AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY PROTOCOL FOR STANDARDIZED PRODUCTION OF CLINICAL PRACTICE GUIDELINES, ALGORITHMS, AND CHECKLISTS – 2017 UPDATE

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ABSTRACT

Clinical practice guideline (CPG), clinical practice algorithm (CPA), and clinical checklist (CC, collectively CPGAC) development is a high priority of the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE). This 2017 update in CPG development consists of (*1*) a paradigm change wherein first, environmental scans identify important clinical issues and needs, second, CPA construction focuses on these clinical issues and needs, and third, CPG provide CPA node/edge-specific scientific substantiation and appended CC; (*2*) inclusion of new technical semantic and numerical descriptors for evidence types, subjective factors, and qualifiers; and (*3*) incorporation of patient-centered care components such as economics and transcultural adaptations, as well as implementation, validation, and evaluation strategies. This third point highlights the dominating factors of personal finances, governmental influences, and third-party payer dictates on CPGAC implementation, which ultimately impact CPGAC development. The AACE/ACE guidelines for the CPGAC program is a successful and ongoing iterative exercise to optimize endocrine care in a changing and challenging healthcare environment. **(Endocr Pract. 2017;23:1006-1021)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACC** = American College of Cardiology; **ACE** = American College of Endocrinology; **ASeRT** = ACE Scientific Referencing Team; **BEL** = best evidence level; **CC** = clinical checklist; **CPA** = clinical practice algorithm; **CPG** = clinical practice guideline; **CPGAC** = clinical practice guideline, algorithm, and checklist; **EBM** = evidence-based medicine; **EHR** = electronic health record; **EL** = evidence level; **G4GAC** = Guidelines for Guidelines, Algorithms, and Checklists; **GAC** = guidelines, algorithms, and checklists; **HCP** = healthcare professional(s); **POEMS** = patient-oriented evidence that matters; **PRCT** = prospective randomized controlled trial

INTRODUCTION

In 2014, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published the third in a series of Guidelines for Guidelines, Algorithms, and Checklists (G4GAC) documents to explicitly describe the organizations' position and development protocols for the production of clinical practice guidelines (CPG), clinical practice algorithms (CPA), and clinical checklists (CC) (1-3). These efforts extend well beyond chronicling a 3-decade experience impelled by the evidence-based medicine (EBM) paradigm. The AACE/ACE have recognized and prioritized the critical importance of communicating and disseminating information vital to an evolving clinical endocrinology practice. Moreover, the AACE/ACE G4GAC documents are not only a description of protocols but also a vehicle by which protocols and logistics are updated and modified. In the last 3 years, health care has realized dramatic chang-

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es in the way clinical research, education, and practice are conducted. Therefore, this 2017 G4GAC will reflect infrastructural change and furtherance of the AACE/ACE commitment to optimal clinical endocrine care.

This 2017 G4GAC document was written by the newly created ACE Scientific Referencing Team (ASeRT) and then iteratively reviewed and modified by the AACE Publication Committee, AACE Board of Directors, and ACE Board of Trustees. The intended audience for this document is:

- those involved with medical white paper development and implementation, specifically CPG,
- those interested in the evolving role of medical white papers in the current healthcare environment, and
- clinical endocrinologists and those health care professionals (HCP) using or considering using CPG, CPA, and CC in their practice.

The reader is encouraged to refer to the glossary at the end of the document and also review prior G4GAC (1-3) since much of this previously published information will not be repeated in this update.

THE EVOLVING ROLE OF CLINICAL PRACTICE GUIDELINES

Historically, medical knowledge has been based on opinion, clinical experience, and evidence, with the last characterized by different levels of scientific substantiation. However, recently, newer "big data" methodologies (e.g., sourced from registries, electronic health records [EHR], and large prospective trial databases) have been enabled by huge increases in computational power and speed. These approaches include high-throughput -omics, informatics, and network analyses. Though not strictly scientific, these discovery techniques furnish information that is now central to various health care analytics but also fuels spirited controversy, as in recent cases of pharmaceuticals removed from the marketplace when big data suggests excessive risk (4), only to be reinstated when scientific data is re-adjudicated (5).

Prior to the advent of EBM, clinical decision making was perceived to be inundated by opinion and subjectivity. Then, with the implementation of EBM, scientifically substantiated information, primarily based on aggregated data, was prioritized and integrated with varying amounts of patient-oriented information. Now, the philosophical dilemma is whether to move forward with an emphasis on population-based data, more heavily incorporate automated technologies that lead to individualization of care (e.g., predictive models and risk-calculators (6), such as the Fracture Risk Assessment Tool [FRAX] (7) or atherosclerotic cardiovascular disease [ASCVD] risk estimator (8)), or seek out other paradigms that more optimally blend the 2 in clinical decision making.

The reality is that this is not merely an academic exercise since HCP must act using the best information available in the context of an individual patient. Therefore, an absolute need for high-quality CPG emerges. In a study by Corriere et al (9), CPG use in diabetes was associated with an improved knowledge base and fewer knowledge gaps. CPG are defined as systematically developed statements to assist HCP in clinical decision making for a specific topic or circumstance. Generally speaking, CPG are implemented through reading a journal, searching an electronic database, interrogating a secondary or tertiary source of evidence (10), or utilizing an EHR that incorporates elements of a CPG. In the near future, CPG use will be pervasive, and G4GAC will be adapted to changing healthcare systems.

Unfortunately, there are still very difficult challenges surrounding CPG. Many protocols exist for the development of CPG, with the U.S. Preventive Services Task Force representing one of the most detailed and referenced, though explicitly focused on prevention and health promotion (11). A thorough, transparent, and codified process for disclosures of a variety of conflicts of interests is included (11) and serves as a reference point for the AACE/ACE G4GAC program. Many HCP oppose the competing nature of different a priori strategies to create CPG and the variation in quality that results (12). For example, the 2013 American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults (13), emphasized lifestyle change and bariatric surgery with only orlistat representing pharmacotherapy, based on an a priori evidence rating system that required randomized, controlled trial data for core recommendations. This contrasts with the AACE/ACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity – 2016 (14), which presented information on all medications with a U.S. Food & Drug Administration indication for weight loss (in addition to lifestyle change and bariatric procedures), based on the totality of evidence and weighted by levels of scientific substantiation.

Austad et al (15) draw attention to the "multimorbid" patient, in which many chronic diseases co-exist and pose significant hurdles to CPG acceptance: confusion with entangled pathophysiologies, excessive nonpharmacological interventions, and polypharmacy. Besides this, many HCP resist and even refuse to read CPG because of their lengthy, highly detailed, and confusing nature, not to mention being counterproductive during a busy workday or outdated after a relatively short time. But most relevant today, HCP may not read and/or implement CPG because many third-party payers essentially determine the use of diagnostic tests, prescribe nonformulary medications or adversely limit options, and adjudicate indications for surgeries based on their own proprietary, or other competing/contradictory professional society white papers (16,17). Moreover, CPG development faces particular

challenges with pharmacy benefit managers (PBM; acting as third party administrators [negotiators] to ostensibly improve value), who have engineered the exclusion of many CPG referenced medications and conspicuous shifts toward increased use of biosimilars (18-21).

Significantly, Misra and Barth (21) highlighted many of the problems evaluating diagnostic testing, such as context in a clinical pathway, individual laboratory or manufacturer issues, derivation of normative data, performance, and ease of implementation. In addition, the potential citation of CPG and other white papers in medicolegal scenarios not only mandates inclusion of appropriate disclaimers (that these documents are only intended to assist clinical decision making), but also illuminates the practical need for individualized care; explicit doctor-patient communication to avoid generalized, dogmatic recommendations; and flexibility that accounts for regional differences in resource availability (22).

CPG are essentially unvalidated tools to improve or optimize clinical care, despite the authors' best intentions and aspirations. Early positive and then later negative sentiments regarding CPG are reflected in the aggregate publication record, represented by a simple analysis of PubMed citations (Table 1). A lack of confidence in how CPG evidence is weighed also stems from differences in technical review protocols, with some methods consistently assigning higher evidence levels (ELs) than others (10). Nonetheless, the AACE/ACE judges CPG development as an organizational priority with a robust G4GAC program and continued publication record of CPG, CPA, and CC (1-3).

THE UPDATED AACE/ACE G4GAC PROGRAM

History and Current Shortcomings

AACE/ACE produced 19 CPG from 1995 to 2004 (1), 7 CPG from 2006 to 2009 (2), 9 CPG from 2010 to 2013, 5 CPA and a CC from 2007 to 2013 (3), and 3 CPG and 4 CPA from 2014 to 2016 (Table 2), for a total of 38 CPG, 9 CPA, and 1 CC. As a leader in clinical endocrinology white paper development, the AACE/ACE created a unique G4GAC in 2004 based on prioritization of EBM, intuitive levels of scientific substantiation, incorporation of subjective factors reflecting HCP expertise, and transparency to the reader. Though other EBM systems exist (reviewed in Table 2 in reference (2)), the current dynamic AACE/ACE system has proven successful in terms of regular updating, citation, and use in various educational materials. In fact, the AACE/ACE diabetes (27) and bariatric surgery (28) guidelines have demonstrated increases in strong ELs and recommendation grades with systematic updates, an experience shared with the ACC/AHA (29). As institutional experience and commitment grew, the AACE/ACE G4GAC program evolved to not only address apparent shortcomings but also build a pragmatic organizational infrastructure to improve white paper development. This iterative process of improvement over the years is given in Table 3.

In the past year, several key changes in health care have further challenged the CPG development process. First, the type of knowledge used; identification and ranking of ELs pertaining to scientific methodologies; and mechanisms by which extenuating circumstances, qualifiers, or subjective factors impact recommendation grades needed to be better defined. Second, the logistics for CPG development (CPA and CC development have been relatively smooth) required further oversight to ensure greater timeliness, accuracy, mastery mapping references, ELs, and recommendation grades in the final documents. Third, the emphasis on personalized, or individualized (31), medicine requires a better understanding of molecular and cellular pathophysiology to direct targeted interventions, as well as factors related to patient-centered care such as environment, culture, ethnicity, clinical effectiveness, economic efficiency, and social acceptability (26,32). Fourth, a

Table 1
Trends Over Time of Guideline Publications According to a PubMed Search[a]

Time Interval	Total (% change)	English (% change)	Non-English (% change)
Before 1992	757	707	50
1992-1996	1,206 (+59)	1,080 (+53)	126 (+152)
1997-2001	1,500 (+24)	1,188 (+10)	312 (+147)
2002-2006	1,949 (+30)	1,609 (+35)	340 (+9)
2007-2011	2,461 (+26)	1,977 (+23)	484 (+42)
2012-2016	2,156 (–12)	1,787 (–10)	369 (–24)
Total	10029	8348 (83)	1681

[a] Searches were based on using the keyword "guidelines," Limited to title "[ti]," and Article Type "guideline" with customized Publication Dates, and Languages with and without "English." A simple analysis of the trends above show that there was an initial increase in guideline publication in the early 1990s, with a subsequent relative decrease in publication rate. The proportion of English (79-93%) guidelines has remained relatively constant over time.

Table 2
AACE/ACE Clinical Practice Guidelines, Algorithms, and Checklists Published from 2014 to 2016[a]

Year	Type	Title	Ref
2016	CPG	American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis	24
2016	CPA	AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm	24
2016	CPA	AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2016	25
2016	CPG	American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity – 2016	14
2016	CPA	AACE/ACE Clinical Practice Algorithm for Patients with Obesity	14
2016	CPA	Transculturalization recommendations for developing Latin American clinical practice algorithms in endocrinology – proceedings of the 2015 Pan-American workshop by the American Association of Clinical Endocrinologists and American College of Endocrinology	26
2015	CPG	American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan – 2015	27

Abbreviations: CPA = clinical practice algorithm; CPG = clinical practice guidelines.
[a] The Updated AACE/ACE Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis were published in 2017.

U.S. healthcare system that necessitates prioritization of cost, value, affordability, and optimal resource utilization (33,34), rendering purely evidence-based recommendations unsuitable for a significant proportion of the population that cannot afford to follow these recommendations or whose insurers will not cover the expenses that following them entails.

In a qualitative document review of CPG published between 2008 and 2012 from 30 physician specialty societies, Schwartz et al (35) found that costs were explicitly integrated in 57%, implicitly in 13%, intentionally excluded in 10%, and without mention in 20%. Lord et al (36) used an economic modeling algorithm to estimate population-level budgets and health impacts of CPG and discovered key limitations such as incomplete data, accessibility, and adaptability. Moreover, the factoring or nonfactoring of economic information into medical decision making carries ethical concerns (37). Contemporary CPG also need to account for quaternary prevention (interventions to avoid overmedicalization and iatrogenesis, see Table 4 for types of prevention) and therefore incorporate a healthy dose of skepticism among primary writers and reviewers that tempers zealous messaging for diagnostic testing, pharmacotherapy, and invasive procedures (40). Taken together, these factors have prompted another re-examination of the G4GAC process emphasizing relevance and pragmatism; respecting the latitude afforded by cost- and patient-centered care; and avoiding unnecessary controversy and quarrelsome behaviors among HCP, the media, and the public (41).

Enhancements to the CPA-CPG-CC Development Process

AACE/ACE has re-engineered the workflow for clinical practice tools to prioritize clinical problem solving and management (Fig. 1). The previous AACE/ACE a priori approach provides a virtually exhaustive compendium of information, but with an unclear potential for utilization. The rationale for starting with CPG in the previous approach, especially for new topics and updates with new information, was to provide a comprehensive information resource, corresponding evidence base, and foundation for derivative products, such as CPA and CC. However, the new 2017 AACE/ACE paradigm begins with an environmental scan of the disease "space" to identify the most relevant clinical problems and needs facing the clinical endocrinologist (e.g., weight loss in patients with excess adiposity, glycemic control in type-2 diabetes, evaluation of incidentally discovered thyroid nodules, or pharmacological management of acromegaly). This process will be supervised by ASeRT (Fig. 2) with primary writing and reviewing by AACE/ACE clinical endocrinologists (decreasing the need for and cost associated with professional medical writers) and proceed with creation of a new, or updated, CPA that specifically address the discovered relevant issues. Bearing in mind that the new process begins with CPA, and not CPG, development, each CPA node (information about data, an action, or a decision) and/or edge (connection, or relationship, between 2 nodes) is then scientifically substantiated, enriched as necessary with expert opinion, elaborated with cascades (or alternatives) based on resource availability and transcultural factors, and finally codified using the updated evidence rating and recommendation grading protocol. This final document houses the CPA and supporting node-/edge-specific information, now in the form of a focused CPG. For example, CPA nodes in the 2016 AACE/ACE Glycemic Control Algorithm (25) referring to patients with a "Entry A1c <7.5%" (node) that should then receive "MONOTHERAPY" (node), would be represented in a

Table 3
Updated Iterative Process of AACE/ACE G4GAC Implementation[a]

G4GAC Version	Attributes	Shortcomings
G4GAC-2004	Formal EBM	Lengthy production timeline
	-evidence rating	High production costs
	-recommendation grading	Burdensome methodology
	Incorporation of subjective factors	Inexact evidence rating/recommendation grading
	Recommendation cascades	Inexact codification of subjective factors/qualifiers
	Transparency	Inexact review process
	Multiplicity of interests disclosures	May lack patient-oriented relevance
	No industry involvement with development	Dependence on PRCT for question framing and recommendation grading
G4GAC-2010	Shorter development timeline (<1 year)	Difficult to implement
	Mandate constrained to clinical question(s)	No electronic implementation
	Middle-range literature searching	Not linked to reader surveys
	Using patient-oriented evidence that matters	No performance metrics
	Formal 4-step evidence-based methodology	No validation studies
	- Evidence rating	
	- Numerical descriptors	
	- Semantic descriptors	
	- Modify with subjective factors	
	- Recommendation grading	
	- Append recommendation qualifiers	
	Formal multilevel review process	
G4GAC-2014	Formalized protocol for instrument selection	Gaps and inconsistencies in scientific methodology codification EL subjective factors, and recommendation grade qualifiers
	Clinical practice guidelines	Persistent issues with production logistics, timeliness, and accuracy
	Clinical algorithm	Not personalized, needs transculturalization, and cascades of alternatives
	Clinical checklist	Inadequate economic and resource analyses
	Actualize and optimize electronic implementation	Needs focus and pragmatism
	Formalize performance metrics and validation studies	
G4GAC-2017	Paradigm change with CPA created first and then CPG created based on specific algorithmic nodes/edges	
	Recodify evidence levels, subjective factors, and qualifiers	
	Incorporate discovery science data	
	Incorporate economic efficiency and social acceptance (relevance, patient-centeredness, POEMS (30))	
	Create new recommendation category A for "Strong Opinion"	
	Create new recommendation category D for "Primarily Based on Expert Opinion"	
	Moving qualifier identification step prior to the mapping step in EBM methodology	
	Shorter, more streamlined and readable	
	Segregating all technical review processes to on-line supplementary material	
	Initiatives for implementation and validation, such as apps and interactive algorithms	
	Transparent process that certifies documents are up to date	

Abbreviations: AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; CPA = clinical practice algorithm; CPG = clinical practice guidelines; EBM = evidence-based medicine; EL = evidence level; G4GAC = Guidelines for Guidelines, Algorithms, and Checklists; POEMS = patient-oriented evidence that matters.
[a] Shortcomings for this G4GAC-2017 will be identified with ongoing (post-publication) critical assessment.

Table 4
Types of Preventive Medicine[a]

Type	Various Descriptions in the Literature
Primordial	Population-based prevention of disease risk Maintain health and avoid risk
Primary	Prevention of disease in patients with disease risk May include primordial prevention Remove the cause of a health problem before it arises Reduce and eliminate risk, avoid clinical disease events
Secondary	Prevention of complications in patients with early, asymptomatic disease Prevention of a health problem in early disease stage by shortening its course/duration Minimize severity of clinical disease events and reduce likelihood of repeat events
Tertiary	Prevention of disease progression in patients with complications or late, symptomatic disease Action to reduce effect/prevalence of a chronic disease by preventing complications Minimize impact of chronic, clinical disease
Quaternary	Prevention of overmedicalization in patients with disease or at-risk for disease Identify patients at-risk for overmedicalization, protect from new interventions, suggest ethically acceptable interventions

[a] See references 38 and 39.

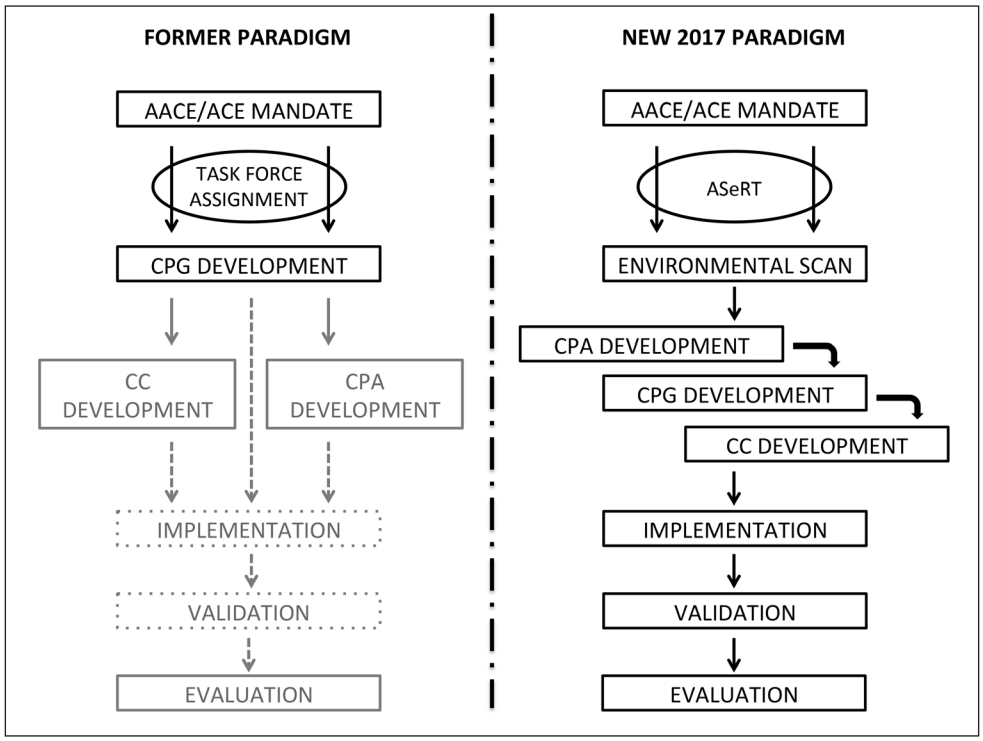

Fig. 1. Paradigm Change in AACE/ACE CPGAC Production Strategy. *Left*, the former paradigms prioritizes CPG development based on the premise that a complete evidence-based review is necessary to derive specific practice standards, which may or may not be developed. *Right*, the new 2017 paradigm prioritizes real-world clinical problem solving by first determining key issues to be examined, then creating a pragmatic CPA approach, and then providing the problem-oriented scientific substantiation in the form of focused CPA-driven CPG and patient safety CC. Though implementation and validation strategies have always been advocated, the new paradigm will facilitate their development. After a CPGAC is validated, a new evaluation step will commence. *AACE* = American Association of Clinical Endocrinologists; *ACE* = American College of Endocrinology; *ASeRT* = ACE Scientific Referencing Team; *CC* = clinical checklist; *CPA* = clinical practice algorithm; *CPG* = clinical practice guidelines.

diabetes CPG recommendation that provided evidence supporting the use of monotherapy for patients with type-2 diabetes and A1c >7.5%. A CC is then derived to maximize patient safety (e.g., including checkboxes for renal function and other diabetes medicines that could increase the risk for hypoglycemia) and included in the global CPGAC document. The AACE/ACE currently imposes 1- and 3-year timestamps on CPA and CPG, respectively, consistent with the findings of Garcia et al (42) that waiting more than 3 years is probably too long. Timestamps for the new global CPGAC documents will range from 1 to 3 years depending on environmental scans and HCP needs. Furthermore, the CPGAC will undergo an annual, transparent process that certifies documents are up to date.

The AACE/ACE has extensive experience with the previous 4-stage EBM protocol and over time, has taken note of various problems, challenges, and gaps. Examples of improvements include codification of methodologies using relevant physiologic animal or in vitro studies, discovery science (e.g., big data, -omics research, and network analysis), network meta-analysis, Bayesian inference, (post hoc) economic analyses, trial extensions, post hoc studies, and nested case-control studies. It should be noted that there is a practical limit to the granularity of evidence levels—too many evidence levels to reflect nuanced differences among study designs is overly cumbersome and risks confusion. Therefore, the AACE/ACE maintains the 4 intuitive evidence levels: "strong," "intermediate," "weak," and "no evidence," with the explicit ability to up- or downgrade the levels based on these nuances.

The mitigating effects of an insufficient sample size, problematic comparator groups, and other methodological flaws need to influence the final recommendation strength more directly. Gartlehner et al (43) found that when using the GRADE EBM, there was a mismatch between the quality of evidence and the treatment effects over time as new information becomes available. The authors conclude that the GRADE system may be overly strict and as a result, introduces too much interpretative variation (43). This further supports the use of less strict, intuitive EL classifiers (none, low, intermediate, high) in the AACE/ACE CPGAC.

Hence, the EL of scientific substantiation, specific EL subjective factors (for individual citations), recommendation qualifiers (for the aggregate evidence base for an individual recommendation), and EL to recommendation grade mapping have been more clearly delineated for transparency, allowing for more interpretative flexibility that avoids overstrictness (Tables 5 through 8). Specifically, EL subjective factors, recommendation qualifiers, and consensus levels are now identified ***PRIOR*** to mapping EL to recommendation grades. Also, this revamped EBM methodology has more EL 2 semantic descriptors (many of which are upcoded from EL 3), so direct comparisons of new CPG with older CPG may not be possible.

There are 3 recognized methods to develop consensus: the expert panel (nominal group technique; used in AACE/ACE CPA/CPG development), the consensus conference (used for AACE/ACE position statements but with greater cost), and the Delphi method (used in the AACE/ACE transcultural guidelines (26) but requiring a distinct infrastructure) (64). Other formalized systems have been developed to scrutinize clinical studies, such as the quality assessment tool for diagnostic accuracy studies (QUADAS) (65). Though potentially advantageous, these more involved process tools will be evaluated but deferred for now since they would add more layers of complexity to an already comprehensive AACE/ACE EBM methodology.

Some housekeeping changes will also be made so that the document is more readable, such as providing all technical review information (Tables 5 through 8) in online supplementary material and not in the main document text, greater use of tables to also minimize text, and limiting referencing to the most up-to-date citations that have direct relevance to the CPA node/edge being substantiated. The AACE/ACE CPGAC will also include better detailing of dissenting opinions, introduction of a new recommendation category of strong expert opinion when there is a higher level of consensus despite insufficient but not contradictory evidence, and an electronic web-based posting to provide an opportunity for member review and comment prior to AACE/ACE Board approvals and final publication. Lastly, CPGAC documents will be designed and formatted for inclusion in the National Guidelines Clearinghouse.

White papers in general and AACE/ACE CPGAC in particular have been criticized based on disclosures and presumed nondisclosures of multiplicity of interests of primary writers and reviewers, with the legitimate prohibition of experts with true conflict of interests, but also the inference that somehow all experts must have at least implicit relationships with industry that bias documents (66-71). The AACE/ACE emphasizes the importance of having expert and experienced real-world clinical endocrinologists (rather than professional medical writers) who may have fully vetted and acceptable industry relationships, perform the critical cognitive steps, technical analysis of evidence, primary writing, and document review. Notwithstanding these points, the AACE/ACE implements various safeguards and highly diligent declarations and oversight, provided by formal organizational policy, that minimizes bias from commercial interests:

- no person involved with the development of AACE/ACE white papers can be employed by industry;
- no financial support from industry is received for the development of AACE/ACE white papers;
- CPGAC Chairpersons must disclose, and are then selected after full evaluation of, potential multiplicity of interests to ensure there are no significant conflicts;
- primary writers and reviewers must disclose all potential multiplicity of interests initially and with regular

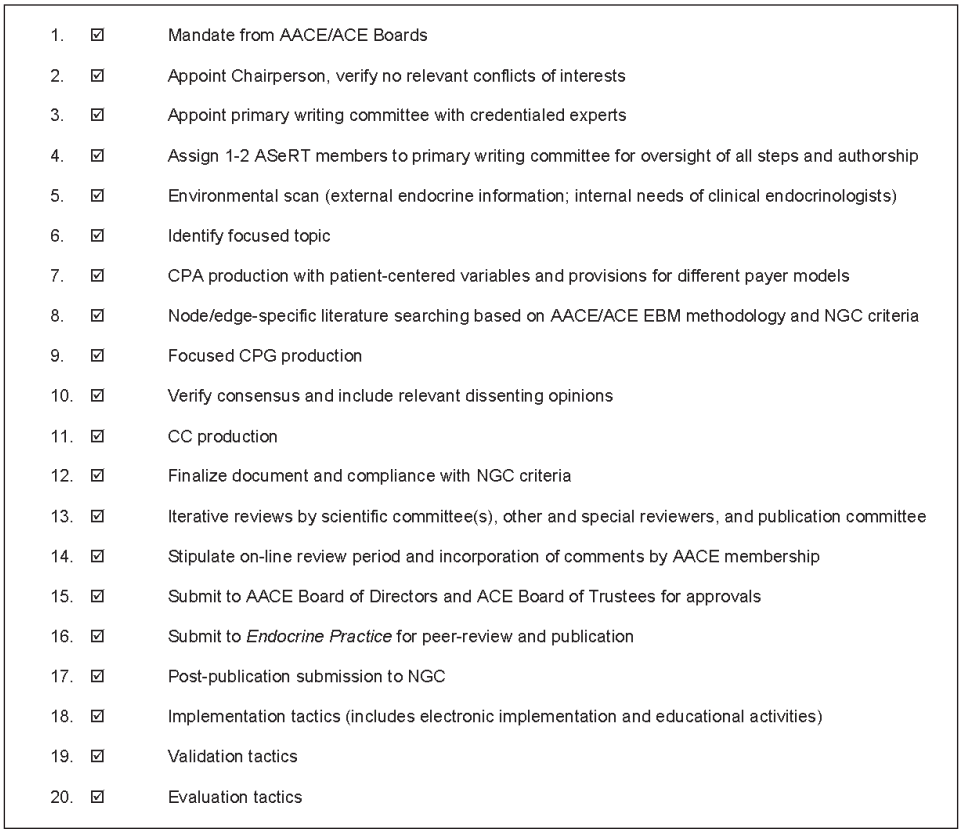

Fig. 2. Checklist for ASeRT supervision of CPGAC. *AACE* = American Association of Clinical Endocrinologists; *ACE* = American College of Endocrinology; *ASeRT* = ACE Scientific Referencing Team; *CC* = clinical checklist; *CPA* = clinical practice algorithm; *CPG* = clinical practice guidelines; *EBM* = evidence-based methodology; *NGC* = National Guideline Clearinghouse.

updates during the development process (e.g., at every conference call); if a potential conflict of interests is found or later occurs, then participation in CPGAC development is denied or terminated;

- each primary writer's or reviewer's disclosures are evaluated by the white paper Chairperson, AACE Publication Committee, and ASeRT to ensure there are no significant conflicts; and
- all CPGAC utilize a rigorous, tractable, transparent, and reproducible EBM methodology, with multi-step review process (e.g., AACE/ACE scientific committees, AACE Publication committee, and AACE/ACE Boards of Directors/Trustees) that can detect and restrain introduction of personal bias.

Implementation Strategies and Tactics

The purpose of the AACE/ACE CPGAC program is to provide up-to-date information that is eminently useful for the highest quality of clinical endocrine practice. The advent of EBM refocused white paper development to a more rigorous level of reference scrutiny and deprioritization of expert opinion. However, the increased resource requirement with CPGAC development had the unintended consequence of poor implementation and validation strategies. Specific barriers to suitable implementation include HCP disagreement with the recommendations, aversion to complexity and inflexibility, confusion among competing CPG, skepticism and pessimism due to current regulatory challenges, and preference to better incorporate patients' input (72,73).

According to implementation science, there are certain factors that facilitate adoption and successful use of CPG, such as having clear policies and procedures, education, and well-trained champions of EBM and CPG development, as well as formal evaluation of performance with feedback and iterative improvement (74). These factors can be assessed with surveys (75) and more structured tools such as the AGREE II instrument (76-78). Dedicated expertise in implementation science, clinical epidemiology, and systems engineering should be merged during the development phase for optimal CPG performance (79). Moreover, CPG adherence is enhanced when organizational culture (e.g., hospitals or clinics) consisting of system-level knowledge, attitudes, and perceived effectiveness is aligned with an evidence-based approach to health care (80). For example, modeling clinical setting parameters and practitioner workflow can reduce confusion and optimize CPG performance (81,82). The larger healthcare

Table 5
Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)[a]

Numerical Descriptor[b]	Semantic Descriptor	Methodology Descriptor
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial[c]
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis (44,45)
2 (2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	CSS	Cross-sectional study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data-mining, with or without retrospective uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study (46)
2 (new)	PHAS	Post hoc analysis study (47)
WEAK EVIDENCE		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling) (48)
3 (new)	ECON	Economic study (includes Markov models, pharmaco-economics) (49-53)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)

Abbreviations: EBM = evidence-based methodology; EL = evidence level.
[a] Based on principle that interventions, scientific control, generalizability, methodological flaws, and evidentiary details determine strength (54), consistent with other EBM systems (reviewed in Table 2 in reference (2)). Numerical and semantic descriptors of ELs provided in on-line supplementary material.
[b] The original numerical description from G4GAC 2004, 2010, and 2014 are provided in parentheses.
[c] The superiority of RCT over all other studies, and in particular MRCT, is discussed in reference (55). MRCT are inferior to RCT due to the bias introduced by being a retrospective analysis (56).

environment will also need to change, with an infrastructure that supports CPG use (72), facilitates the development of consistent G4GAC, and accesses more electronic and computerized vehicles.

Several innovations have been designed to automate continuous CPG frameworks, composed of decision support systems, a central patient database (e.g., EHR), a central medical knowledge base (e.g., peer-reviewed published literature), and an engine applying the knowledge base to the database (83-87). Diagnostic errors can result from a variety of cognitive issues and though managed superficially with CC, have been addressed with more advanced computational methods such as a semantic web framework composed of case-based fuzzy cognitive maps and Bayesian belief networks (88). Systematic errors are a byproduct of uncertainty, which is a necessary part of complexity (89). Nevertheless, a full range of subjective components (patient values and HCP judgment) and validated complex scenarios can be a vital part of any successful automated CPG (90). Vesely et al (91) were able to include health insurance and other economic data as part of an adaptation of an obesity CPG into a practice operations system. A truly collaborative approach including multiple professional societies, health

Table 6
Revised Evaluation of Studies (Step II: Scientific Analysis and Subjective Factors)[a]

Study design[b]	Data analysis[b]	Interpretation of results
Allocation concealment (randomization)	Intent-to-treat	Generalizability
Blindingc	Modeling (e.g., Markov)	Incompleteness
Comparator group	Network analysis	Logical
Endpoints (real clinical vs. surrogate)	Statistics	Overstated
Hypothesis	Appropriate follow-up (57)	Validity
Power analysis (too small sample size)	Appropriate trial termination (58)	
Premise		
Type I error (e.g., adjusted for PHAS)		

Abbreviation: PHAS = post hoc analysis study.
[a] These subjective factors pertain to an individual citation. Subjective factors are provided in on-line supplementary material.
[b] Are these elements appropriate for the given study?
[c] Including patients, clinicians, data collectors, adjudicators of outcome, and data analysts.

Table 7
Revised Evaluation of Recommendations (Step III: Recommendation Qualifiers)[a]

Cascades (are there other recommendation versions based on ethnocultural factors? (26))
Dissenting opinions (based on HCP and patient preferences (59,60))
Economic (e.g., cost-effectiveness, cost-benefit, value (36,37,47-51))
Evidence Base (are there significant gaps or is there overwhelming evidence? (9,61))
Relevance (patient-oriented evidence that matters vs. disease-oriented evidence; social acceptability (43))
Resource availability (limited or sufficient (62))
Risk to benefit (63)

Abbreviation: HCP = healthcare professional.
[a] Each of these elements pertains to the recommendation statement with the evidence considered in aggregate. The element may be positive or negative, and therefore modify a final recommendation grade in Table 8. Recommendation qualifiers are provided in online supplementary material.

insurance companies, government and regulatory agencies, patient advocacy groups, and others would clearly advance CPG development and implementation (16). Additionally, simpler patient versions of CPG will need to be developed and implemented as shared decision making becomes more prevalent (92). This patient-centered implementation strategy will also need to include input from users (e.g., HCP, patients, and patients' families) to take into account culturally sensitive acceptable medical outcomes and then formulate clear health-related quality of life metrics for optimal results (93,94). In lower income settings, the more facile CPA and CC, as well as buy-in and promulgation by local governmental health officials, will have demonstrable advantages (95). The AACE/ACE has invested, and will continue to invest, more effort into CPGAC implementation strategies and tactics based on the principles in this document (Table 9).

CONCLUSION

CPGAC development is a high priority of the AACE/ACE. This 2017 update in CPGAC development consists of (*1*) a paradigm change wherein environmental scans identify important clinical issues that direct CPA construction, with subsequent CPG providing node-/edge-specific scientific substantiation, evidence levels, recommendation grades, and CC; (*2*) inclusion of new semantic and numerical descriptors of evidence, subjective factors, and qualifiers; and (*3*) incorporation of patient-centered care components such as economics, transcultural adaptations, implementation, validation, and evaluation strategies. The dominating factors of personal finances, governmental influences, and third-party payer dictates on CPGAC implementation are now clear and require a focused response. The AACE/ACE guidelines for the CPGAC program is an ongoing iterative exercise that addresses many important issues, and although never intending to provide absolute directives, it can assist other professional medical societies in white paper development while optimizing endocrine care in a changing and challenging healthcare environment.

DISCLOSURES

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Table 8
Revised and Detailed Mapping Protocol (Step IV: Creating Initial Recommendation Grades)[a]

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any[b]	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any[b]	Yes/no	Yes/no	≤66%	Rule	Any → D (new)

Abbreviations: BEL = best evidence level; EL = evidence level; RQ = recommendation qualifiers; SF = subjective factors.
[a] See Table 6 for SF and Table 7 for RQ. Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion." Mappings are provided in on-line supplementary material.
[b] Rule-based adjustment wherein any recommendation can be a "Very Strong" Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a "Primarily Based on Expert Opinion" Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important. Rule-based adjustments are provided in online supplementary material.

Table 9
AACE/ACE Implementation Strategies and Tactics[a]

Electronic formats
Computer-interpretable algorithm (96,97)
Mobile device (98,99)
Patient health records (83-87)
Web-based (100)
Informatics
Registries (101-104)
Validation
CME Programs (105)
Surveys (75)
Registries (106-108)

Abbreviations: AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; CME = continuing medical education.
[a] References from AACE/ACE and other sources demonstrating feasibility.

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Glossary

Bayesian inference	Statistical method to update a hypothesis' probability as more information becomes available
Bayesian belief networks	Graphical representation of interconnected nodes, causal relationships, and beliefs/certainties for each node that are updated as more information becomes available
Big data	Very large data sets that are computationally analyzed to reveal information
Biosimilar	Subsequent entry biologic medical product, with high molecular complexity, that is nearly identical to the original ("innovator") product but differs based on manufacturing processes, which may affect biologic/pharmacologic activity
Case-based fuzzy cognitive maps	Linguistic IF-THEN constructions that incorporate real-world cases (experience) and a knowledge base to create more complete representations of human reasoning
Conflict of interest	Pragmatically, where a person derives personal benefit from actions made in their official position; more technically, when a person's concerns from 2 different capacities are incompatible
Delphi method	A structured, mediated, interactive process among experts to reach a preset level of consensus and correctness in response to 1 or more questions
Discovery science	A branch of rational inquiry based on the analysis of large amounts of data to reveal new information, leading to hypothesis generation
Environmental scan	Organizational monitoring of internal and external events and information to detect early signs of opportunity and concern
Evidence-based medicine	A learning strategy for the deliberate use of clinical evidence in the care of individual patients, composed of 4 parts: formulating a clinical question from a patient's problem, searching the medical literature for relevant clinical publications, critically appraising the evidence for validity and usefulness, and implementing useful findings in clinical practice
Middle-range literature searching	Focusing on citations situated between overly detailed descriptions and overly generalized models
Multiplicity of interest	Formal disclosure of interests regardless of perceived conflict, but the disclosure is subject to formal evaluation for actual conflict of interest
Nested case-control study	Lower cost and more efficient case-controlled study where only a subset of controls from the cohort are used to compare with the incident cases; statistical methods to manage missing covariates may be used
Network analysis	Mathematical (computational) analysis of interconnected variables; this technique is becoming more popular in the understanding of complex biological systems

Network meta-analysis	A type of systematic review in which multiple clinical trials are evaluated using direct and indirect comparisons; a way to determine comparative effectiveness of interventions that have not been evaluated directly against each other
Nominal group technique	A structured method to obtain input from different people that includes problem identification, problem solving, and decision making
-omics	An English language neologism referring to the totality and sets of biological entities (e.g., epigenomics, genomics, proteomics, transcriptomics, and metabolomics)
Patient-centered care	Care and clinical decision making that respects and responds to individual patient preferences, needs, and values
Post hoc analysis	Data analysis after the study concludes for relationships not stipulated a priori; important for exploratory studies and hypothesis generation but requires *P* value adjustments to avoid false-positives
Risk calculator	A shared decision-making tool that uses multiple current and historical risk factors and a predictive model (based on large population-based datasets) to derive an actionable estimate of event/outcome risk for a specified time period
Transcultural adaptation	Changing an evidence-based clinical practice algorithm or guidelines recommendation based on ethnocultural variables (e.g., body mass index cutoffs, food preferences, resources, socio-economics, beliefs, and customs)
Type I error	In statistics, the incorrect rejection of a true null hypothesis (detecting an effect that is not present; a "false-positive")
Type II error	In statistics, the incorrect retaining of a false null hypothesis (not detecting an effect that is present; a "false-negative")
White paper	An official, authoritative document from a specific organization providing information and/or recommendations on a specific topic

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