

# Inside Guidelines

## Comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries

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**OBJECTIVE** — To compare guidelines on diabetes from different countries in order to examine whether differences in recommendations could be explained by use of different research evidence.

**RESEARCH DESIGN AND METHODS** — We analyzed 15 clinical guidelines on type 2 diabetes from 13 countries using qualitative methods to compare the recommendations and bibliometric methods to measure the extent of overlap in citations used by different guidelines. A further qualitative analysis of recommendations and cited evidence for two specific issues in diabetes care explored the apparent discrepancy between recommendations and evidence.

**RESULTS** — The recommendations made in the guidelines were in agreement about the general management of type 2 diabetes, with some important differences in treatment details. There was little overlap in evidence cited by the guidelines, with 18% (185/1,033) of citations shared with any other guideline, and only 10 studies (1%) appearing in six or more guidelines. The measurable overlap in evidence between guidelines increases if multiple publications from the same study and the use of reviews are taken into account. Research originating from the U.S. predominated (40% of citations); however, nearly all (11/12) guidelines were significantly more likely to cite evidence originating from their own countries.

**CONCLUSIONS** — Despite the variation in cited evidence and preferential citation of evidence from a guideline's country of origin, we found a high degree of international consensus in recommendations made for the clinical care of type 2 diabetes. The influence of professional bodies such as the American Diabetes Association may be an important factor in explaining international consensus. Globalization of recommended management of diabetes is not a simple consequence of the globalization of research evidence.

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Additional information for the article can be found in an online appendix at <http://care.diabetesjournals.org>.

**Abbreviations:** ADA, American Diabetes Association; AGREE, Appraisal of Guidelines for Research and Evaluation; DCCT, Diabetes Control and Complications Trial; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Over the past 20 years, clinical guidelines have been developed to bridge the gap between research and practice (1). There has been a concerted effort to base clinical decisions on research evidence (2) and, particularly through the Cochrane collaboration, to make this evidence available globally (3). Guideline development groups aim to use the totality of relevant research evidence to formulate recommendations (4). Since bibliographic databases (for example Medline and Embase) are easily available, one might expect that this would lead to international consensus on the evidence chosen to underpin recommendations for clinical care and a consequent convergence of recommendations made in guidelines.

Nevertheless, recommendations often differ in guidelines on the same topic, particularly when evidence for treatment decisions is weak. For example, Eisinger et al. (5) found substantial differences between recommendations from the U.S. and France about prophylactic mastectomy or oophorectomy in high-risk women. Differences were attributed to cultural variation in ideas about patient autonomy and involvement in health care, differing national views on esthetics of the breast, and fertility. Even where there is good trial evidence, recommendations vary. For instance, analysis of hypertension guidelines from New Zealand, U.S., Canada, U.K., and the World Health Organization showed wide variation in the criteria for blood pressure treatment decisions (6). Differences persisted between more recent editions of national hypertension guidelines, even with more systematic and transparent methods of guideline development (7).

It is evident that there are disparities in recommendations in guidelines for a range of different clinical conditions. Investigators hypothesize that differences are due to insufficient evidence (6,8,9), differing interpretations of evidence (10), unsystematic guideline development methods (11,12), the influence of professional bodies (13), cultural factors such as

Table 1—Description of selected guidelines

Country (ID code)	Organization responsible for guideline development	Title in English	Year of publication
Australia (AU)	NSW (New South Wales) Health Department	Improving diabetes care and outcomes. Principles of care and guidelines for the clinical management of diabetes mellitus	1996
Canada (CA)	Canadian Medical Association	Clinical practice guidelines for the management of diabetes in Canada	1998
Denmark (DK)	Danish College of General Practitioners	Non insulin demanding diabetes - NIDDM. A practical guidance for therapists	1998
England (EN)	East London Clinical Guidelines Project. Department of General Practice and Primary Care	Clinical guidelines for the management of diabetes in East London	1996
Finland (FI)	Finnish Diabetes League	Type II diabetes clinical guideline	1994
France (FR)	Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	a. Strategy for monitoring of type 2 diabetics, excluding monitoring of complications	1999
		b. Strategy for management of type 2 diabetics, excluding management of complications	2000
Italy (IT)	Italian Society for Diabetology	Diabetes mellitus. Practical guide for diagnosis and treatment	1997
The Netherlands (NL1)	Dutch Institute for Healthcare Improvement CBO	Guidelines diabetic nephropathy and cardiovascular diseases with diabetes mellitus	1998
The Netherlands (NL2)	Dutch College of General Practitioners (NHG)	Practice guideline diabetes mellitus	1999
New Zealand (NZ)	New Zealand Guidelines Group	Guidelines for the management of core aspects of diabetes care	1999
Scotland (SC)	Scottish Intercollegiate Guidelines Network (SIGN)	Management of diabetic cardiovascular disease	1997
Spain (SP)	Catalan Society of Primary Care	Guideline on treatment of diabetes mellitus type 2 in primary care	1996
Switzerland (SW)	University Hospital of Geneva	Detection of diabetes mellitus. Guidelines for the outpatient's clinic	1996
USA (US1)	American Diabetes Association	Standards of medical care for patients with diabetes mellitus	2000
USA (US2)	Institute for Clinical System Improvements	Management of type 2 diabetes mellitus	2000

differing expectations of apparent risks and benefits (5,6), socioeconomic factors, or characteristics of health care systems (14).

In this study, we compared recommendations among a range of guidelines on the management of type 2 diabetes and analyzed to what extent the variation (or concordance) among recommendations was explained by the evidence cited in the guidelines.

## RESEARCH DESIGN AND METHODS

### Selection of guidelines

We applied the Institute of Medicine's definition of clinical guidelines: "system-

atically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (15). Systematic reviews and evidence reports that did not contain specific recommendations were not included in this study. Because of the large number of clinical issues related to diabetes, the selection of guidelines was limited to two areas: 1) ambulatory or outpatient care, excluding guidelines exclusively covering type 1 diabetes, complications of diabetes that need specialist care (retinopathy, diabetic foot, nephropathy, and neuropathy), and gestational diabetes; and 2) treatment of diabetes, excluding guidelines on prevention and diagnosis.

The sample consisted of a total of 15 guidelines for the clinical care of type 2 diabetes (Table 1) representing the national guidelines of the Appraisal of Guidelines for Research and Evaluation (AGREE) collaboration. This international group of researchers has investigated variation between guidelines and guideline development models with the aim of advising the European Commission on guideline development, dissemination, and implementation. The east London guideline was chosen because there were no national English guidelines available. Two French guidelines were complementary and were analyzed as one guideline. The guidelines from Australia, New Zealand, Canada, and the U.S. were

Table 2—Length of guidelines, number of references, and shared references

ID code	Number of references	Number of pages	Number of references linked to relevant sections	% (n) of shared references	Weighted shared score (ranking)*
FR	590	312	422	20.4 (86)	16.0 (9)
CA	302	29	158	46.2 (73)	19.6 (6)
NL1	246	164	127	42.5 (54)	18.8 (7)
US1	233†	93†	171	42.7 (73)	18.1 (8)
IT	218	350	83	31.3 (26)	15.2 (11)
NL2	190	18	132	44.7 (59)	20.6 (5)
SP	95	85	73	39.7 (29)	15.5 (10)
SC	77	21	56	42.9 (24)	18.1 (8)
US2	67	52	57	63.2 (36)	35.3 (1)
AU	65	92	12	66.6 (8)	24.3 (3)
NZ	44	19	25	56.0 (14)	33.5 (2)
EN	40	36	30	53.3 (16)	21.8 (4)
SW	2	3	Excluded from further analysis	—	—
FI	1	55	Excluded from further analysis	—	—
DK	0	15	Excluded from further analysis	—	—
Total	2,170	1,344	1,346	37.0 (498)	

\*Weighted shared score = number of shared references × 100, divided by maximum possible number of shared references according to publication dates of the guideline and its linked references; †for the 11/42 selected ADA position or consensus statements only.

identified through a web-based search and consultation with colleagues. Four guidelines (CA, NL2, US1, and US2) were updated versions of earlier guidelines. Two guidelines (CA and DK) were funded by pharmaceutical companies, and the others were funded by national or regional government agencies (EN, FR, NZ, SC, and SP) or state health care systems (AU and US2), national professional organizations (FI, IT, NL2, and US1), or hospitals (NL1, SW).

### Selection of comparable sections

Because the guidelines varied in their scope, we selected sections that covered the treatment and monitoring of hyperglycemia and cardiovascular risk.

The guidelines were in seven different languages. Members of the study team translated those guidelines written in French or Dutch; relevant sections of guidelines in Finnish, Danish, and Spanish were translated by guideline developers in their respective countries. The Italian guideline was excluded from the analysis of recommendations because of its length and lack of structure.

### Extraction and comparison of recommendations

We defined recommendations as any statements that promote or advocate a particular course of action in clinical care.

Two investigators with medical training, working independently, extracted the recommendations. We resolved discrepancies through discussion within the study team. A panel of four investigators (J.S.B., J.V.B., G.F., and N.S.K.) judged the extent of concordance or discordance of recommendations across guidelines.

### Extraction and measurement of overlap of citations

One member of our team selected all references linked to the relevant sections chosen for study and another cross-checked this selection. Each citation was entered onto a reference manager database (version 8.5), adding a unique identifier code for each guideline. We excluded the Danish, Finnish, and Swiss guidelines from this part of the study because they cited fewer than three references each. We used the reference manager search facility to quantify the numbers of citations in common with other guidelines, the type of citation (e.g., meta-analysis, review, or guideline), and the address of the first author as a proxy for the country of origin of the cited study. The proportion of shared references between guidelines was expressed as a percentage of the maximum possible score according to the publication dates of both the guideline and its linked references.

### Examination of link between recommendations and citations

To explore the discrepancy between disparate citations and largely concordant recommendations, we purposively selected (16) two areas for further analysis: use of metformin in obese patients and self-monitoring of blood glucose. We selected citations that were explicitly linked to the recommendations or listed at the end of relevant sections and compared citations between guidelines. For each citation, we tabulated the type of study, country of origin, study subjects, conclusions, and any recommendations made by the authors. Where secondary citations were used (i.e., meta-analyses, systematic reviews, or other guidelines), we included the evidence cited by these documents. We compared the publication dates of citations and the dates of the latest evidence cited by guidelines (censoring dates). We did not appraise the quality of the studies but examined the consistency between the study conclusions and recommendations made in the guidelines.

**RESULTS** — Guidelines varied considerably in length (range 3–350 pages), format, and number of references (Table 2). Nine guidelines linked their recommendations to citations; four of these (FR, SC, CA, and US2) also used grading systems to appraise the evidence.

Table 3—Countries of authors of citations (%)

ID code	AU/NZ	CA	UK/IR*	FR	IT	NL	SP	US	SCAN†	Other	Multinational	Unknown
AU	<b>8</b>	—	17	8	—	—	—	67	—	—	—	0
NZ	<b>16</b>	—	40	—	—	—	—	16	12	16	—	0
CA	3	<b>6</b>	13	1	3	1	—	45	17	7	1	5
EN	10	—	<b>37</b>	—	—	—	—	27	23	—	—	3
SC	2	—	<b>39</b>	4	—	2	—	23	23	5	—	2
FR	2	4	11	<b>11</b>	4	3	—	38	11	11	1	4
IT	—	1	6	1	<b>30</b>	—	—	41	4	2	4	10
NL1	—	1	13	1	3	<b>18</b>	1	32	21	6	2	1
NL2	3	1	13	1	1	<b>36</b>	—	24	12	10	—	0
SP	3	—	11	1	—	1	<b>11</b>	51	11	7	1	3
US1	1	1	9	1	3	1	—	<b>59</b>	18	5	1	2
US2	2	2	14	2	—	—	2	<b>63</b>	7	5	2	2
Total	2.6	2.7	11.8	5.2	4.7	7.1	1.0	40.4	11.8	7.8	1.3	3.8

Bold types contain percent of citations of studies from authors of the own country; \*IR, Ireland; †SCAN, Scandinavia.

Guidelines varied in their coverage. For example, the Danish and Spanish guidelines allocated >10% of the text to detailed dietary recommendations, whereas the English and New Zealand guidelines only made a few general statements. Guidelines also varied in their scope; for example, the Scottish, Australian, and Dutch guidelines (NL1) did not cover drug treatment of hyperglycemia.

### Comparison of recommendations

The guidelines largely agreed on general management of patients with type 2 diabetes, which was covered by the following recommendations: 1) all patients should be offered dietary advice and overweight/obese patients should be offered weight management advice; 2) the diet should be low in sugar, fat content, and overall calories and should be combined with exercise; 3) all patients should stop smoking to reduce cardiovascular risk; 4) patient education is necessary to promote good diabetes control; 5) poor glycemic control should be tackled initially with diet alone, followed by oral medication and insulin if necessary, unless the patient is acutely unwell; 6) sulfonylureas or biguanides are recommended in patients with normal BMI, and metformin is recommended in obese patients; 7) a second oral agent should be added to maximum doses of an initial agent in case of poor glycaemic control; 8) HbA<sub>1c</sub> is suitable for long-term monitoring and should be <8%; 9) if on insulin, self-monitoring of blood glucose is recommended; 10) screening and treatment of raised blood pressure, microalbuminuria, and hyperlipidemia is

recommended; 11) ACE inhibitors are recommended in patients with hypertension and renal disease; and 12) aspirin is recommended for secondary prevention of cardiovascular disease.

Differences between the recommendations were found in the following areas: 1) length of trial of diet and exercise before oral treatment ranged from 2 to 9 months—some guidelines recommended a longer period in obese than nonobese patients; 2) BMI used to define obesity ranged from 25 to 30 kg/m<sup>2</sup>; 3) widely varying indications were suggested for the use of  $\alpha$ -glucosidase inhibitors; 4) there was no consensus on the value or indications of combination therapy with oral hypoglycemics and insulin; 5) target HbA<sub>1c</sub> ranged from 6.5 to 7.5%, and target blood pressure ranged from <130/80 to <160/90 mmHg; 6) frequency of monitoring HbA<sub>1c</sub> and blood pressure ranged from one to four times a year and one to six times a year; 7) there was no consensus on self-monitoring of blood glucose in patients on diet alone or on oral medication; 8) there was no consensus on the first-line drug for raised blood pressure; 9) widely differing opinions were given on the value of aspirin use as primary prevention in high-risk patients; 10) widely differing targets were given for lipid control (e.g., total cholesterol 4.5–6.5 mmol/l)—there was no consensus on the use of absolute cardiovascular risk or isolated lipid levels for treatment decisions; and 11) routine annual electrocardiogram was recommended by half of the guidelines, whereas others recommended electrocardiogram

for specific indications or did not mention it.

### Comparison of linked citations

We selected a total of 1,346 references from 12 guidelines (Table 2); 1,033 of these were different citations. Only 18% (185/1,033) of the unique citations were shared with any of the other 11 guidelines. Considering all of the references made in the guidelines, on average of 37% (498/1,346) of these were shared with any other guideline (range 20–67%). The Diabetes Control and Complications Trial (DCCT) (17) was most frequently cited (in 11 guidelines). A randomized controlled trial addressing intensive insulin therapy with patients with type 2 diabetes was cited by eight guidelines (18). If all 45 publications of the American Diabetes Association (ADA) were analyzed as one document, it would be shared between eight guidelines. Two studies (one randomized controlled trial and one cohort study) were shared among seven guidelines, and six trials were shared among six guidelines. Six guidelines referred to the WHO St. Vincent Declaration. Four of the 12 most frequent citations were from the U.S., 3 were from the U.K. (all three U.K. Prospective Diabetes Study publications), 2 were from Israel, 1 each was from Finland and Japan, and 1 was a WHO document.

The largest proportion of lead authors of papers cited in the guidelines (40%) originated from the U.S. (Table 3). All guidelines, except the Australian, cited a significantly higher proportion of studies from authors of their own countries than



the origin overall of citations in the database ( $P < 0.02$ ). Citations in the English, Scottish, and New Zealand guidelines were predominantly from the U.K., and citations in all other guidelines, except the Dutch general practice guideline (NL2), were predominantly from the U.S.

Sixteen of the total 1,033 citations (2%) were meta-analyses, 89 (9%) were reviews or overviews (including 4 systematic reviews), and 55 (5%) were existing guidelines (including practical guides and clinical practice recommendations) or consensus statements. Twenty of these 160 secondary citations (13%) were ADA publications.

### Examination of link between recommendations and citations (case studies)

#### Use of metformin in obese patients

Eleven guidelines covered the use of oral medication. Nine explicitly recommended metformin as a first choice oral treatment for hyperglycemia in the obese, while the Canadian and US1 guidelines recommended tailoring treatment for the individual. We compared the citations from six guidelines, and the others had no citations linked to their recommendations on use of metformin (online appendix, <http://care.diabetesjournals.org>). There was little overlap in the 20 citations given: 1 (U.K. Prospective Diabetes Study [UKPDS] 34) was shared by four of five guidelines with a censoring date that would allow use of this paper (19). The UKPDS 13 paper was shared by three of six guidelines (20), and three other citations were shared by two. Over half of the linked citations (11/20) were randomized controlled trials; 1 was a meta-analysis, and the remainder were nonsystematic reviews. All studies concluded that metformin was useful in obese patients. While the choice of citations varied, publications from one trial (UKPDS) predominated and each guideline cited at least one publication that explicitly supported the recommendation.

#### Self-monitoring of blood glucose

Nine guidelines covered self-monitoring and were unanimous in recommending the self-monitoring of blood glucose in type 2 diabetes treated with insulin. We compared the citations from seven guidelines (online appendix). Only two citations were present in more than one

guideline: the DCCT trial (17) was cited in two and the ADA consensus statement (21) was shared by four. However, when we considered the primary studies in systematic reviews, meta-analyses, or guideline and consensus documents, the overlap between citations increased substantially: 17 of 33 references were then shared by at least two guidelines. For example, the Dutch and French guideline had seven citations in common by virtue of a systematic review conducted by Faas et al. (22). Of the seven citations that specifically addressed self-monitoring in type 2 diabetes, five (two randomized controlled trials, one cross-sectional study, one review, and one comment) concluded that there was no evidence to support its use. The two supportive citations were guidelines (an ADA consensus statement and a Canadian guideline).

**CONCLUSIONS**— This is the first study comparing both guideline recommendations and cited evidence across national guidelines. Our bibliometric analysis included >1,000 citations. We minimized selection and observer bias by prospective choice of inclusion criteria for recommendations and citations and independent extraction by two researchers.

We found a high degree of international consensus on the clinical care of people with type 2 diabetes, despite differences in detailed recommendations. This was in contrast to what we expected, considering the range of influences on the guideline development process and the variation in organization of care and health care system among countries (23). Yet the citations linked to and presumably justifying the guideline recommendations were widely disparate. The influence of large pragmatic treatment trials (e.g. DCCT [17]) and UKPDS studies (19,24,25) was nevertheless visible in most of the guidelines and apparent even in guidelines without references.

Little use was made of systematic reviews (for example Cochrane reviews), which is consistent with the findings of Silagy et al. (26). National guidelines were significantly more likely to cite research from investigators from the same country, explaining some of the variation in citations between guidelines. Others have found that local sources of evidence are overrepresented in guidelines (27) and that the results of trials conducted in the

same country may be given more prominence (28).

We used the case studies to generate hypotheses to explain the small degree of overlap in citations between guidelines. Recommendations for the use of metformin in obese patients drew on supportive trial and review evidence. The different studies linked to these concordant recommendations often had similar conclusions. We also observed a consensus in recommendations for the use of self-monitoring of blood glucose, despite citation of evidence that did not support this position. The overlap in evidence would have been larger if we had aggregated citations from the same study (e.g., UKPDS) and if we had included the primary citations made within reviews and meta-analyses. Even taking this into account, the evidence cited in type 2 diabetes guidelines largely does not overlap. Therefore, we hypothesize that there are other potential influences on guideline developers. For example, the recommendations of the ADA strongly influenced the other guidelines on diabetes, with the exception of the English and Scottish. Similarly, Littlejohns et al. (13) found that professional opinion expressed in a consensus statement from the Royal College of General Practitioners and the Royal College of Physicians influenced the recommendations made in nine U.K. guidelines for the treatment of depression in primary care.

Guideline development is a social as well as technical process that is affected by access to and choice of research evidence and decisions about the interpretation of evidence and formulation of recommendations (29–31). Our study suggests that research evidence is not necessarily the most powerful influence on the content of recommendations in the current generation of guidelines on the management of type 2 diabetes. Guideline developers might first aim to achieve consensus about recommendations and then switch to the evidence as a rhetorical device to support decisions post hoc. Thus, the relationship between choice and interpretation of research evidence and the formulation of guideline recommendations is neither necessarily linear nor unidirectional. However, we are not suggesting a complete epistemological divide between evidence as represented by research papers and guidelines recommendations. As Greenhalgh and McCor-

mack (32) have argued with regards to the UKPDS study, the interpretation of results within primary research studies is also debatable, influenced by prior beliefs, and open to challenge.

There are several sources of imprecision in our analysis. First, the guidelines were partly selected by researchers participating in the AGREE Collaboration. Therefore, the sample might be biased toward guidelines developed with more explicit and robust methods, such as systematic searching and the use of evidence grading systems. Nevertheless, the extent and format of the guidelines differed widely. Six guidelines did not link their recommendations to evidence, which complicated the data extraction.

Second, we did not record the extent of initial agreement on choice of recommendations, judgement on concordance or discordance of recommendations, or linkage between citations and recommendations. However, there were few disagreements and these were easily resolved by panel consensus.

Third, some of the variation in the content of the guidelines might be explained by the different publication dates of the guidelines and the rapid shift of information during the period studied. For instance, nine of the guidelines included in our study could not consider the UKPDS data that were published in 1998. In our analysis of the citations, we dealt with this confounding factor by correcting for publication dates of the guidelines and the cited evidence.

Finally, analysis of shared references is a blunt instrument for exploring the relationship between guideline recommendations and evidence. High-quality and large trials should be given more weight in the analysis. That is why we included two case studies exploring in more detail the relationship between recommendations and evidence in diabetes guidelines. Other clinical issues will need this kind of analysis to test the generalizability of our findings.

The process of formulating guideline recommendations and the social determinants of guidelines require further investigation. Decisions about choice of evidence and the role of international conferences, pharmaceutical companies, and opinion-forming bodies, such as the ADA, on national guidelines is not well understood. The growing availability of high-quality systematic reviews may sup-

port more uniformity in the use of research evidence in guidelines (33). Nevertheless, guidelines go beyond simple reviews of available evidence and necessarily reflect value judgements in considering all the issues relevant to clinical decision making. Transparency by guideline developers about how their judgements have been made would allow clinicians to evaluate the applicability of guideline recommendations to their own health care context and to individual patients.

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## APPENDIX

### The AGREE Collaboration

The following individuals participated in the AGREE Collaboration: José Asua, MD, PhD, Basque Office for Health Technology Assessment, Spain; Anne Bataillard, MD, Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France; Melissa Brouwers, PhD, McMaster University and Cancer Care Ontario, Hamilton, ON, Canada; George Browman, MD, Hamilton Regional Cancer Center, Hamilton, Canada; Jako Burgers, MD, Center for Quality of Care Research, University Medical Center Nijmegen, the Netherlands; Bernard Burnand, MD, MPH, Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland; Françoise Cluzeau, MSc, PhD, St George's Hospital Medical School, London, U.K.; Isabelle Durand-Zaleski, PhD, Hôpital Henri Mondor, Cedez, France; Pierre Durieux, MD, Hôpital Européen Georges Pompidou, Paris, France; Cindy Farkuhar, MD, PhD, New Zealand Guidelines Group, Auckland, New Zealand; Gene Feder, MD, FRCG, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London, U.K.; Béatrice Fervers, MD, Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France; Roberto Grilli, MD, Agenzia Sanitaria Regionale, Bologna, Italy; Jeremy Grimshaw, MB, PhD, Ottawa Health Services Research Institute, Ot-

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