

Critical View of the Guidelines or Guidelines for a Critical View. A New Scholastic Dogma?

Visión Crítica de las Guías o Guías de la Visión Crítica. ¿Un Nuevo Dogma Escolástico?

I hope that the "Guidelines International Network" efforts are successful, but until then, we cannot trust the guidelines."

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INTRODUCTION

"The Evolution and Future of ACC/AHA Clinical Practice Guidelines: A 30-Year Journey" has just been published, (1) a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. This publication commemorated the 30th anniversary of the first ACC/AHA joint communication of a clinical practice guideline (CPG). It is said that: "since then, fuelled by a shared sense of responsibility to translate available evidence into clinical practice in order to guide cardiovascular clinicians, the ACC and AHA have developed 23 CPGs across the spectrum of cardiovascular diseases and procedures".

"The "why" and "how" of CPGs continue to evolve. Although the "why" is based on the directives to develop evidence-supported recommendations for selection of diagnostic tests, procedures, and treatments to improve quality of care and outcomes for patients with cardiovascular disease, it is precisely where evidence is lacking or is controversial that clinicians need the most guidance... The results highlight a natural tension between the needs of clinicians for comprehensive clinical advice from seasoned experts and for a clear delineation of diagnostic and therapeutic measures for which strong scientific evidence exists." And continues with an expression of surprise "Notably, there has been an increased focus on the "how" of CPGs and changes in the methodology used to collect and evaluate the evidence"; it is here that they put the finger in the critics on the need of changing how CPGs are developed and applied.

To perform a critical analysis of guidelines, as they have been developed until now, we must know: a) if all the research studies are published and readily accessible to physicians; b) if there is confidence that the presentation and conclusions of the published studies are reproducible in a new analysis of their data; c) if the meta-analyses performed to mathematically summarize published results are not biased in their development; d) if the methods to classify guideline evidences are adequate, or only vague recommendations proliferate; e) if the implementation of CPGs follow

quality guidelines and those who delineate them have no conflicts of interest; f) if general CPG decisions can or should fit the personal decisions taken by physicians; and g) if the context and preference of patients should be considered.

We will enter into these discussions.

DO GUIDELINES HAVE ALL THE INFORMATION OR IS A GREAT PART INACCESSIBLE?

As we are, as never before, in a time of great, almost instant, digital communication, we may believe that all research may be found in the web of webs, i.e. in the Internet.

However, to mention a recent example, The Lancet published (2) that only half of health studies funded by the European Union with a cost of 6,000 million euros between 1998 and 2006 reached publications that could be identified in a 9-year follow-up period.

In clinical trial of oseltamivir for the treatment of influenza, the non-communicated studies, including the greatest clinical trial known, turned inaccessible 60% of overall patient data at 2011. (3)

With a new review, which incorporated all the available data of neuroaminidase inhibitors after a two-year litigation, the previous perspective has changed substantially and currently they do not seem to be recommended, as in prophylaxis and treatment studies there is no convincing evidence that they produce a decrease in the risk of hospitalizations, complications and even death. (4) Furthermore, reviewers found that oseltamivir causes vomiting and nausea and increases the risk of cephalaea, renal problems and psychiatric syndromes.

Another example is that of reboxetine, a new selective inhibitor of serotonin reuptake, which was being used for major depression based on favourable outcomes. However, when unpublished clinical trials were included in a meta-analysis, it was shown that reboxetine is more harmful and even not more efficient than the simple placebo, a finding completely different from the one where only the published studies were included. (5)

At present, the rule that half of the completed pre-clinical and clinical studies are not published persists and this has not changed in the last 30 years.

It is well known that positive studies are more published, but also they that they are published, in

average, a year earlier than negative studies, which are released, if ever, various years after being finished.

Therefore, we must abandon the innocent presumption that all research is published, as the scientific literature published represents only a subgroup of research findings; so, the information we read is biased besides being incomplete. This means that, unfortunately, we cannot be certain that the supposedly informed decisions we take with our patients are real, as these decisions are based on incomplete information.

This is summarized in what happened to a patient, Alejandro Liberati, also a physician, who in 2010 explained the difficulties he encountered in making a rational decision about a new line of treatment, due to the initial therapy failure for the multiple myeloma affecting him. He expressed: "When I had to take the decision of making a second bone marrow transplant, I found four clinical trials that could have answered my question, but I was forced to take the decision without knowing the results because, although the clinical trials had been completed some time ago, they had not been conveniently published... I believe that the results of an investigation should be regarded as a public good belonging to the community, especially patients." (6)

However, even if studies were published, access to published research is restricted, due to the need to subscribe to different journals, with a cost hardly accessible to physicians and institutions, particularly in low-income countries, and even for leading private academic institutions. Though much is claimed, "open access" to different medical journals is just starting to develop, and still 78% access to medical research publications is restricted to paid journal subscriptions.

Another difficulty is that publications in languages other than English are much more difficult to find, and hence most of the times are excluded from systematic reviews (meta-analysis) due to language unfamiliarity and difficult access. For example, there are more than 2,500 biomedical journals published in Chinese, and less than 6% of them are indexed in Medline. (6)

WOULD PUBLISHED STUDIES BE REPRODUCIBLE IN A NEW ANALYSIS?

It is a matter of controversy whether researchers should be asked to make randomized clinical trial data public and available for new analysis, as since the new analysis of original data with oseltamivir arrived to completely different conclusions, some authors have argued that clinical trial data paid by the public (the consumers through the State or by direct purchase) should be of "open access" in ad-hoc repositories, to be shared and freely reanalysed in the scientific community, with complete transparency and beneficial consequences both for public healthcare and for patients.

Shanil Ebrahim et al. published new analyses of randomized clinical trials, identifying published reanalysis studies at the level of clinical trial patients, to

assess the same hypothesis as the original article. The meticulous search in Medline from inception (1966) to March 9, 2014 was surprising, as it showed how infrequent a new analysis of clinical research data is. They only found 37 publications meeting these reanalysis criteria out of 36 randomized clinical trials. (7)

In these few reanalyses, one of the authors belonged to the original research group in 84% of cases, clearly showing that in addition to being very rare most were not independent from the authors or the institutions that had performed the work, and that hence real independent reanalysis was even rarer.

It was seen that almost half of the reanalysed studies differed in the analytical approach and statistical analysis, but what is even more important, a third of the articles differed in result definitions or measurements. And even more surprising is that one third of reanalyses produced different interpretations and conclusions from the ones originally published.

This means that publication of research studies in medical journals implies a synthesis and selection of some research data, and therefore, it does not replace the free knowledge and analysis of original data to reach conclusions, which in a significant number of cases could be different from those published in the original article.

This criterion should be met when complete results and data are sent to the US Food and Drug Administration (FDA) agency. But a review comparing the evaluation of clinical trials provided to the FDA with published articles showed that 9% had discordance in the conclusions, which as expected, all favoured the drug. (8)

Another way of looking for inconsistencies is using the clinical trial registry in ClinicalTrials.gov comparing it with what is published in medical journals. In a randomized sample, the principal endpoint published was different from that communicated to ClinicalTrials.gov in 15% of cases. Moreover, in 22% of cases the primary endpoint was inconsistent, and in some of them it even differed in the number of deaths. (9) Thus, up to 37% of primary endpoints were discordant between what was published and what was communicated to the registry.

Krumholz and Peterson say that "full availability of trial registration data is essential to allow peer reviewers and journals to monitor trial protocols and analytic plans to ensure consistency and thereby reduce some of the variation that may occur in the reporting of results, particularly with respect to primary, secondary, and exploratory outcomes".

"Second, raw data and metadata (all the information about the data) from the original trial should ideally be made available to those who seek the opportunity to replicate the findings. Such independent verification would markedly increase the scientific community's confidence in the study findings. Even when results differed importantly, it would allow for open dialogue that would promote a deeper under-

standing of the study and its interpretation.” (10)

Although the article by Ebarhim et al. shows that 65% of reanalyses do not show changes in the interpretation of results and allow us to trust the diagnosis or treatment established, 35% of published reanalyses alter original article conclusions, so that many patients are treated. (7) Therefore: “Rather than the rare exception, open science and replication should become the standard for all trials and especially those that have high potential to influence practice.” (10)

ARE META-ANALYSES BIASED?

When guidelines are developed, a systematic review using a very large meta-analysis of well-performed clinical trials, simulating the experimental conditions better than any other design and involving patients similar to those found in clinical practice, is placed at the top of the search pyramid to answer with the best evidence questions about prevention and treatment.

“As a general principle, generating, summarizing, and understanding the best available evidence is essential for establishing the benefits and safety of interventions. Meta-analysis has become a valuable tool toward these ends. There has been a proliferation of guidelines by professional societies and others, aimed at ensuring that the best preventive interventions or treatment options are provided to the appropriate patients at the appropriate time; these guidelines often incorporate meta-analyses as a key evidence support for their recommendations.” (11)

However, there are problems and limitations in meta-analyses which researchers, those developing the guidelines, medical journal editors, and even critical readers struggle with. Understanding the limitations of meta-analytical evidences is crucial for all of them. This great challenge may be divided into two great categories: the problem of “heterogeneity” and “methodological” dilemmas.

“Heterogeneity”, inherent to the meta-analysis per se, is the variation in true effect sizes and also in the factors that might influence them. This heterogeneity is due to a clinical component, as for example, diversity in patient population or interventions, and a statistical component, as differences in the method used (e.g. fixed or random). Although there are statistical approaches to investigate and quantify heterogeneity (Q statistics, I² and t²) these statistics do not eliminate heterogeneity as a problem, when the cause, as commonly occurs, is not found. Sometimes, the interpretation can be improved when heterogeneity is associated to study characteristics, as for example when the treatment shows a different effect in patients with severe disease compared with those with moderate or mild disease.

One of the problems of concealed heterogeneity is the meta-analysis use of cumulative data presented in the publications of the original studies, which is discovered when individual data at patient level (fusion of each study database into a single database) show

unidentified relationships.

Considering the cumulative (published) data with aspirin in primary prevention, we may assume that the initial analysis was paradigmatic. The antiplatelet trial research collaboration group arrived at the conclusion that the increase in hemorrhagic stroke was fixed at 0.2% in 10 years, and that therefore, above a certain risk of ischemic coronary disease, > 10% at 10 years, the reduction of almost 30% in these events, exceeded the risk of hemorrhagic stroke, and so low-dose aspirin should be administered to reduce cardiovascular risk. Thus, it was recommended in all primary prevention guidelines. However, when these same clinical trials were examined at an individual level in a single database including all patients, it was seen that the same risk factors increasing ischemic diseases, as age, diabetes, smoking, hypertension and obesity, similarly and simultaneously increased the risk for bleeding. (12)

Therefore, in the homologation to secondary prevention of > 20% risk at 10 years, although the major coronary event was reduced by 4% (from 32% to 28%), bleedings now increased by 2% (from 3.4% to 5.4%). If we consider that in this situation, a statin has a precise indication reducing risk by half, the benefit and the damage are balanced. That is why guidelines, taking a 180-degree turn, currently do not recommend aspirin in cardiovascular primary prevention, a conclusion based on the same clinical trials that previously recommended it but using a different methodology.

Moreover, it is not uncommon to find conflicting, or even opposed results among meta-analyses investigating the same subject, because they often include different clinical trials. This happened recently with meta-analyses published almost simultaneously to evaluate percutaneous coronary intervention added to optimal medical treatment versus optimal medical treatment alone in patients with stable coronary disease.

In the 2012 meta-analysis, Pursnani et al. (13) included 7,182 patients from 12 randomized clinical trials performed between 1987 and 2005. Although stable patients were incorporated to percutaneous coronary intervention studies with or without stent, they could enter the study 7 days after an unstable angina episode, as in fact happened, or without spontaneous or induced angina symptoms. A marginally significant 15% reduction in all-cause death was observed (RR 0.85, 95% CI 0.71-1.01) between percutaneous coronary intervention and optimal treatment. Conversely, in the meta-analysis by Stergiopoulos et al. (14) also published in 2012 and with a similar number of stable patients (7,229) but a lower number of clinical trials (8 randomized clinical trials), the exclusion of all studies presenting acute coronary syndrome and those with percutaneous coronary intervention in which stents had been used in < 50% of patients, showed that overall death was similar for both groups (OR 0.98; 95% CI 0.83-1.15).

What was the difference between both studies? Only 4 clinical trials were included in the two meta-analyses, which had 4 or 8 different studies that they did not share. One trial included percutaneous coronary intervention with and without stent and the other only studies with > 50% stents implanted, the latter with more recent studies and without acute coronary syndrome patients. When the meta-analysis with marginal reduction in mortality was restricted to the analysis of only the 4 randomized clinical trials with > 50% stents implanted, the difference in mortality disappeared (RR 0.93; 95% CI 0.78-1.11). Which meta-analysis should be used in a guideline?

Different strategies can also be used when a meta-analysis is performed. Deschartres et al (15) compared 5 different strategies: meta-analysis of all trials, the most precise trial (i.e. trial with the narrowest 95% CI), meta-analysis restricted to the 25% largest trials, meta-analysis of the largest trials and meta-analysis restricted to trials at low overall risk of bias according to the Cochrane criteria. The authors found that the different strategies gave different results, making it difficult to determine which was "the best".

The difference in treatment outcomes between these strategies was substantial: subjective outcomes were different in 51% of meta-analyses and objective outcomes in 39%. Outcomes were more dissimilar and with greater treatment effect between clinical trials with higher or unclear risk of bias compared with those of lower risk of bias, both on subjective as objective outcomes.

It is possible that due to the simple management of meta-analysis computer programs these are performed by researchers without methodological experience or limited training, easily creating mediocre or poor meta-analyses that end being published.

This has led to a plethora of these investigations; "the annual number of Pubmed publications indexed under "meta-analysis" has increased from 1,289 in 2003 to 7,053 in 2013. Many of them are of dubious quality and address questions of limited importance". (11)

The critical reader must approach these studies as he does with the rest of studies in the medical literature: as imperfect information whose findings need a critical assessment of their applicability to individual patients. It is not an easy task, but it should receive a treatment similar to that of other evidence, because the information they provide would not be, for the moment, at the top of the pyramid, but at the same level.

ARE THE METHODS TO QUALIFY GUIDELINE EVIDENCES SUITABLE?

The strength of guideline "recommendations" is the primary information always sought by clinicians. The writing committee members in charge of guideline recommendations find support on the "level of evidence" classification which describes the truth or accuracy of the information on which recommendations

are based.

Both "Class I" as well as "Class III" classifications are strong recommendations to either use or not use, respectively, but "Class II" classification is a dubious recommendation. "Class II" is divided into "Class IIa" which is an intermediate and moderate recommendation, and "Class IIb" which is even a weaker and marginal recommendation. Now, they also propose to divide "Class III" recommendation into "Class III: No benefit" where the benefit is equal to the risk, which would be equivalent to a moderate non-recommendation and a "Class III: Harm" where the risk is greater than the benefit, and hence a strong recommendation of not use.

The purpose of the "level of evidence" is to quantify the quality and accuracy of scientific evidence, supporting the effects of an intervention based on consistency, quality and quantity of randomized clinical trials or other relevant evidences. Even if published scientific evidence is absent, a consensus of expert opinion can make a recommendation based solely on expert clinical experience, which is classified as "Level E".

Recently the quality of levels of evidence categories has been extended. "Level A" refers to high quality evidences from one or more randomized clinical trials or a meta-analysis of these trials; "B-R Level" to moderate quality evidences from one or more randomized clinical trials or their meta-analysis; "Level B-NR" to moderate-quality evidences from one or more well-designed, well-executed non-randomized studies, studies or observational registries; "Level C" to evidence arising from randomized trials or nonrandomized observational studies or registries with limitations of design or execution, or meta-analyses of such studies; and "Level E" refers to consensus of expert opinion when evidence is insufficient, vague or conflicting. (1)

Out of the 3,271 recommendations made by the 19 ACC-AHA CPG analyses published up to 2013, "Class I" recommendations were approximately 50%, but in the "level of evidence" less than 10% were "Level A" and 50% were "Level C" "with very limited quality information.

Worse still, only about 5% were "Class I A" recommendations. Another surprising finding was that 25% were "Class I C," recommendations, which as mentioned above have very limited quality information. The remaining recommendations were "IIa", "IIb" and "III" with moderate, ambiguous or weak levels of evidence. (1)

It is argued that practicing physicians should adhere and standardize their conduct and treatment to that of the guidelines, which appears as a synonym of evidence guided practice, thus reducing variations in practice which is desirable for the patient and for the cost of medicine. However, other authors "explain that this position is based on a false concept of the guidelines' reliability and that to do everything possible to standardize the practice as an end in itself leads

to a wrong behavior.”

“In these cases, confidence in the estimate of the effects will often be low or very low. Furthermore, if the values and preferences differ widely in the spectrum of patients (which is often the case, albeit not uniformly), the right choice for a patient may be the wrong decision for another”. (16)

Guidelines should be very clear to distinguish between those medical situations in which confidence in effect prediction is high with a clear balance between desirable and undesirable consequences, and medical situations where these conditions are not present. In the first situation, the guidelines should include strong and conclusive recommendations to ensure the desired consistency in clinical practice. In the latter, recommendations should be weak and conditional or contingent which may be different for each patient and where a uniform practice would not be appropriate.

We would all agree, for example, that aspirin and statins after acute myocardial infarction or beta-blockers and angiotensin-converting enzyme inhibitors in patients with systolic heart failure, are measures that deserve a strong recommendation to ensure uniform practice and which should also be audited as criterion of medical quality. Conversely, the use of anticoagulation for patients with very low risk atrial fibrillation or the indefinite anticoagulation of patients with unexplained venous thromboembolism deserve a mild recommendation, and in these circumstances with low possible effectiveness or balance between risks and benefits, the variation in clinical practice according to the patient's circumstances and co-morbidities is a characteristic of good medical practice.

How often does the latter situation make clinical uniformity inappropriate? The answer is “in most situations”: “from over 9,400 recommendations classified in UpToDate, an online popular resort, about two thirds are weak recommendations.”

“Rather than justify an impulse for medical care uniformity, these principles emphasize the convenience [in most clinical situations] of tailoring medical care to the patients' individual circumstances and their values and preferences.” (16)

ARE CLINICAL PRACTICE GUIDELINES TRULY FOLLOWING THE GUIDELINES?

In the last two decades the number of clinical practice guidelines has proliferated exponentially, and almost 6,400 guidelines are filed in the “Guidelines International Network.” (17)

Although clinical practice guidelines could be useful, many are wondering about their validity and reliability, since they are performed by a multiplicity of different organizations, with a tendency to promote greater medical care rather than more effective medical care.

In response to these concerns, in March 2011 the “Institute of Medicine” (IOM) in the United States

published a new set of standards for clinical practice guidelines, trying to emphasize their transparency and objectivity and to standardize the formats with which they are developed (18)

Kung et al (19) examined 130 randomly selected guidelines from the National Guideline Clearinghouse (NGC) (with about 2,700 guidelines) to see if they adhered to 18 of 25 IOM recommendation standards.

The overall median (percentage) of IOM standards satisfied was 8 (out of 18) (44.4%), with an interquartile range of 6.5 (36.1%) to 9.5 (52.8%).

Less than half of the guidelines surveyed met more than 50% of IOM standards. Information on author “conflicts of interest” (COI) was present in less than half of these guidelines. Of those guidelines including such information, COI were present in over two-thirds of writing committee chairpersons (71.4%) and 90.5% of co-chairpersons, although the IOM recommends that none or at most a small number of panel members should have conflicts and that the chair and co-chair should not have conflicts.

It may be even more important that panel members with significant COI should not participate in discussions or vote recommendations in which they have COI, but they could give their written opinion, and thus the balance in the committee with clinical experience or clinical research expertise would be preserved

The criteria used to select committee members and the process of selection are seldom described, and rarely experts in information analysis are included. In the era of care focused on the patient, the same patients or patients' representatives should be included in guideline development panels, as they offer perspectives that the clinicians or scientists do not have.

Other situations scarcely taken into account are the literature in languages different from English, unpublished data and/or summaries, and the differences among committee members with respect to recommendations and benefits mentioned more often than potential damages. No improvement has been observed in guidelines' development in the last decade compared to the previous one.

Although it is always claimed that guidelines are open to public discussion before their publication, few guidelines specify “how” they will be reviewed, and it is also unclear how these comments (if they exist) will be incorporated to the guidelines' review process.

It is probable that until medical journal editors demand well-specified quality criteria from clinical practice guidelines, biased, scarcely applicable, and with unreliable consensus guidelines will be issued.

There would not be multiple guidelines on the same subject, making conflictive recommendations, with panels whose members have COI, if those in charge of developing the guidelines were centrally commissioned on the subjects in which guidelines are necessary, with multidisciplinary panels composed of all the relevant interested persons that should be guided and

responsibly sustained by international standards to develop guidelines. (20)

Shaneyfely says: "How will the next decade of guidelines' development be? I am not very optimistic that it will improve much. Nobody seems interested in restricting the out-of-control guideline industry". (21)

It is necessary for guidelines to be certified by a national, independent scientific committee with relevant personalities, so that guideline publications adhere to standards of quality and, after being certified, are published in a national repository.

Shaneyfelt ends: "I hope that the efforts of 'Guidelines International Network' are successful, but until this happens, in guidelines we cannot trust." (21)

Or as Jeane Lenzer finishes: "Even these and other guidelines are still followed despite bias concerns, because as a lecturer said in a meeting on geriatric care in the Virgin Islands at the beginning of this year, 'we like to adhere to medical care standards, because when problems are made public we all need to say we were doing what any other doctor is doing, even if what this other doctor is doing is not very good'." (22)

CONCLUSIONS

Are clinical practice guidelines a new scholastic dogma? In the Middle Ages, when a scholar was asked about the foundation of some measure, the invariable response was "Aristotle says so". Nowadays, when a young doctor is asked about the rationale to take some clinical decision, the invariable answer is "The Guideline says so". Have we replaced Aristotle for the Guideline? To trust so blindly in them, we should know how they are made.

We now know that even the guidelines that best follow international or United States IOM standards are biased, because half of the clinical trials conducted are not published, when they are published many of them are of difficult access because they are not in English, and in addition open access, without need for paying, is available in only 22% of publications.

Moreover, in the only article assessing a new database analysis of already published articles, a third of reanalyses arrived to interpretations and conclusions different from the ones originally published.

Therefore, a large part of the information is inaccessible, either intentionally or not, and another part can have a different interpretation from the original publication, adding a new bias to the written presentation.

Regarding methodology, we place meta-analyses of large randomized clinical trials at the top of the evidence pyramid, without considering that they may present heterogeneity, whose cause or causes are very difficult to identify. Sometimes, if combined data from several publications are used or the analysis is performed at the individual level of a single database, methodology can show contradictory results. Such was the case of aspirin recommendation for cardiovascular primary prevention when a meta-analysis

of combined data was performed, whereas when the same data was analysed at the individual level, the recommendation changed drastically to one not including aspirin for primary prevention.

Results can be contradictory depending on what trials are included in the meta-analysis, and also on the type of clinical trial: the ones of large dimensions, of the best methodological quality, etc. Therefore, it is necessary to analyse meta-analysis evidence as that of randomized clinical trials, since they are at the same level of evidence.

But we must also consider whether those in charge of making the clinical guidelines follow quality rules according to already established standards.

The great guideline industry, with approximately 6,400 guidelines registered in the Guidelines International Network, does not follow these quality criteria. More than half (56%) do not fulfil IOM requirements, more than 50% do not report the conflicts of interest of those making the guidelines, and when they report them, most of the writing committee directors and co-directors as well as a great number of its members present conflicts of interest. Neither is the criteria used to choose the members explained, and the experts in research methodology and patient representatives are absent.

Finally, Class I, level of evidence A recommendations, which if accepted would be medical care quality criterion, are 5% to 10% of all recommendations. Most are Class IIa or IIb, with levels of evidence which are not conclusive. This leads Shaneyfelt to declare "in guidelines we cannot trust".

Some may think that physicians who provide a uniform guideline-based care are undertaking medical practice built on strong evidence. Such uniformity with guidelines is correct in situations with strong definitive recommendations (usually classified as I A). But in many, or better still in most situations, clinicians must make important decisions where these conditions are not met. Guidelines should always distinguish clearly between those situations in which the confidence on effect estimation is high and the balance between desired and unwanted consequences is patent, and when these conditions do not exist.

In this last situation the recommendation is weak, conditional or contingent. The recommended course of action could be good for some patients and bad for others. In this condition, uniformity of practice is not appropriate. Guidelines should recommend considering the individual patient's history and circumstances as well as his values and preferences before adopting an adequate conduct that may be different for each patient.

We declare with Harlan M Krumholz that "what emerges from these documents and others is an understanding that guidelines should inform but not oppose, guide but not force and support but not restrict. Guidelines may provide options and recommendations for those seeking to improve the quality and ex-

tension of their lives.” (23) And concludes “They [the guidelines] may enhance the uncertainty points. But they should not reduce physicians to automats and patients to passive recipients of guideline sentences.”

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