

CAN CONTRAINDICATIONS COMPROMISE EVIDENCE-BASED, PATIENT-CENTERED CLINICAL PRACTICE?

Victor M Montori^{1,2}, Teresa W Leung², PJ Devereaux², Holger J Schünemann^{2,3}, Elie A Akl³, Amiram Gafni², Gordon H Guyatt²

¹Knowledge and Encounter Research Unit, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA, ²Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada, ³Department of Medicine and of Social and Preventive Medicine, University at Buffalo, Buffalo, NY, U.S.A.

Corresponding Author: montori.victor@mayo.edu

ABSTRACT

Background

Despite their often weak evidence base, contraindications convey the unequivocally adverse risk-benefit profile of an intervention in a specific clinical context. However, some patients in that context may nonetheless prefer the contraindicated intervention (with its potential benefits and risks) to the available alternatives. The impact of contraindications on treatment decisions remains unexplored.

Objective

To provide an estimate of the impact of the “contraindication” label on treatment decisions.

Methods

We conducted an international 6-wave email/internet and fax survey of practicing clinicians who were members of the American Diabetes Association or the College of Physicians and Surgeons of Ontario and had available email addresses and fax numbers. Each participant considered one of two patient scenarios. In each scenario, the patient expressed a strong preference for use of a medication that carried a “contraindication” label despite weak evidence of harm. We designed these scenarios so that respondents who placed greater weight on patient preferences and research evidence than on the label “contraindication” would be ready to prescribe the contraindicated medication. We determined the frequency with which the label “contraindication” dominated participants’ treatment decisions despite patient preferences and weak evidence of harm.

Results

466 participants responded (22% response rate). Depending on the group and scenario, contraindications dominated the decisions of 47% to 89% of surveyed clinicians, superseding patient preferences and research evidence.

Conclusions

The label “contraindication” may often dominate clinicians’ decisions about treatment and may compromise evidence-based, patient-centered clinical practice. Further research should elucidate the process that leads to the formulation of contraindications and its impact on treatment decision-making.

Key Words: *Drug label, contraindications, decision-making, evidence-based medicine*

In the practice of evidence-based medicine, treatment decisions require attention to the best available evidence, the patient's values and preferences, and the context in which clinician and patient will implement the decision.¹ Among the issues that clinicians consider is whether the patient's clinical situation constitutes a contraindication to an intervention under consideration. The ultimate decision about recommending the intervention involves comparing the potential benefits and downsides of the intervention against those of alternative courses of action.

If a patient is at appreciable risk of suffering an important adverse effect of an intervention without potential benefits sufficient to outweigh the potential harm, authorities often apply the label "contraindicated" to the intervention. For example, most practitioners will agree that the potential harm from administering a medication to which a patient has had a previous anaphylactic reaction outweighs any possible benefits. Thus, taking such contraindications into account is not only reasonable, but also essential.

Not all contraindications, however, refer to such clear-cut decisions. Some reflect a closer balance of potential benefits and harms, sometimes because only limited research evidence or equivocal findings support the "contraindication" label. Examples of these situations include the use of metformin in diabetic patients with some degree of renal impairment,^{2,3} and the use of triptans in patients with migraines at-risk of vascular events.⁴ In these instances, fully informed individuals with different values and preferences could arrive to different conclusions: e.g., one person may conclude that the risk of harm outweighs any potential benefits, while the other can conclude that the potential benefits justify accepting the risk of harm. Those decisions represent differences in values and preferences and not in information.

The values and preferences of the informed patient, the person who will live with the consequences of this choice, should inform such judgments. The informed patient's values and preferences may not coincide with those of the drug manufacturer and the government regulatory agency, the authorities who have applied the "contraindication" label. Furthermore, clinicians

may erroneously perceive contraindications as guidelines based on high-quality evidence of harm that require mandatory implementation. Also, clinicians may perceive that failure to adhere to contraindications may cause them adverse legal and ethical consequences. Thus, legal issues, defensive practice, and ethical concerns are all aspects of the cultural context that may influence decision-making. In this particular situation, the cultural context in which published contraindications exert their influence may lead clinicians to ignore both patient preferences and the relevant evidence.

To understand the extent to which contraindications affect treatment decision-making, and in particular to evaluate the possibility that published contraindications may impair the ability of patients and clinicians to make evidence-based, patient-centered decisions, we conducted a survey of clinicians in North America.

METHODS

Participants

We drew random samples of members of the American Diabetes Association (ADA) Professional Section and of the College of Physicians and Surgeons of Ontario (CPSO). We selected these groups because of convenience: contact information (e-mail addresses and fax numbers) for most members of these organizations was publicly available and reasonably up-to-date, and their answers could offer insights about the influence of context on their response to contraindications. Eligible participants were clinicians who were active in general practice, family medicine, or internal medicine (general or specialty). We excluded retired clinicians and professionals who were involved primarily in research or administration with minimal patient contact.

Participant contact

We designed our survey approach based on the Tailored Design Method of Dillman, adapted to internet-based surveys.⁵ We set out to contact participants using 6 personalized email invitations to participate (waves) with successive invitations targeting the non-responders to the previous

waves. Between the 3rd and 4th waves, we took a random sample of 500 non-responders for whom we had phone and fax numbers and contacted them on the phone to verify their fax numbers and send them the questionnaire by fax. We called back 1 week later to remind participants of our faxed questionnaire.

The email invitation indicated our purpose was “to understand clinicians’ perceptions of drug labels”. The subject line was “An invitation to participate in research” and came from the lead author’s institutional email account (VMM). The email indicated the investigators’ names, email address, phone number and affiliations, the funding source, and the approval of the research by the McMaster University Ethics Board. The email message included a link to the internet-based survey webpage. The survey website included a cover page that offered the same information as the email invitation and offered respondents the options of declining to participate or continuing responding to the questionnaire. The fax cover sheet and the faxed questionnaire were identical to the email and web version.

Survey

We developed the questionnaire after discussing scenarios and contraindications with clinicians and clinical pharmacologists. We refined the content and presentation through testing successive versions of the questionnaire with clinicians in training in Northern Ontario, with a sample of practicing clinicians at Mayo Clinic, and with a sample of practicing clinicians at Northwestern University in Chicago. These pilots allowed us to improve the clarity of our questions and to ensure that responders felt their answers to the questionnaire reflected their thoughts. The results of these pilots, available from the authors upon request, were consistent with those presented in this report.

In the first section of the questionnaire, respondents read a clinical vignette describing a patient who strongly preferred a contraindicated medication. Without specifically informing respondents about the contraindication, we asked them whether they would consider prescribing the contraindicated medication to that patient (with answer options “yes”, “no”, and “not sure”). We asked the same question after informing them of the contraindication and then again after a

description of the weak evidence supporting the contraindication (Box 1 and 2 describe the scenarios as initially presented, how we presented the contraindication label, and how we described the evidence supporting the label). In the remainder of the questionnaire, participants responded to general questions about contraindications and about their previous history of prescribing contraindicated interventions, and provided information about their demographic characteristics.

To determine the extent to which clinicians’ responses to contraindications generalized across situations, we developed two questionnaires. One presented a patient with type 2 diabetes with a creatinine level exceeding the contraindicated threshold to metformin who was unwilling to use antihyperglycemic agents that would cause hypoglycemia or weight gain, with a particularly informed and strong preference against insulin (Box 1). The other presented a patient with difficult to control migraines eager to use triptans but suffering from coronary artery disease, a contraindication to triptan use (Box 2). Participants were randomly assigned to receive either the metformin or the triptan scenario, stratified by country and in blocks of 8.

Analysis

We present the proportion of participants, tabulated by scenario (metformin and triptan), whose treatment decisions were dominated by the label “contraindication”: that is, they would never prescribe the contraindicated intervention despite patient preferences and weak evidence of harm.

To evaluate the validity of our survey results, we assessed the consistency of responses to successive survey waves using tests commonly employed in meta-analyses.⁶ These tests evaluate the extent to which responses to successive survey waves (that sample from non-responders to prior waves) are similar to those in the first wave; greater consistency makes response bias increasingly unlikely. We also used the technique that Drane proposed to impute the answers from non-responders.⁷ This technique assumes a trend in responses as a function of the wave to which the person responded. Because of our finding that non-responders in Ontario were older and more generalists, we determined the relation between age and generalist/specialist and survey responses.

Can contradictions compromise evidence-based, patient-centered clinical practice?

BOX 1 – Metformin vignette. As presented to the ADA members (bold type used in actual questionnaire)

Case, preferences, efficacy	Contraindication	Evidence in support of contraindication
<p>A 75-year-old overweight woman with type 2 diabetes presents with frequent hypoglycemia, weight gain and inadequate glycemc control on 5 mg of glyburide. Her creatinine is elevated at 168 µmol/L. Her weight is 67 kg. Her blood pressure is now under adequate control with an ACE inhibitor and a thiazide diuretic. She is also on simvastatin 40 mg/d. Her HbA1c is 9.2%. She dislikes self-monitoring and skips meals. One year ago, she used insulin for 1 month. She found the insulin injections a significant burden in her life, and expresses a strong preference for avoiding resumption of insulin, if at all possible. To the extent examined, she has no history of evidence of micro or macrovascular complications. As you may know, the reports from the UKPDS randomized trial showed that metformin was associated with minimal hypoglycemia (never severe), minimal weight gain, and an important reduction in the risk of all diabetes-related complications, including myocardial infarction and mortality.</p> <p>Would you offer metformin to this patient?</p>	<p>As you may know, metformin’s package insert indicates that this patient’s creatinine level (>124 µmol/L) represents a contraindication to the use of metformin.</p> <p>Use in patients with decreased kidney function may be associated with a higher risk of lactic acidosis, which could require intensive care and may be fatal.</p> <p>Given this information, would you offer metformin to this patient?</p>	<p>As you may know, a systematic review pooled data from 176 comparative trials and cohort studies and revealed no cases of fatal or nonfatal lactic acidosis in 35,619 patient-years of metformin use or in 30,002 patient-years in the non-metformin group. The authors of this review reported the upper limit for the true incidence of metformin-associated lactic acidosis was 8.4 cases per 100,000 patient-years, and the upper limit for the true incidence of lactic acidosis in the non-metformin group was 9 cases per 100,000 patient-years.</p> <p>Given this information, would you offer metformin to this patient?</p>

Can contradictions compromise evidence-based, patient-centered clinical practice?

BOX 2 – Triptan vignette. As presented to the ADA members (bold type used in actual questionnaire)

Case, preferences, efficacy	Contraindication	Evidence in support of contraindication
<p>A 52-year-old postmenopausal woman presented to your office complaining of frequent and severe migraines and asking for a refill of her oral sumatriptan prescription. She had unsuccessfully treated her migraine with combination aspirin/acetaminophen/caffeine tablets. Her previous primary care physician (your office partner who has since relocated) had prescribed prophylactic beta-blockers and oral sumatriptan with adequate control. She had a myocardial infarction 2 years ago and received coronary angioplasty with stents without recurrence of chest pain or shortness of breath. Her most recent thallium scan was normal. She quit smoking 2 years ago. Her blood pressure and lipids are under control with medications which include aspirin and a statin. She is otherwise healthy. As you may know, systematic reviews of placebo-controlled randomized trials have consistently demonstrated the efficacy of oral sumatriptan in patients with migraine headaches.</p> <p>Would you agree to renew her oral sumatriptan prescription?</p>	<p>As you may know, sumatriptan’s package insert indicates that this patient’s history of ischemic heart disease represents a contraindication to the use of sumatriptan.</p> <p>Use in patients with any form of ischemic heart disease may be associated with a higher risk of myocardial infarction which could be fatal.</p> <p>Given this information, would you agree to renew her oral sumatriptan prescription?</p>	<p>As you may know, systematic reviews of randomized trials of sumatriptan reveal that at most 5% of participants had chest pain with this medication (in some trials 3% of participants in the placebo group had the same symptom). According to the manufacturer, 2 of 6438 participants in clinical trials experienced symptoms suggestive of coronary vasospasm. In patients receiving oral sumatriptan, all these episodes were mild. In postmarketing studies, there has been one coronary death associated with the subcutaneous administration of sumatriptan. There have been at least 5 published cases of myocardial infarction and one of cardiac arrest following the subcutaneous administration of sumatriptan. Sumatriptan is one of the top 200 drugs prescribed in 2002.</p> <p>Given this information, would you agree to renew her oral sumatriptan prescription?</p>

TABLE 1 Participant characteristics and survey responses

	American Diabetes Association (n=233)			College of Physicians & Surgeons of Ontario (n=233)		
	Metformin	Triptan	Total	Metformin	Triptan	Total
Would not offer contraindicated intervention despite patient preferences and weak supporting evidence for harm, i.e., did not answer “yes” after receiving complete presentation, n/N (%)	113/127 (89)	65/99 (66)	178/226 (79)	51/109 (47)	79/110 (72)	130/219 (59)
Expressed fear of adverse legal consequences if contraindication is ignored, n (%)	68/128 (53)	21/105 (20)	89/233 (38)	25/115 (22)	40/118 (34)	65/233 (28)
Approach to contraindications						
Rarely or never prescribed contraindicated interventions	85 (69)	46 (47)	131 (59)	63 (59)	69 (62)	132 (61)
Believed contraindications are based on high-quality evidence	44 (36)	37 (38)	81 (37)	32 (30)	33 (30)	65 (30)
Believed contraindications provide clear information on benefits and harm	40 (32)	36 (37)	76 (34)	33 (31)	30 (27)	63 (29)
Would not present contraindicated medication to an informed patient	37 (30)	21 (21)	58 (26)	17 (16)	25 (22)	42 (19)
More inclined to discuss medication if “recommended against” rather than “contraindicated”	76 (61)	68 (69)	144 (65)	75 (70)	78 (70)	153 (70)

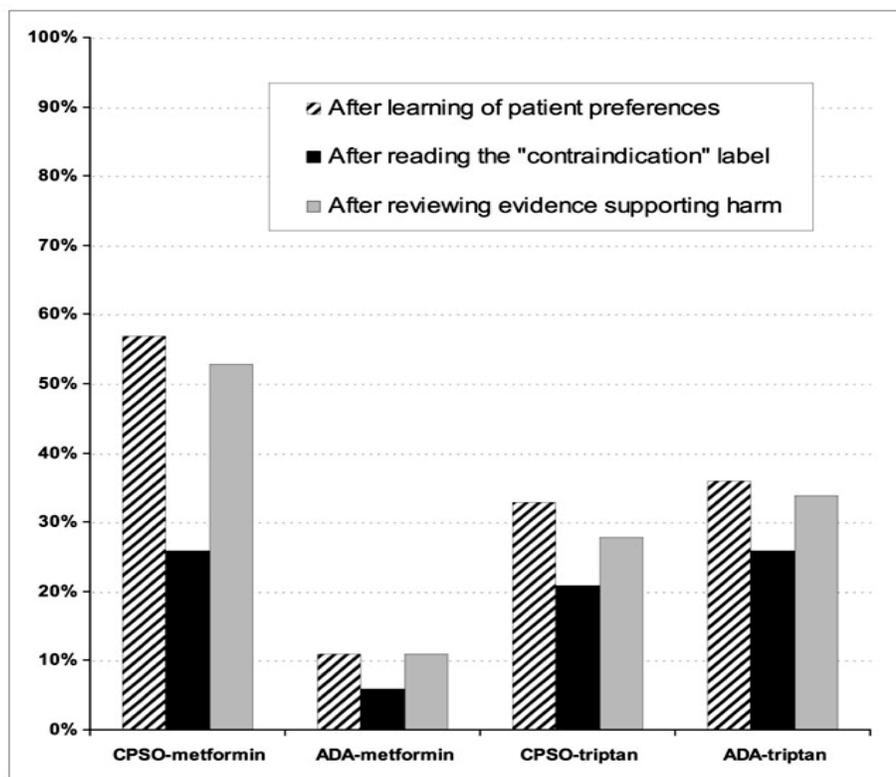
RESULTS

Response rate

Between January and March of 2004, 466 clinicians responded to the survey yielding response rates of 25% for ADA members (233 of 920) and of 19% for CPSO physicians (233 of 1207). Overall, 22% of respondents were women, and 89% had been medical graduates for 10 or more years. There was no difference in age,

gender, or practice type between ADA responders and non-responders. Ontario non-responders were older and more likely to have a generalist practice than Ontario responders, but the groups were otherwise similar. Of all eligible participants, 67 declined to participate (in contrast to simply not responding) (34 ADA, 33 CPSO) and 48 gave reasons for declining: the top three reasons were lack of interest (14), general rejection of email/internet surveys (14), and lack of time (12).

FIG. 1 Proportion of responders that would offer the contraindicated intervention to the patient.



Bar graphs represent the proportion of responders that offered the contraindicated intervention after being presented with (1) the vignette including the patient's statement of preference; (2) the contraindication label; and (3) the best available evidence in support of the recommendation. ADA, American Diabetes Association group; CPSO, College of Physicians and Surgeons of Ontario; metformin, refers to the case vignette in **Box 1**; triptan, refers to the case vignette in **Box 2**.

Survey responses

Table 1 shows the proportion of clinicians in whom the label "contraindication" dominated their treatment decisions. Figure 1 shows how respondents changed their answer in response to patient stated preferences, the contraindication

label, and evidence supporting that contraindication. Contraindications dominated the choices of the majority of responding clinicians, superseding patient preferences and research evidence. Depending on the group and the specific contraindication, contraindications dominated the

decisions of 47% (metformin, CPSO group) to 89% (metformin, ADA group) of responding clinicians.

Analyses of responses by survey wave showed consistency across waves and between survey modalities (i.e., responses across successive email waves and between email vs. fax questionnaires yielded similar answers).⁶ Later respondents, however, showed a trend towards an even greater dominance of the contraindications label than in the earlier respondents (205 of 312 (66%) in the first 3 waves, 64 of 83 (77%) in the last 3 waves). Indeed, Drane's imputation technique suggests that had all eligible clinicians responded, the proportion with decisions dominated by contraindications may have been as high as 83%.⁷

Table 1 also shows that although 60% of respondents report prescribing contraindicated interventions rarely or never, and although their own responses tended to be dominated by the contraindications label, only a third believed that contraindications are based on high quality evidence and reflect clear information about risks and benefits. Only 25% declared that they would omit a contraindicated option when discussing treatment choices with a patient. Of the respondents, 66% felt that they would be more likely to present interventions to patients if these were "recommended against" rather than if they were "contraindicated". Clinicians in whom the "contraindication" label dominated their decisions had similar number of years since graduation than their colleagues, and were more likely to omit a contraindicated option when discussing treatment choices with a patient (30% vs. 5%, $P < .001$).

DISCUSSION

Our survey results suggest that contraindications may dominate the decision making of many clinicians in North America, superseding patient preferences and research evidence. The results raise the possibility that the "contraindication" label compromises evidence-based, patient-centered clinical practice. Differences between the triptan and metformin scenarios indicate that the extent to which the "contraindication" label dominates clinical practice may depend on the situation. Our survey had a low response rate. A number of considerations suggest, however, that

the low response rate does not threaten our primary finding of the importance of the contraindication label in physicians' decisions.

First, the decision not to respond was almost always made unaware of the questions, and was likely motivated by lack of time or interest. In addition, non-response may have been in part due to the concomitant circulation in the Internet of email "worms" that threatened our potential participants and may have precipitated blind erasure of our email invitations. Second, our analysis of consistency across waves suggests that the impact of the "contraindications" label in our respondents is unlikely to differ substantially from that of the entire sample frame. Indeed, this analysis suggested that, if anything, the contraindication label was more likely to dominate the non-responders' decisions than the responders' decisions. Third, pilot questionnaires with questions similar to those in the final version, yielded similar answers. Fourth, to reverse our findings, and warrant a conclusion that the contraindications label does not have an important impact, the non-responders would have to be dramatically different from the responders. All these considerations suggest that the low response rate does not seriously threaten our primary finding.

A key assumption of this survey is that clinicians who believe in the primacy of patient values, and are reluctant to let weak evidence dictate practice will, and indeed should, ignore published contraindications when the evidence in support of harm is weak and when abiding by those contraindications would conflict with informed patient preferences. Is this assumption tenable?

According to the precautionary principle, a legal principle of precaution in the face of uncertainty,⁸ those responsible for introducing a risky intervention (the pharmaceutical manufacturer and the government regulator) should, until the safety or harm are clearly established, prohibit use of the intervention. The precautionary principle dictates erring on the side of caution before compelling causal evidence of harm becomes available. Clinicians may find this reasonable (and consistent with doing no harm), but the narrow application of this principle fails to account for harms caused by non-exposure, including missed opportunities for benefit from

using the contraindicated intervention. Such harms will exist whenever alternatives to the contraindicated intervention do not yield similar benefits, or cause other potential harms (for which stronger evidence may exist).

When avoiding the contraindicated medication robs informed patients of potential benefits and subjects them to appreciable risk from alternate interventions, clinicians may prefer to deliberate with patients as to the best course of action. A process by which clinicians and patients together consider the evidence of potential harm, and the patient's values, preferences and circumstances, is most consistent with evidence-based and patient-centered clinical practice. In the last decade, tools have become available that explain complex treatment options to patients and facilitate this process.^{9,10} When, as in the scenarios we presented, evidence for contraindications is weak, and the contraindicated medication confers well-established benefit that the patient values highly, many would conclude that use of the contraindicated medication is appropriate.

A final limitation of our methods is that because we used a questionnaire and case vignettes, we cannot draw strong inferences about how participants would behave in clinical practice—for example, because they gave a socially acceptable answer (indicative of a strong social norm that enforces adherence to contraindications), but not one reflecting how they would proceed. Also these inferences may not apply to situations dissimilar to those reflected in the vignettes. The inference we can draw with confidence, however, is that the contraindication label may dominate clinical practice, and further investigation should address whether this is indeed the case.

Given the major impact that contraindications appear to have on clinical decision-making, how they are developed becomes an issue of interest. Currently, we know little about who participates, the extent to which the values of patients and clinicians are considered, and how labels are revised in the face of new evidence of harm or safety.

In summary, our research suggests that contraindications dominate clinicians' actions and may impair evidence-based and patient-centered clinical practice. Implications include the need for further exploration of this phenomenon,

elucidation of the process by which authorities apply the “contraindication” label, and a possible reassessment of the way we use the term “contraindication”.

Acknowledgements

Robert Golub, MD and colleagues from the Division of General Internal Medicine at Northwestern University (Chicago, IL), Hui Lee, MD (we dedicate this manuscript to his memory) and Sault-Ste Marie staff and residents of the Northeastern Ontario Medical Education Corporation, and Mayo Clinic colleagues for their enthusiastic participation in piloting and validating our questionnaire. We are also grateful to Anne Holbrook, MD (Centre for Evaluation of Medicines, Hamilton Ontario), Steven A. Smith, MD and Kelly Fleming, MD (Mayo Clinic College of Medicine, Rochester, MN) for helpful comments and suggestions about the scenarios. Finally, we thank Rosamaria de los Heros for her clerical assistance.

Funding

Dr. Montori is a Mayo Foundation Scholar. Ms. Leung was funded in part by a Bachelor of Health Sciences research scholarship. Dr. P.J. Devereaux is supported by a Canadian Institutes of Health Research, Senior Research Fellowship Award. There were no other funding sources. The funding sources played no other role in this research.

Contributors

Dr. Montori conceived and led the project, designed the questionnaire, collected, analyzed, and interpreted the data, drafted this report, and is guarantor of the data. Ms. Leung designed and conducted the survey, analyzed the data, and made critical revisions to this report. Drs. Devereaux, Schünemann, Akl, and Gafni participated in questionnaire design and made critical revisions to this report. Dr. Guyatt designed the questionnaire, analyzed and interpreted the data, and made critical revisions to this report.

REFERENCES

1. Haynes RB, Devereaux PJ, Guyatt GH. Physicians' and patients' choices in evidence based practice. *BMJ*. Jun 8 2002;324(7350):1350.

2. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. *BMJ*. Jan 4 2003;326(7379):4-5.
3. Misbin RI. The Phantom of Lactic Acidosis due to Metformin in Patients With Diabetes. *Diabetes Care*. Jul 2004;27(7):1791-1793.
4. Dodick D, Lipton RB, Martin V, et al. Consensus Statement: Cardiovascular Safety Profile of Triptans (5-HT_{1B/1D} Agonists) in the Acute Treatment of Migraine. *Headache*. May 01, 2004 2004;44(5):414-425.
5. Dillman D. *Mail and Internet Surveys: The Tailored Design Method*. New York, NY: John Wiley & Sons; 2000.
6. Montori VM, Leung TW, Walter SD, Guyatt GH. Procedures that assess inconsistency in meta-analyses can assess the likelihood of response bias in multiwave surveys. *J Clin Epidemiol*. 2005 Aug;58(8):856-8.
7. Drane JW. Imputing nonresponses to mail-back questionnaires. *Am J Epidemiol*. Oct 15 1991;134(8):908-912.
8. Grandjean P. Implications of the precautionary principle for primary prevention and research. *Annu Rev Public Health*. 2004;25:199-223.
9. Levine MN, Gafni A, Markham B, MacFarlane D. A bedside decision instrument to elicit a patient's preference concerning adjuvant chemotherapy for breast cancer. *Ann Intern Med*. Jul 1 1992;117(1):53-58.
10. Whelan T, Levine M, Willan A, et al. Effect of a decision aid on knowledge and treatment decision making for breast cancer surgery: a randomized trial. *JAMA*. Jul 28 2004;292(4):435-441.