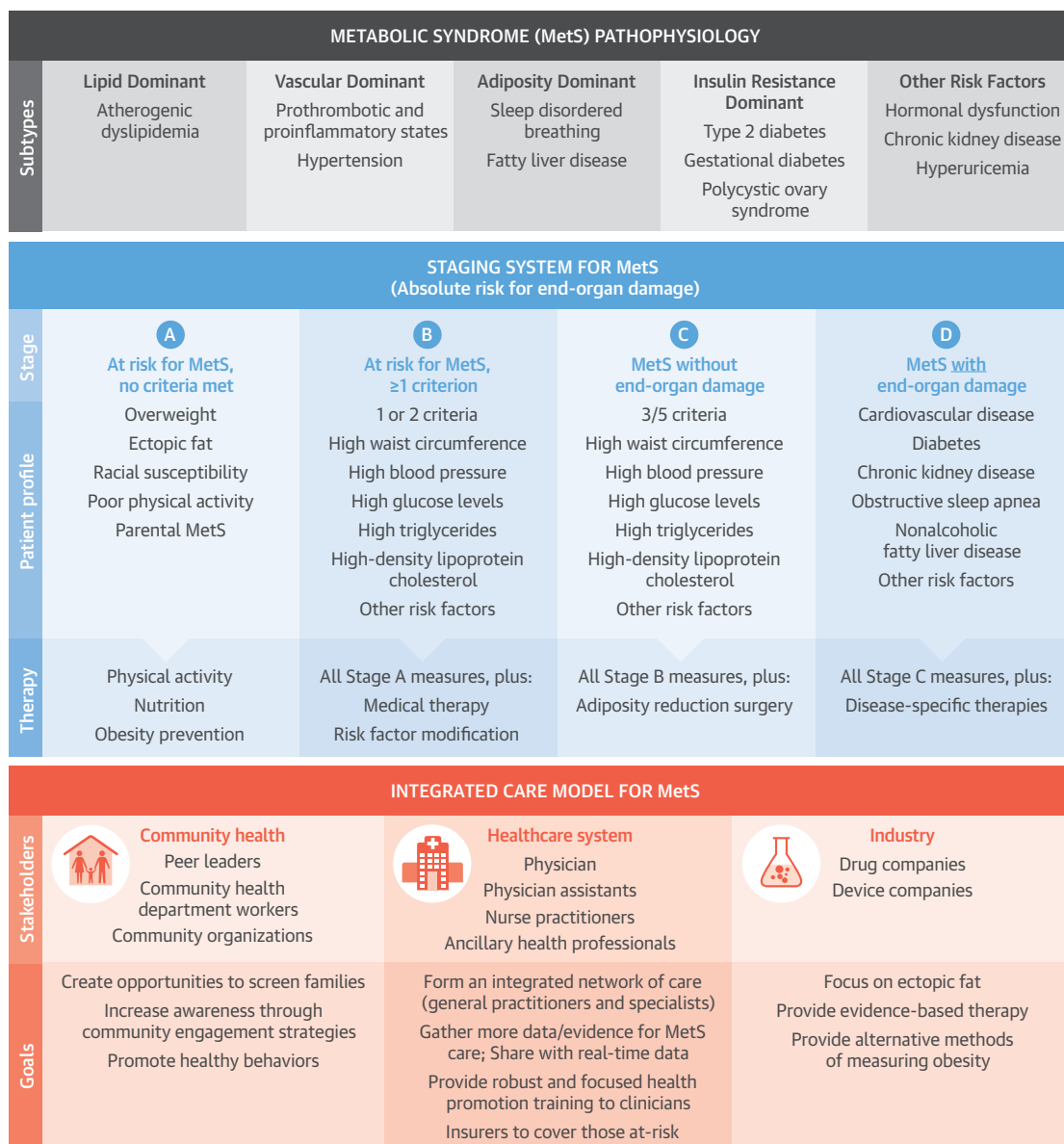
acknowledges that the concepts of staging and subtyping are works in progress and require further modification, testing, and validation before they can be used routinely in clinical care.

BUILDING A NEW CARE PARADIGM: THE INTEGRATED CARE MODEL. The TT agreed that care for patients with MetS should focus on disease prevention and management within a continuum of individual, community, and public/global health (Central Illustration). Focusing on prevention requires more comprehensive screening for MetS in the community. Some examples include opportunities to screen families at well-child pediatric or pharmacy visits; using electronic medical records to improve screening/case finding; and expanding screening efforts to schools, worksites, places of worship, and community businesses. Screening should use measurable biomarkers (e.g., blood pressure, lipids, BMI, and waist circumference), as well as better assess and target behaviors, such as physical inactivity and nutritional quality. Taking advantage of emerging technologies (e.g., wearable devices) should be further explored to enhance screening. Community engagement strategies can

augment screening by increasing awareness of MetS and promoting healthy behaviors. These include making healthy eating and regular physical activity accessible, affordable, and acceptable. One successful example of this approach is the community-based practice network, where community leaders partner with health care practices to create public health awareness, with real-time feedback and data analysis for quality improvement (73). This approach can be improved by increasing patient access to ancillary services using ZIP code analysis to focus resources on high-risk areas (74) and using public health and community initiatives. By engaging the community more broadly, the focus can begin to shift from the individual to larger units (families, communities, neighborhoods, and populations), which will increase the effectiveness of screening and start to change the culture of care.

Second, participants felt that better metrics are needed to define *abdominal obesity*, as current definitions are imprecise and not well suited for many populations. As technology develops and the critical role of ectopic fat and/or visceral adipose tissue continues

CENTRAL ILLUSTRATION Integrated Care Model for Patients With MetS: Proceedings of the CardioMetabolic Health Alliance Think Tank



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Care for patients with MetS should be focused on prevention and disease management within a continuum of individual, community, and public/global health. MetS = metabolic syndrome.

to emerge, metrics should evolve to consider alternative methods of measuring obesity. Simpler and less expensive methods than computed tomography and cardiac magnetic resonance imaging to measure fat distribution are needed to better characterize cardiometabolic risk. In the interim, other potentially

modifying factors should be taken into account, including race susceptibility, lifestyle, and evidence for metabolic dysfunction beyond the specific MetS criteria, such as NAFLD or sleep-disordered breathing.

Finally, with the advent of the PCMH and ACOs, care of patients with or at risk for MetS will likely

change dramatically, with an increasing emphasis on interdisciplinary care and greater involvement of family and community resources. The vision of the TT was to integrate care across general practitioners and specialists, in addition to ancillary resources, with a patient-centered and culturally sensitive approach. This will create a virtually integrated network of care providers sharing information with real-time data gathering and quality improvement to help patients reach their goals. For example, the ACO Shared Savings Program has reported substantial improvements in blood pressure screening (76%), achieving glycosylated hemoglobin (HbA_{1c}) <8% (69%), LDL cholesterol <100 mg/dl (55%), and aspirin use (75%) in participants with T2D compared with current NHANES reports for the general population with T2D (75).

Integrated health networks allow patients to monitor their own progress, which improves self-motivation and patient engagement in self-care. The TT recognized several key issues required to achieve this goal. First, time constraints placed on clinicians necessitate more robust and focused training to address health promotion during brief patient-provider encounters. Second, funding should extend beyond covering end-organ consequences to include covering those at risk for MetS. Payers and employer-based insurers must see MetS as a priority. Increased emphasis on MetS staging paradigms should help demonstrate that early intervention prevents more costly end-organ consequences. Finally, there is a need for more data/evidence for MetS care within diverse populations. One example is the new Diabetes Collaborative Registry (76), housed in the ACC and linked to the PINNACLE registry, which will facilitate crosstalk between registries and improve research. As health care evolves to become more prevention-focused, a new care model for patients with MetS should continue to encourage high-intensity lifestyle interventions to reduce morbidity and mortality from MetS and its consequences (31,77).

WHAT IS THE OPTIMAL STRATEGY FOR IMPLEMENTING A NEW CARE MODEL FOR MetS?

The final challenge for TT participants was implementation of a new care model for MetS. Clear consensus was that stakeholders from the community and public health arena, the health care system, and industry must be involved and that patient advocates, community health workers, and peer leaders are essential to bridging the community and the health care system. Stakeholders include physicians, nurse practitioners, and physician assistants, as well

as ancillary health professionals such as dietitians, exercise physiologists, psychologists, behavioral specialists, and certified diabetes educators. Disciplines to be involved include family practice, pediatrics, internal medicine, obstetrics and gynecology, geriatrics, and specialists in cardiology (hypertension and lipid) and endocrinology (diabetes and obesity). Other medical specialties that may also be involved with this population presenting with a particular phenotype include gastroenterology (NAFLD), sleep medicine (obstructive sleep apnea), nephrology (cardiorenal syndrome), surgery (bariatric, vascular, and cardiothoracic), psychiatry (depression, other behavioral), and oncology (obesity-associated malignancies). Finally, industry is another key stakeholder, as pharmaceuticals and surgical interventions comprise important treatment options for patients with MetS. It is important to note that many of the provisions of the Affordable Care Act (ACA) would support this implementation.

Dissemination of the Diabetes Prevention Program (DPP) in community settings can serve as a model for the MetS population. The DEPLOY (Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA) study was a pilot cluster-randomized trial comparing group-based DPP lifestyle intervention through a Young Men's Christian Association (16 group sessions with goals of 5% to 7% reduction in baseline body weight and 150 min/week of moderate exercise) with brief counseling. Among 92 randomized participants, at both 4 to 6 and 12 to 14 months, the percent change in weight and BMI, as well as the change in total cholesterol, was significantly greater in the intervention group (78). An extension study in which both the control and intervention arms were offered an 8-month lifestyle maintenance program found that both groups maintained weight changes compared with baseline, and those in the initial intervention group lost a further 1.5% of body weight, with significant decreases in total cholesterol and systolic blood pressure (79). A larger implementation of the DPP intervention across 14 Young Men's Christian Associations in New York demonstrated that among 254 participants, 40.2% and 60.8% achieved a weight loss $\geq 5\%$ at 16 weeks and 10 months, respectively (80). Lessons could be drawn from these interventions to benefit other communities, such as the workplace, where many large employers already offer wellness programs. A systematic review of randomized controlled trials on worksite wellness programs demonstrated a statistically significant 3-lb weight reduction and 0.5 kg/m² BMI reduction over 6 to 12 months (81).

The TT also recognized the National Physical Activity Plan as an overarching framework for implementation. The plan has 5 primary strategies and proposes evidence-based interventions within 8 economic sectors. Strategies include launching advocacy efforts to increase public support, mounting a national physical activity education program, disseminating best practice models, creating a national resource center, and establishing a center for physical activity policy development and research. Involved sectors include: business and industry; education; health care; mass media; parks, recreation, fitness, and sports; public health; transportation; land use; community design; volunteer; and nonprofit. Specific strategies within these sectors include providing incentives to increase active transportation (walking, biking) through community design, making physical activity a “vital sign” in the health care setting, and ensuring access to high-quality physical activity programs in early childhood education and grade school (82).

The TT proposed that community health workers and peer leaders play an integral role in implementing the new care model and discussed several examples. The Healthy Living Partnerships to Prevent Diabetes Study implemented a DPP-like lifestyle weight-loss program over 2 years by using a local diabetes education program with community health workers, involving weekly visits over the first 6 months and twice monthly visits over the next 18 months (83). Among 301 randomized patients, the intervention group achieved significant reductions in weight, BMI, waist circumference, glucose, insulin, and homeostatic model assessment of insulin resistance measures compared with control subjects, with 46.5% of the intervention group achieving $\geq 5\%$ weight loss and 21.3% achieving $\geq 10\%$ weight loss (83). The Look AHEAD (Action for Health in Diabetes) trial provides the longest-term evidence of the effect of an intensive lifestyle intervention in overweight and obese adults with T2D. The curriculum was modified from the DPP and included structured meal plans and moderate exercise up to 200 min/week. At 8 years, 50.3% in the intervention group versus 35.7% in the usual care group lost $\geq 5\%$ of body weight, and 26.9% versus 17.2% lost $\geq 10\%$ of body weight (84).

In Colorado Heart Healthy Solutions, community health workers conducted screenings, assessed readiness for change, and provided education and medical referrals to patients with an uncontrolled risk factor for coronary heart disease or a Framingham Risk Score $\geq 10\%$. They provided further phone follow-up, and found significant reductions in Framingham Risk score, blood pressure, and cholesterol at retesting. In

multivariable models, those receiving a follow-up call had greater improvement in Framingham Risk Score than those who did not (85). A randomized controlled trial in 2 community health centers enrolled 525 patients with uncontrolled ASCVD, T2D, hypertension, or hyperlipidemia; results showed that pairing nurse practitioners and community health workers demonstrated significant reductions in blood pressure, cholesterol, and HbA_{1c} over 1 year of follow-up compared with usual care (86). Finally, peer leaders can effectively provide education and support for lifestyle. This was demonstrated in a study where 116 Latino adults with T2D were randomized to receive diabetes self-management education and either 12 months of weekly group sessions with peer leaders or 12 months of telephone outreach with health workers (87). Both groups achieved significant HbA_{1c}, blood pressure, and waist circumference reductions and improved diabetes support with less distress. However, only the peer leader group sustained HbA_{1c} and blood pressure reductions over 18 months (87).

To further highlight lifestyle change, the TT proposed campaigns such as the Exercise is Medicine initiative (88), which assesses patient readiness for exercise and provides handouts to help patients start a program. It also provides materials to help fitness professionals communicate with health care personnel. To emphasize the importance of addressing disparities, the TT discussed key studies such as the Lawrence Latino Diabetes Prevention project (89), which recruited 312 participants at high risk for T2D for a lifestyle intervention involving 3 individual and 13 group sessions over 12 months versus usual care. The curriculum was adapted to address knowledge gaps and language barriers, customize dietary advice to Latino cuisine, and use the popular novella media format to deliver messages. At 1 year, there was a significant reduction in weight, BMI, and HbA_{1c} in the intervention group as compared with usual care (89). Another cultural adaptation of the DPP in African-American churches involved 37 participants and compared an abbreviated 6-week program to a longer 16-week program; it found that fasting glucose and BMI decreased significantly in both groups at 12 months (90). A program targeting a predominantly low-income non-Caucasian urban population delivered a lifestyle intervention in 12 weeks using group sessions and found significant reductions in the proportion of subjects meeting the MetS waist circumference (90% to 68%; $p = 0.009$) and hypertension (68% to 48%; $p = 0.04$) criteria over 6 months. At 3 months, 46.4% lost $\geq 5\%$ of body weight and 26% lost $\geq 7\%$ of body weight, with 87.5% and 66.7% sustaining these losses at 6 months, respectively (91).

Araneta et al. (92) piloted a 12-week Zumba fitness program in sedentary obese women with ≥ 2 MetS criteria (77% ethnic minorities), demonstrating significant blood pressure and fasting triglyceride reductions among the participants. The investigators also conducted a 48-week randomized controlled trial comparing restorative yoga to active stretching among adults with MetS, finding significantly lower fasting glucose in the yoga group at 12 months (93).

Principles for implementing a new care model within the health care system should include: care coordination and team-based care; education in MetS recognition and treatment; technology to facilitate communication among providers and patients; disease registries for population management; social media for distributing health messages; reimbursement alignment to facilitate coordinated care; and further development of strategies to address health care disparities and barriers to care. The TT recognized that the ACA supports 2 emerging models that seek to address these issues and improve integrated care for complex patients.

PATIENT-CENTERED MEDICAL HOME. To varying degrees, the PCMH addresses each of the aforementioned principles of care model implementation. The PCMH is organized around several core principles: 1) comprehensive team-based care; 2) patient-centered care; 3) care coordination; 4) accessible services; and 5) quality improvement and safety (94). A systematic review of 31 studies found a positive effect of components of the PCMH model on patient and staff experiences, as well as positive effects on preventive services, with reduction in emergency department visits in older adults, but no effect on hospital admissions or total costs (95). However, comparisons across studies on the PCMH are often difficult because of differences in definition and focus. In another study of 36 family practices implementing PCMH components over 26 months, improvement was seen in prevention and chronic care quality metrics, but not in patient-assessed outcomes (96). Long-term data is also limited, as most of these models were implemented over the last 5 to 10 years.

The Group Health Cooperative reduced physician panel sizes, increased ancillary staff, lengthened visit times, and provided time for team care planning, in addition to expanding technology to better engage patients. Comparison with control clinics in the area demonstrated better patient satisfaction scores, reduced provider burnout, improved performance on quality of care metrics, and reduced emergency department visits and inpatient admissions for ambulatory sensitive conditions over a 12- to 24-

month follow-up (97). The PCMH model affects MetS sequelae and outcomes. For example, the Geisinger ProvenHealth Navigator demonstrated a reduction in the incidence of end-stage renal disease and amputation among patients with T2D over 4 years, although without a change in myocardial infarction or stroke (98). Evaluation of another such model in West Virginia found that an EHR-based screening tool identified 11% of over 94,000 patients as being at risk for T2D (99), enabling the facility to better screen and connect patients to local lifestyle intervention programs.

There is less published data available to assess PCMH reimbursement strategies to facilitate coordinated care or on how this model addresses health care disparities. Although different financial models have been proposed and are incorporated in some PCMH models, evaluations do not specifically address the effectiveness of these strategies, nor have most studies demonstrated overall short-term cost savings (100). A recent review of 27 PCMH studies found that only 11 provided any detail on their financial models (101). There is also a limited evidence base for addressing disparities. In fact, in a retrospective cohort study of 1,457 diabetic patients receiving care in a PCMH academic practice, African-American patients were less likely to receive HbA_{1c} testing or influenza vaccination or to meet LDL or blood pressure targets than non-Hispanic Caucasians, after adjusting for multiple demographic factors and comorbidities (102). Similar to the cultural adaptations of the community-level interventions discussed earlier, new PCMH models must be modified to specifically address the needs of particular populations.

ACCOUNTABLE CARE ORGANIZATIONS. The ACO is another mechanism relevant to implementing a new MetS care model. Although the PCMH focuses on coordination at the level of primary care, the ACO is a larger organization that includes hospitals and specialty care. Compared with many PCMH models, the ACO's reimbursement changes and cost-saving goals are more explicit and are better aligned to facilitate coordinated care. Most ACO models are very new, but available evaluations indicate that health care spending has declined. Medicare beneficiaries in the same market as a commercial ACO realized decreases in total health care spending over 2 years, primarily due to reduced outpatient office visits, minor procedures, imaging, and laboratories. There were some improvements in LDL testing for patients with T2D and ASCVD but not on other quality metrics (103). An evaluation of Medicare enrollees in the Medicare Physician Group Practice Demonstration compared with control subjects found that the savings were highest for acute

care and dually-eligible beneficiaries, with an overall reduction in 30-day medical readmissions (104). According to a Centers for Medicare & Medicaid Services release of 1-year data, ACOs have also slowed cost growth (0.3% vs. 0.8% in 2012), reduced readmission rates, improved blood pressure control, and better assessed LDL in patients with T2D (105).

In addition to cost savings, ACOs have successfully implemented quality improvement initiatives, as demonstrated by 1 evaluation in 11 primary care clinics that employed care coordination, a care gap summary tool, staff education, and workflow redesign (106). Although integration of care into larger organizations may address health care disparities, this has not been specifically addressed in ACO design. An evaluation examining differences in care provided to Caucasian and African-American Medicare beneficiaries according to size of provider group found that beneficiaries assigned to larger groups were more likely to be Caucasian with lower poverty rates and higher educational attainment compared with those in small or medium groups. African-American beneficiaries with T2D were less likely to receive LDL testing and retinal examinations and were more likely to be hospitalized than Caucasian beneficiaries. Although larger provider groups attenuated racial disparities in some areas, they did not change disparities on other metrics, such as hospitalization rates (107). ACOs will need to specifically address health care disparities among patients with MetS.

CONCLUSIONS AND FUTURE DIRECTIONS

Several important challenges remain in the care of patients with MetS. These include collecting more data and developing expert consensus on MetS

diagnostic subtyping and staging to improve risk stratification and personalized medical care. Future TT initiatives will provide objective data on the combined use of pharmaceuticals, structured lifestyle, behavioral interventions, and surgical/non-surgical bariatric procedures to improve morbidity and mortality among patients with or at risk for MetS. A greater emphasis on assessing nutritional quality and levels of physical activity, with a focus on filling the gap between public health approaches and implementation in clinical practice, will be needed. Care models will continue to incorporate ACOs, but uncertainty exists as to how the ACA will affect MetS care in the future. It is foreseen that health care will transition to a greater degree from the clinic to the community, improving access to care, and that there will be a broadening of stakeholders to include public health, community, and industry sectors. Screening and performance metrics will enhance implementation of new care models in the future. Finally, the TT affirmed a call to action to encourage ongoing partnerships, funding, and initiatives to improve the lives of people with or at risk for MetS.

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