AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS PROTOCOL FOR STANDARDIZED PRODUCTION OF CLINICAL PRACTICE GUIDELINES—2010 UPDATE

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ABSTRACT

In 2004, the American Association of Clinical Endocrinologists (AACE) published the "Protocol for Standardized Production of Clinical Practice Guidelines," which was to be implemented in forthcoming clinical practice guidelines (CPG). This protocol formally incorporated subjective factors and evidence-based medicine (EBM) methods that tightly mapped evidence levels to recommendation grades. A uniform publication template and multilevel review process were also outlined. Seven CPG have been subsequently published with use of this 2004 AACE protocol. Recently, growing concerns about the usefulness of CPG have been raised. The purposes of this report are to address shortcomings of the 2004 AACE protocol and to present an updated 2010 AACE protocol for CPG development. AACE CPG are developed without any industry involvement. Multiplicities of interests among writers and reviewers that might compromise the usefulness of CPG are avoided. Three major goals are to (*1*) balance transparently the effect of rigid quantitative EBM methods with subjective factors, (*2*) create a less onerous, less time-consuming, and less costly CPG production process, and (*3*) introduce an electronic implementation component. The updated 2010 AACE protocol emphasizes "informed judgment" and hybridizes EBM descriptors (study design type), qualifiers (study flaws), and subjective factors (such as risk, cost, and relevance). In addition, by focusing on more specific topics and clinical questions, the expert evaluation and multilevel review process is more transparent and expeditious. Lastly, the final recommendations are linked to a new electronic implementation feature. **(Endocr Pract. 2010;16:270-283)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **CIG** = computer-interpretable guidelines; **CPG** = clinical practice guidelines; **DOE** = disease-oriented evidence; **EBM** = evidence-based medicine; **GRADE** = Grading of Recommendations, Assessment, Development, and Evaluation; **POEMS** = patient-oriented evidence that matters

INTRODUCTION

In 2004, the American Association of Clinical Endocrinologists (AACE) published the "Protocol for Standardized Production of Clinical Practice Guidelines" ("2004 AACE protocol") (1). That report outlined (*1*) the need for evidence-based medicine (EBM) clinical practice guidelines (CPG), (*2*) attributes of successful CPG, (*3*) a document template, (*4*) a specific method for evidence rating, incorporation of subjective variables, and transparent formulation of recommendation grades, and (*5*) a rigorous multilevel review process (1). The mandate for this document resulted from the increased number of AACE CPG being published without a consistent methodologic approach to provide an EBM recommendation. The major issues confronting AACE CPG task forces before 2004 were related to the controversies surrounding various EBM methods and how to distinguish EBM CPG from other types of publications, such as "white papers," clinical algorithms, road maps, consensus reports, opinion papers, position papers, conference proceedings, technical reviews, and review articles. Before the existence of the 2004 AACE protocol, there were 19 published AACE CPG documents, of which 18 were consensus reports—leaving only 1 that used EBM technical review procedures (2). Subsequently, and after a 1-year hiatus to reengineer CPG already in progress, 7 AACE CPG were published, all of which were in strict adherence with the 2004 AACE protocol (Table 1).

Since 2004, important advances have been made in the area of CPG development. First, and probably most importantly, is the popularization of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which has been extensively discussed in the literature (3-12) and subsequently garnered acceptance from a host of medical societies, including The Endocrine Society (13-15). Attributes of the GRADE system and other EBM methodologies (3-26) are outlined in Table 2. After a review of these methodologies, however, it would appear that an optimal CPG strategy might not be entirely evidence-based. Hence, an improved CPG would merge the elements of scientific substantiation with elements of transparency, intuitiveness, subjective factors, and relevance. In addition, shortcomings of evidence-based methods should be addressed, such as being too complex, using imprecise terms ("semantic imprecision"), and being too costly and labor-intensive to adapt and implement.

What constitutes the major difference between the 2004 AACE protocol and other current CPG protocols is the EBM methodology. The 2004 AACE protocol EBM methodology was outlined in Table 2 of the original reference (1) and is based on similar evidence ratings and recommendation grades used by the American Diabetes Association, the National Heart, Lung, and Blood Institute, and the American Gastroenterological Association. Furthermore, it incorporates many of the attributes of other CPG methodologies summarized in Table 2, herein. The 2004 AACE protocol incorporates 4 intuitive evidence levels (strong, intermediate, weak, or none) based on research methodology and stresses an explicit and rigid numerical descriptor. These evidence levels are then discussed among the CPG authors, and various subjective factors are incorporated as needed, such as risk-benefit analysis, cost-benefit analysis, clinical relevance, and others. A final quantitative recommendation grade for DOING an action or NOT DOING an action is then determined. This is almost always linearly

Table 1
American Association of Clinical Endocrinologists (AACE)
Clinical Practice Guidelines Published Since 2004 and
in Strict Adherence With the 2004 AACE Clinical Practice Guidelines Protocol[a]

Year	Title	Reference
2006	AACE/AME Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules	*Endocr Pract*. 2006;12:63-102
2006	AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension	*Endocr Pract*. 2006;12:193-222
2006	AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause	*Endocr Pract*. 2006;12:315-337
2007	AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus	*Endocr Pract*. 2007;13(suppl 1):3-68
2008	AACE/TOS/ASMBS Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient	*Endocr Pract*. 2008;14(suppl 1):1-83[b]
2009	AACE/AAES Medical Guidelines for the Management of Adrenal Incidentalomas	*Endocr Pract*. 2009;15(suppl 1):1-20[b]
2009	AACE Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients—2009 update	*Endocr Pract*. 2009;15(suppl 2):1-29[b]

[a] AAES = American Association of Endocrine Surgeons; AME = Associazione Medici Endocrinologi; ASMBS = American Society for Metabolic & Bariatric Surgery; TOS = The Obesity Society.
[b] Published online only (www.aace.com).

mapped to the best evidence level. Any deviations in this mapping are explicitly described and explained. The advantage of this evidence rating-grade recommendation protocol is the intuitive simplicity (strong, intermediate, weak, or none).

Growing criticisms still surround CPG in the medical literature. Important issues, such as cost-containment, geographic variations in resource availability, industry involvement, conflicts or multiplicities of interest, bias, paucity of credentialed authors, and time limitations, plague professional medical societies and produce CPG results that may not be credible or reproducible (27). This situation creates confusion and mitigates the intended benefit of CPG: to foster a consistent practice of high-quality medicine. In addition, the notion that evidence must be rated in accordance with some rigid hierarchy might be misguided. For example, in a recent article in *The Lancet*, Rawlins (28) pointed out that the presumed "gold standard" of clinical evidence—a randomized controlled trial—has many pitfalls. Foremost among these pitfalls are nongeneralizability and overdependence on non-Bayesian statistical analysis (see Appendix for Glossary of Terms).

Even more problems exist. Systematic literature searches are subject to study publication and reporting biases, in which medical journals are more likely to publish studies with positive findings rather than negative findings (29,30). Other issues that mitigate clinical evidence in medical decision making are stopping randomized controlled trials early because of apparent benefit (31), poor overall quality of meta-analyses (32,33), failure to include adequate intent-to-treat analysis (30,34), allocation concealment (randomization), and appropriate "blinding" (30). Tricoci et al (35) highlighted the impact and dominance of flawed and "weak" studies on CPG. On analysis of the evolution of CPG recommendations by the American College of Cardiology and American Heart Association, they concluded that improved CPG methodologies will need to address the effect of a surplus of lower levels of evidence.

Current protocols for literature searching may also fail to account for complex interactions among multiple interventions. Additionally, there are complexities that result from social networks among caregivers and other clinical practice idiosyncrasies that account for differences between "real-world" outcomes and "proof-of-concept"

Table 2
Attributes of Various Evidence-Based Methodologies Used for Clinical Practice Guidelines[a]

Methodology	Positive attributes	Negative attributes	References
ACC/AHA	Highly detailed methodology	4 × 3 matrix of "size of treatment effect" × "estimate of certainty," which maps to recommendation grades A-C; is nonintuitive and confusing	16,17
ACCP	Links methodologic strength with high-priority RBA; 15-year evolution and highly vetted	Final grade hybridizes RBA with methodology (matrix 1-2 × A-C+); is nonintuitive and confusing	18
AGREE	Validated instrument	Survey and consensus among writers and not an a priori evidence rating; primarily subjective	19
ANHMRC	Relevance has priority over strength of evidence	De-emphasizes methodology (even though 6 ELs); no effect of RBA or costs	20
GRADE	Links ELs with recommendation grades; highly vetted and also validated in literature and among several professional medical societies; addressed shortcomings of ITT analysis, randomization, and blinding in RCTs	Nonintuitive mapping of full spectrum of 4 evidence levels to 2 (strong or weak) recommendation grades; costly and labor-intensive to implement	3-15
OCEBM	Detailed evaluation of evidence	Highly complex analysis based on 4 parameters producing 10 levels mapping to 4 grades; no input from RBA, cost, or relevance, and mapping algorithm not transparent	21
SIGN	Validated, reproducible ELs with questionnaire; able to differentiate designs based on the study question	Unstructured recommendation grades; not reproducible	22
USPSTF	Transparent mapping of ELs to recommendation grades; includes RBA and subjective factors	Complex multilevel analysis; inadequate for diagnostic questions; does not incorporate individual patient factors	23-25
USTFCPS	Many kinds of evidence included in final ELs, which map directly to recommendation grades (good for public health questions)	Complex; not very reproducible	26

[a] ACC/AHA = American College of Cardiology/American Heart Association; ACCP = American College of Chest Physicians; AGREE = Appraisal of Guidelines for Research and Evaluation; ANHMRC = Australian National Health and Medical Research Council; ELs = evidence levels; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ITT = intent-to-treat; OCEBM = Oxford Centre for Evidence-Based Medicine; RBA = risk-benefit analysis; RCTs = randomized controlled trials; SIGN = Scottish Intercollegiate Guidelines Network; USPSTF = United States Preventive Services Task Force; USTFCPS = United States Task Force on Community Preventive Services.

outcomes. Incorporation of other sources of complexity, physiologic and pharmacologic, is now being addressed by using a systems biology approach to clinical medicine (see Appendix). Simply typing keywords into a search engine, and then performing an analysis, will potentially miss important, clinically relevant complex interactions. Shepperd et al (36) examined this problem and proposed the formulation of middle-range theory to guide literature searching (see Appendix).

Systematic literature searching should also be able to gauge clinical relevance (37-40). "Disease-oriented evidence" (DOE)—research focusing on intermediate or surrogate outcomes—dominates the medical literature and arguably misinforms clinical decision making (36). This is distinguished from "patient-oriented evidence that matters" (POEMs), in which, with little extrapolation, clinicians can easily derive information about diagnostic, therapeutic, or preventive procedures that help patients live longer or better (37). POEMs is considered highly relevant and valid information. Examples in the endocrinology literature include (*1*) fluoride therapy increasing bone mineral density in postmenopausal women with osteoporosis (DOE) versus fluoride therapy increasing nonvertebral fractures (POEMs) and (*2*) weight gain occurring in patients in the United Kingdom Prospective Diabetes Study (except those treated with metformin) (DOE) versus quality of life not being affected, positively or negatively, by tight blood glucose control (POEMs) (36). Although various position papers supporting the use of POEMs have had little effect on the predominance of DOEs in the medical literature, these position papers raise a valid point that CPG need to be relevant to actual clinical problems. Furthermore, by incorporating POEMs, CPG move closer to truly hybridizing EBM with medical humanism (41).

THE UPDATED 2010 AACE PROTOCOL

Currently, chairpersons and primary writers actively involved in AACE CPG task forces have had several years of experience with the 2004 AACE protocol. Three general categories of shortcomings have been articulated and serve as the impetus for the updated 2010 AACE protocol: methodology, review process, and implementation.

The 4-Step EBM Methodology

The entire AACE CPG development process is conducted free of industry involvement. Once the CPG topic is assigned, the chairperson and primary writers are identified. Then middle-range theories are generated that will guide the systematic literature search. Once this has been completed, there are 4 sequential steps in the integration of clinical evidence into recommendation grades:

- Step I: evidence rating based on methodology
- Step II: analysis of evidence and identification of subjective factors
- Step III: phrasing, determining level of consensus, and alphabetic grading of recommendations
- Step IV: appending qualifiers to recommendations

In the first step, credentialed experts on the writing committee assign numerical and semantic descriptors to the clinical evidence (Table 3). In the second step, comments are provided regarding evidentiary strengths and weaknesses (Table 4). In the third step, recommendations are phrased and discussed, levels of consensus are determined, and recommendation grades are conferred (Table 5). Relevant dissenting opinions can be briefly and explicitly provided in the Appendix section of the CPG. The recommendation phraseology will be engineered in the 2010 AACE protocol to create a clinical algorithm that reflects the process flow of the clinical encounter and can be used in the electronic implementation component to reduce errors (42,43). Nodes in the clinical algorithm will be numbered and then explicitly linked with graded recommendations in the Executive Summary and the evidence base in the Appendix section of the CPG (44,45). In the fourth and final step, miscellaneous qualifiers are considered that were not incorporated as subjective factors to determine the recommendation grade but are still deemed important (Table 6). An explicit description of these miscellaneous attributes of the evidence base and the subsequent expert discussion are provided in the Appendix section of the CPG in an effort to optimize transparency.

An optional procedural step may be appended to the recommendations in step IV if the experts conclude that alternative recommendations can be formulated. These alternatives may be due to variations of resource availability and cultural factors in different geographic areas. An alternative graded recommendation would be provided in the Executive Summary, and the rationale would be inserted in the Appendix. In other words, globally relevant recommendation "cascades" (46) are produced, which can broaden the utility and applicability of specific recommendations around the world, based on economic and educational differences. For instance, the routine evaluation of thyroid nodules may not necessitate ultrasonography in some countries that cannot afford the widespread purchase of ultrasound equipment or in which there is a shortage of experienced thyroid ultrasonographers.

Transparency for this 4-step methodology will be realized by maintaining a record of the CPG development process. Aron and Pogach (47) reviewed the importance of transparency as applied to the divergent EBM recommendations for target hemoglobin A1c levels in diabetes.

Table 3
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]

Numerical descriptor (evidence level)	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trial (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, or review) (NE)

[a] 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence.

Unfortunately, transparency is confounded by semantic imprecision and is a common shortcoming among all protocols in Table 2. In other words, human language is still relatively imprecise when technical concepts, human subjectivities, and vague or ambiguous terms are being described. Accordingly, despite the best intentions, the concept of full transparency is untenable. The 2010 AACE protocol addresses semantic imprecision by (*1*) using a controlled medical vocabulary in the recommendation phraseology for easy adaptation into computer-interpretable guidelines (CIG) (48-51) and (*2*) including both numerical and semantic descriptors of clinical evidence. The key procedural steps for the 2004 and 2010 AACE protocol methodologies are summarized and compared in Table 7.

Review Process

The multilevel review process requires iterations of review by the chairperson and primary writers after each revision by assigned "reviewers," the AACE Publications Committee, the AACE Board of Directors, and, finally, the editorial process of *Endocrine Practice*. Special reviewers

Table 4
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors

Study design	Data analysis	Interpretation of results
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate end points (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis versus Bayesian statistics		

Table 5
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade[a]

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BEL), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA = not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).

(non-AACE members) may be invited to participate in the review process. All authors and reviewers will be selected on the basis of expert credentials covering the topic (or topics) of interest, absence of any multiplicity of interests that would compromise the usefulness of the CPG, and commitment to complete their assignments according to the stated timeline. This review process will be expedited by selecting topics that are amenable to an abbreviated (6-month) timeline. This can be accomplished by focusing on more specific topics and by using a question-oriented approach and theory-driven literature search.

Implementation

Implementation of CPG adherent with the 2010 AACE protocol will include the following factors:

1. Development of continuing medical education credit linked to the reading of and correct responses to questions on the content of the CPG

Table 6
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step IV: Examples of Qualifiers That May Be Appended to Recommendations

Cost-effectiveness
Risk-benefit analysis
Evidence gaps
Alternative physician preferences (dissenting opinions)
Alternative recommendations ("cascades")
Resource availability
Cultural factors
Relevance (patient-oriented evidence that matters)

Table 7
Comparisons Between the 2004 and 2010 American Association of Clinical Endocrinologists (AACE) Clinical Practice Guidelines (CPG) Protocol Methodologies[a]

Procedural step	2004 AACE CPG protocol	2010 AACE CPG protocol
Mandate (topic)	New CPG: AACE BOD Updates: AACE CPG subcommittee requires BOD approval	Same approval process as 2004 Topic constrained to clinical question or problem
Appointment of task force chairperson	New CPG: AACE BOD Updates: same chair reappointed by AACE CPG subcommittee requires BOD approval	Same approval process as 2004 Chairperson explicitly commits to task and timeline Chairperson completes CPG training
Selection of task force members (primary writers)	New CPG: task force chair Updates: task force chair Both: require CPG subcommittee chair approval	Same approval process as 2004 Task force members explicitly commit to task/timeline and complete CPG training
Selection of cosponsoring and/or endorsing societies	Nominated by task force chairperson Requires BOD approval	Same approval process as 2004
Primary literature search	By primary writers	By primary writers with assistance by AACE staff; will be guided by middle-range theories to account for complex interactions in patient management
Step I (see Table 3)	Papers cited in Appendix text and in reference section appended by [EL 1], [EL 2], [EL 3], or [EL 4]	Papers cited in Appendix text and in reference section appended by numerical and semantic descriptors: for example, [EL 1; RCT], [EL 2; PCS], [EL 3; SCR], or [EL 4; NE]
Step II (see Table 4)	No comments based on study flaws	Subjective factors are provided as annotations in reference section and may also be discussed in Appendix: for example, [EL 1; RCT; small sample size (N = 12) with selection bias and not generalizable to patients >65 years old]
Step III (see Table 5)	Grade and BEL appended to recommendation in Executive Summary: for example, (Grade B; BEL 2 [nonrandomized])	Recommendation phraseology to create clinical algorithm Grade, level of consensus, and BEL appended to Executive Summary: for example, (Grade B [unanimous consensus]; BEL 2; NRCT) Optional alternative recommendation ("cascade") may be provided: for example, (Grade B [unanimous consensus]; BEL 2; NRCT; this recommendation may not apply where thyroid ultrasonography is not available)
Step IV (see Table 6)	Additional qualifiers not given	Additional qualifiers are part of annotation in reference section and may also be discussed in Appendix: for example, [RCT; EL 1; small sample size (N = 12) with selection bias and not generalizable; study is relevant but intervention is costly; cost-effectiveness analysis not reported]
Review process	Multilevel: chair, primary writers, reviewers, special reviewer (if needed), publications committee, BOD, peer review by *Endocrine Practice*	Multilevel: chair, primary writers, reviewers, special reviewer (if needed), publications committee, BOD, peer review by *Endocrine Practice*
CME credit	None	Linked to CPG
Reader surveys	None	Used for CPG updates
Electronic implementation	None	Clinical knowledge management system integrated with EMR and other health care information systems

[a] BEL = best evidence level; BOD = Board of Directors; CME = continuing medical education; EL = evidence level; EMR = electronic medical records. For other abbreviations, see text abbreviation box and Table 3.

2. Distribution of surveys to AACE membership regarding the relevance and utility of the CPG and then incorporation of responses into CPG updates
3. Development of electronic implementation of clinical knowledge management systems that are evidence-based and can be integrated with electronic medical records and other health care information systems

CONCLUSION

AACE is committed to enhancing the ability of clinical endocrinologists to provide the highest quality of medical care and improve public health. In fulfilling this AACE mission, CPG can be invaluable assets. The metamorphosis of CPG from informal, biased, opinion papers and consensus reports into formalized EBM documents may now evolve further. Moving forward, AACE CPG will be user-friendlier and more transparently developed. They will hybridize hard evidence, soft experience-based impressions, and pragmatic implementation tools for the electronic age of medicine. Ultimately, the target is a clinical decision support system (52) emphasizing "informed judgment," in which science, beliefs, and computerization are each necessary, but not sufficient, components. Examples include, but are not limited to, CIG (53), "neuro-fuzzy systems" (54), and Bayesian networks (55).

DISCLOSURE

Chairperson and Primary Writer:

Dr. Jeffrey I. Mechanick reports that he has received speaker honoraria from Abbott Nutrition and sanofi-aventis U.S. LLC.

Primary Writers:

Dr. Pauline M. Camacho reports that she has received research grant support for her role as principal investigator from the Alliance for Better Bone Health (Procter & Gamble and sanofi-aventis U.S. LLC), Eli Lilly and Company, and Novartis AG.

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Dr. Alan J. Garber reports that he has received speaker honoraria from GlaxoSmithKline plc, Merck & Co., Inc., Novo Nordisk Inc., and Daiichi Sankyo, Inc., consultant honoraria from GlaxoSmithKline plc, Merck & Co., Inc., Novo Nordisk Inc., and Roche Diagnostics, and research grant support from Bristol-Myers Squibb, GlaxoSmithKline plc, Metabasis, Novo Nordisk Inc., Merck & Co., Inc., sanofi-aventis U.S. LLC, and Roche Diagnostics.

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Dr. Hossein Gharib reports that he does not have any relevant financial relationships with any commercial interests.

Dr. Steven M. Petak reports that he has received speaker honoraria from Amgen Inc., Novartis AG, and sanofi-aventis U.S. LLC.

Dr. Helena W. Rodbard reports that she has received advisory board honoraria from AstraZeneca, Biodel, Inc., GlaxoSmithKline plc, and Mannkind Corporation, speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Merck & Co., Inc., and Novo Nordisk Inc., and clinical research grant support from Biodel, Inc., Novo Nordisk Inc., and sanofi-aventis U.S. LLC and that her spouse has received consultant fees from DexCom™ and sanofi-aventis U.S. LLC.

Dr. Dace L. Trence reports that she has received research grant support for her role as principal investigator from Bayer AG and is a stockholder of sanofi-aventis U.S. LLC and Medtronic, Inc.

Special Reviewers:

Dr. Mor Peleg reports that she does not have any relevant financial relationships with any commercial interests.

Dr. Wael Haddara reports that he does not have any relevant financial relationships with any commercial interests.

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APPENDIX: GLOSSARY OF TERMS

Allocation concealment. Prevention of the next assignment in a clinical trial from being known; necessary for randomization.

Bayesian network. A decision-theoretic model that can express conditional dependencies in a manner that is both accessible to humans and comprehensible to computers. Accessibility to humans refers to availability over the Internet, or other computer-based system, and in a language that is understandable.

Bayesian statistics. Method in which new assumptions about parameters are continually revised on the basis of new sample data and a synthesis of information about previous assumptions ("prior distribution"). "Degrees of belief" or levels of certainty—which are subject to change as more evidence emerges—that a hypothesis is correct are used instead of numerical frequencies, which are used in non-Bayesian statistics. The use of Bayesian statistics is important during evaluation, for example, of the probability that a positive test result is a false positive, which is critically important in determining the utility of a diagnostic test for a rare disease.

Beta error. A form of statistical error ("of the second kind" or type II)—concluding that something is negative when it actually is positive (a "false negative"). Beta error is a function of sample size, among other variables.

Blinding. In single-blind clinical studies, the study subjects are not aware of the treatment they are receiving. In double-blind clinical studies, the researchers and the subjects are unaware of which treatment is allocated to whom. Blinding is used to prevent bias in clinical research.

Clinical algorithm. A step-by-step procedure for solving a clinical problem with use of conditional "if/then" logic statements.

Clinical decision-support systems. Systems that aid clinicians in gathering relevant data, making clinical decisions, and managing medical actions more effectively.

Clinical knowledge management systems. Systems that help health care organizations use practices that, through more effective utilization of their knowledge assets, increase the competitive advantage of an organization in a highly dynamic environment. Such systems are applicable in a setting where medical knowledge changes rapidly and where health care providers and patients interact in distributed and collaborative processes. Distributed processes refer to a network of coordinated centers that provide complementary services in different locations—ranging from the highly complex such as referral hospitals to the less complex such as solo practices.

Clinical practice guidelines (CPG). Systematically developed documents that assist practitioners make appropriate health care decisions for specific clinical problems.

Computer-interpretable guidelines (CIG). A guideline representation that is accessible to humans and supports computer-based execution that requires automatic inference. CIGs can deliver patient-specific knowledge at the point of care during clinical encounters.

Controlled medical vocabulary. A list of term identifiers that disambiguate words used in clinical practice and the medical literature.

Evidence-based medicine (EBM). A learning strategy. The deliberate use of clinical evidence in the care of individual patients and 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.

Intent-to-treat. Pertaining to clinical trials: based on the initial treatment allocation and not the treatment that was eventually administered.

Medical humanism. Relationship between caregiver and patient that is compassionate, empathetic, and sensitive to patient values, autonomy, and ethnocultural background.

Middle-range theory. Theories organize facts or observations into a structurally coherent system that can ultimately explain reality. A middle-range theory lies between detailed descriptions and generalized models.

Neuro-fuzzy system. Combining humanlike reasoning with artificial neural networks; a form of artificial intelligence.

Non-Bayesian statistical analysis. Method in which probabilities are expressed in terms of numerical frequencies. This is the conventional method used in clinical studies.

Nonparametric. Statistical tests that are not based on any assumption, such as a normal distribution of data. They are also known as distribution-free tests, and the data are generally ranked or grouped.

Null hypothesis. The statistical hypothesis that predicts that there is no difference or relationship among the variables studied that could not have occurred by chance alone.

Patient-oriented evidence that matters (POEMs). Evidence that directly informs clinicians about procedures that help patients live longer and better.

Process flow. As applied to actual clinical encounters, the real-life sequence of data-gathering, decision making, and actions.

Scientific substantiation. Evidence arising from well-designed clinical studies with use of the scientific method: induction to create a model, deduction of a testable hypothesis, observation and experimentation to gather data, reasoning to revise the initial model, and then repeating the process. EBM attempts to categorize clinical evidence in terms of "levels" of scientific substantiation, from weak to intermediate to strong.

Semantic imprecision. Inability of language to describe a phenomenon, such as levels of scientific substantiation, in a reproducible way for all readers of a document. Vagueness and ambiguity are forms of semantic imprecision.

Systems biology. An interdisciplinary approach that focuses on complex interactions, aims to discover emergent properties, and eventually leads to understanding the entirety of a biologic process.

Technical review. Process in which clinical publications are rated on the basis of their levels of scientific substantiation (levels of evidence).

Transparency. Manner in which the complicated process of producing CPG is explicitly described, written for easy comprehension, and made accessible. This pertains to the technical review of the evidence, incorporation of subjective factors, reporting of levels of consensus, and assignment of the final recommendation grade.