

Heterogeneous Uncertainties in Cholesterol Management

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Abstract

Physicians use clinical guidelines to inform judgment about therapy. Clinical guidelines do not address three important uncertainties: (1) uncertain relevance of tested populations to the individual patient, (2) the patient’s uncertain preferences among possible outcomes, and (3) uncertain subjective and financial costs of intervention. Unreliable probabilistic information is available for some of these uncertainties; no probabilities are available for others. The uncertainties are in the values of parameters and in the shapes of functions. We explore the usefulness of info-gap decision theory in patient-physician decision making in managing cholesterol level using clinical guidelines. Info-gap models of uncertainty provide versatile tools for quantifying diverse uncertainties. Info-gap theory provides two decision functions for evaluating alternative therapies. The robustness function assesses the confidence—in light of uncertainties—in attaining acceptable outcomes. The opportuneness function assesses the potential for better-than-anticipated outcomes. Both functions assist in forming preferences among alternatives. Hypothetical case studies demonstrate that decisions using the guidelines and based on best-estimates of the expected utility are sometimes, but not always, consistent with robustness and opportuneness analyses. The info-gap analysis provides guidance when judgment suggests that a deviation from the guidelines would be productive. Finally, analysis of uncertainty can help resolve ambiguous situations.

Keywords: Clinical guidelines, cholesterol management, judgment under uncertainty, patient satisfaction, info-gap decision theory.

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1 Introduction

The emergence of probability theory in the early 17th century brought to the fore the diversity of categories of knowledge. On the one hand the astronomer, for instance, could aspire to certain, almost apodeictic, knowledge of the laws of celestial motion. In contrast, the physician could at best make judgments of plausible truth. The deductive certainty of Aristotelian logic was inadequate for the inferences made in the ‘low’ sciences of medicine, alchemy etc., and new modes of inference for uncertain induction began to emerge [1].

The twentieth century saw a diversification of models of uncertainty, reflecting a broadening diversity of categories of knowledge which underlie judgment and inference: Linguistic knowledge; observed frequencies; hunches and beliefs; microscopic or fundamental quantum randomness as distinct from the macroscopic randomness of ensembles; randomness which arises from partial knowledge of a deterministic system (“Like the queen of England, determinism reigns but does not govern.” [2, p.63]); ignorance one is aware of, and ignorance one is ignorant of.

Great strides have been made in the much needed synthesis of a coherent system for the diverse types of knowledge and their attendant uncertainties [3]. Nonetheless, “As our island of knowledge grows, so does the shore of our ignorance.” [4]. In particular, the integration of non-measure-theoretic models of uncertainty, such as info-gap models [5], into a system of measure theoretic formulations, has not yet been accomplished [6, p.37].

Once again, as in the 17th century, we find that medical decisions confront us with a heterogeneity of uncertainties for which we are incompletely prepared. Clinical trials are rendered to the practitioner as probabilistic functions, expressing outcome-likelihoods in specified conditions. However, as we will explain in section 2, these probability estimates can be subject to uncertainties for which we have no probabilistic information. Furthermore, patients are challenged to quantify their anticipated utility (or dis-utility) from future outcomes of treatments with which they have no experience. The enlightened physician assists the patient to fold these anticipated utilities into the selection of a therapy, while these anticipations are fraught with severe uncertainty as we will discuss in section 4.1. For these uncertainties we have limited or no probability models. The challenge is to develop decision tools and, not less importantly, evaluate the quality of these tools. The diversity of types of information, and of the associated uncertainties, has impeded the development of generic and universal decision methodologies.

This paper illustrates a methodology for quantifying severe non-probabilistic uncertainties, for combining uncertainties of different types, and for then using these results to support a medical decision. We make no claim for the optimality of this methodology, which is based on info-gap decision theory [5]. However, we suggest that the formidable task of developing generic methodologies which can support the evaluation of optimality can be supported by Baconian induction: the study of diverse methodologies. Info-gap theory is thus of methodological interest not only because (we believe that) it is powerful, but because it stretches the realm of uncertainty-modelling beyond the pale of measure-theoretic techniques.

In section 2 we review the role of clinical guidelines in medical decision-making, and discuss the attendant uncertainties. In section 3 we present a standard probabilistic model for cholesterol risk assessment which underlies medical intervention. In section 4 we formulate the info-gap models of the relevant diverse uncertainties. We then formulate the info-gap robustness and opportuneness functions which underlie the choice of an intervention. In section 5 we apply the info-gap analysis to 4 plausible clinical cases. We conclude with a discussion in section 6.

2 Clinical Guidelines

The dissemination of clinical guidelines has significantly impacted medical practice. Inaugurated as algorithms for common problems in clinical medicine, guidelines now encompass all aspects of medical practice. The National Guideline Clearinghouse indexes over 2100 guidelines [7]. Mehta *et al* [8] conclude: “Improved application of existing therapies, directed by evidence-based guidelines, may offer immediate savings of life and function to patients with cardiovascular disease.” Frei *et al* [9] report significant improvement in clinical outcomes from “guideline-concordant antibiotic therapy” in treating community-acquired pneumonia.

But how well do clinical guidelines deal with the diverse uncertainties facing both patient and clinician? How can patient and physician assess these uncertainties and incorporate this assessment in their decisions? This paper studies the management of low density lipid (LDL) cholesterol as a framework for illustrating the construction of non-probabilistic info-gap models of uncertainty. We consider diverse types of uncertain information—some probabilistic, some not—which must be combined in assessing and choosing among therapeutic alternatives. We construct robustness and opportuneness functions to support these tasks.

A criticism of clinical guidelines is that they constitute “cookbook medicine” and externally applied restrictions on clinical judgment and autonomy [10]. Advocates of guidelines also stress that “it is important to tailor treatment to the needs of each individual patient” [11].

In addition, guidelines do not readily facilitate consideration of three challenging uncertainties which physicians regularly face.

First, guidelines are based on clinical trials with populations which may not reliably reflect the individual patient. Both patient and physician are sometimes quite uncertain about the relevance of the clinical trials to their specific case. Greenfield *et al* [12] note that randomized control trials, which underlie clinical guidelines, typically enroll patients with less severe disease and exclude older patients, making the resulting guidelines of uncertain applicability to the excluded populations. Feinstein and Horwitz [13] warn against the prevalence of randomized clinical trials in which “the data do not include many types of treatments or patients seen in clinical practice”. Morimoto *et al* [14] note that clinical guidelines, developed in the U.S. for use of aspirin in primary prevention of cardiovascular events, need modification before application in Japan. McLaughlin [15] reports the conclusions of a roundtable discussion of implications of heterogeneity of treatment effects (HTE). He concludes that, due to HTE, and especially in the absence of “sound data”, “care has to be individualized, using the clinician’s best judgment regarding available treatment options.”

The *second* challenge is that guideline recommendations do not account for the individual patient’s uncertain preferences among possible outcomes of treatment, especially adverse outcomes unfamiliar to the patient.

The *third* challenge is that guidelines often fail to account for the cost of intervention, either the subjective cost of lifestyle change or the quantitative financial cost.

This paper presents a quantitative decision-theoretic methodology for addressing these uncertainties when using clinical guidelines. Quantitative decision theory underlies computer-based clinical decision-support. Availability of decision-support technology has resulted in substantial increase in physician compliance with clinical guidelines [16].

We apply the methodology to LDL cholesterol reduction. In a series of plausible clinical examples, the guideline recommendations are sometimes, but not always, found to be consistent with the info-gap analysis of uncertainty. The examples illustrate how physician judgment to deviate from the guidelines can be supported, or refuted, by the analysis of uncertainty, as well as how patient preferences can be incorporated in the decision process.

This paper employs info-gap decision theory [5], which has been applied in a large array of decision problems under severe uncertainty, including biological conservation [17, 18], resource management [19], ethology [20], statistical testing [21], homeland security [22], engineering design [23, 24, 25, 26, 27] and fault diagnosis [28], project management [29, 30], portfolio investment [31] and conflict resolution [32].

3 Cholesterol Management and the LDL Risk Model

Alteration of cholesterol concentration is a common intervention in primary and secondary prevention of heart disease. Population studies, like the longitudinal Framingham study [33], demonstrate that cholesterol level is a major risk factor for cardiovascular events, and that alterations in cholesterol level can reduce the incidence of stroke and heart attacks.

Debate continues about altering LDL and high density lipid (HDL) cholesterol levels. Brindle *et al* [34] review the applicability of the Framingham data to diverse populations, concluding that caution is needed in applying the Framingham score to some sub-populations such as lower socio-economic groups. Kostis [35] suggests that the 10-point cardiac risk assessment based on the Framingham study may not deal adequately with some sub-populations such as young women. Pharmacological interventions such as statins are costly and have measurable toxicity, especially for young people facing life-long treatment [35]. Some patients resist life-long intervention if it is only ameliorative. Robson [36] observes that there “is most uncertainty about treating the many people at intermediate risk . . . [which] can turn large numbers of people into lifelong patients.”

The patient considering intervention is uncertain how he or she matches the study population. The Framingham study examined free-living, healthy, middle-aged white suburbanites west of Boston [33], and may not be applicable to an Hispanic in Chicago or Lima. Although the application may be valid, patients and physicians are legitimately uncertain. The patient may also be uncertain regarding the future utility or disutility of the treatment outcome.

Wilson *et al* [33] estimate the probability of a cardiac event based on the patient’s condition which is characterized by a vector, c , of known, non-negative numbers. c_1 and c_2 equal the patient’s age and age-squared. c_{13} and c_{14} each equal 1 if the patient has diabetes or smokes, and equal zero otherwise. Elements 3–7 specify the patient’s HDL level, where $c_{2+i} = 1$ for patients in the i th HDL group. Only one of c_3, \dots, c_7 is non-zero. Elements 8–12 specify the patient’s blood pressure group, where $c_{7+i} = 1$ for patients in the i th group. Only one of c_8, \dots, c_{12} is non-zero. Elements 15–19 specify the patient’s LDL level, where $c_{14+i} = 1$ for patients in the i th LDL group. Only one of c_{15}, \dots, c_{19} is non-zero. Therapeutic intervention is chosen by deciding which of c_{15}, \dots, c_{19} , equals unity.

The probability of a cardiac event for members of the ℓ th LDL group is [33]:

$$P_\ell(\beta) = 1 - S^{e^{L-G}} \quad (1)$$

$S = 0.90017$ for men and $S = 0.9628$ for women, and $G = 3.00069$ for men and $G = 9.914136$ for women. $L = c^T \beta$. The best estimate of the vector β is $\hat{\beta}$. These statistically estimated values, based on the Framingham study [33], are shown in table 6. The subscript ℓ indicates that $c_{14+\ell} = 1$ while the other elements of c_{15}, \dots, c_{19} equal zero.

4 Info-Gap Analysis with Uncertain Expected Utility

In section 4.1 we discuss several info-gap models for representing different types of uncertainty: uncertainty in the parameters of a probability function, uncertainty in estimated utility coefficients, and uncertainty in the shape of a utility function. In section 4.2 we

discuss the info-gap robustness and opportuneness functions and explain how they are used to choose among the alternative therapies.

4.1 Uncertain Expected Utility

Many utility and quality-of-life functions are used in medical decision making [37]. We will use expected utility, which is a generally accepted, versatile, and powerful method for exploiting the probability model developed in the Framingham study, though one could use other quality-of-life functions.

The patient has positive utility u_h from health, negative disutility u_e from a cardiac event, and negative disutility $u_i(\ell)$ from the cost of intervention to bring the patient's LDL concentration to the ℓ th level. The expected utility is the average of u_h and u_e , weighted by $P_\ell(\beta)$, plus the fixed disutility of intervention, $u_i(\ell)$. Expected utility for the ℓ th LDL level is:

$$E_\ell(\beta, u) = P_\ell(\beta)u_e + [1 - P_\ell(\beta)]u_h + u_i(\ell) \quad (2)$$

u_h , u_e and $u_i(\ell)$ are uncertain: people poorly predict future feelings. $P_\ell(\beta)$ is uncertain because of uncertain relevance of the population study to the individual. These uncertainties are information gaps between what we *do know*, and *need to know*, in order to dispel reasonable doubt. Info-gap models quantify these uncertainties [5]. Roughly, u_h , u_e , $u_i(\ell)$ and $P_\ell(\beta)$ are estimated, but we don't know how wrong those estimates are. An info-gap model of uncertainty quantifies the unbounded range of possibilities which this entails, without using probability distributions or presuming knowledge of a worst case. Furthermore, quite diverse sorts of information is available to represent different aspects of the situation. The task facing the decision maker is to quantify the available information without introducing unwarranted assumptions, and in a way which facilitates subsequent assessment and decision. While there are certainly various alternative possible quantification, one seeks a quantification which is plausible and which facilitates subsequent decision. We now consider uncertainty quantifications for u_h , u_e , $u_i(\ell)$ and $P_\ell(\beta)$.

Uncertain probability. The probability $P_\ell(\beta)$ is uncertain because the coefficients β are uncertain. (One could also consider uncertainty in the form of the function, but we will not consider that here.) Our best statistical estimate of the β -coefficients is $\tilde{\beta}$, table 6. If we have a standard error, σ_i , of the estimate $\tilde{\beta}_i$, then define $\rho_i = \sigma_i/|\tilde{\beta}_i|$ or $\rho_i = 1$ if $\tilde{\beta}_i = 0$ (which applies to terms marked ‘*’ or ‘†’ in table 6). If the standard error is not available, then define $\rho_i = 1$, which is the case in all of our numerical examples. We now define a fractional-error info-gap model [5] for uncertainty in the β_i 's:

$$\mathcal{U}(\alpha, \tilde{\beta}) = \left\{ \beta : \left| \beta_i - \tilde{\beta}_i \right| \leq \alpha \rho_i |\tilde{\beta}_i|, \quad i = 1, \dots, 19 \right\}, \quad \alpha \geq 0 \quad (3)$$

Like all info-gap models of uncertainty, $\mathcal{U}(\alpha, \tilde{\beta})$ is a family of nested sets of possible realizations of the uncertain quantity, β in this case. In the absence of uncertainty (when $\alpha = 0$) the set $\mathcal{U}(0, \tilde{\beta})$ contains only the estimated vector, $\tilde{\beta}$. The set $\mathcal{U}(\alpha, \tilde{\beta})$ becomes more inclusive as the horizon of uncertainty, α , increases. The horizon of uncertainty, α , is unknown, so this is an unbounded family of nested sets of β -vectors. We have estimates, $\tilde{\beta}$, but we are unable to specify maximum deviations of these estimates from the true values, and we know no probability distribution for the error of $\tilde{\beta}$.

Uncertain utility coefficients u_e and u_h . The individual's personal utility coefficients, u_e and u_h , reflect introspection, conversations with family, friends and physicians, and so on. (We will consider the disutility of intervention, $u_i(\ell)$, separately.) The choice of u_e and u_h is highly uncertain. The best estimate of these utility coefficients is denoted by the vector $\tilde{u} = (\tilde{u}_e, \tilde{u}_h)$. u_e is a disutility and thus must be negative, while u_h must be positive. The same holds for the best estimates, \tilde{u}_e and \tilde{u}_h . We have no information about

how differently the patient might choose the utility coefficients in other circumstances, for instance following experience of a subsequent cardiac event. Lacking more detailed information about the uncertainty in the utility coefficients, u , we adopt the following fractional-error info-gap model. Let us define the following function: $h(x) = x$ if $x \geq 0$, and $h(x) = 0$ if $x < 0$. The info-gap model for uncertainty in the utility coefficients is:

$$\mathcal{U}_u(\alpha, \tilde{u}) = \{ u : (1 + \alpha)\tilde{u}_e \leq u_e \leq h(1 - \alpha)\tilde{u}_e, \\ h(1 - \alpha)\tilde{u}_h \leq u_h \leq (1 + \alpha)\tilde{u}_h \}, \quad \alpha \geq 0 \quad (4)$$

This info-gap model is an unbounded family of nested sets of utility-vectors, $u = (u_e, u_h)$. In the absence of uncertainty (when $\alpha = 0$) the set contains only the estimate, \tilde{u} . The set $\mathcal{U}_u(\alpha, \tilde{u})$ becomes more inclusive as the horizon of uncertainty, α , increases. α is unbounded so there is no known worst case.

Uncertain disutility of intervention, $u_i(\ell)$. The disutility of intervention, $u_i(\ell)$, is highly uncertain. The monetary cost varies with patient condition [38], full lifetime costs are difficult to identify and evaluate [39], it is hard to identify individuals who currently are free of disease but would develop disease in the future if intervention is not taken now [40], and the subjective impact of lifestyle change is hard to evaluate beforehand. One can formulate plausible disutility functions, and the attendant uncertainty, which is large, can be represented with an info-gap model as we now explain.

Let ℓ_c denote the patient's current LDL level. The disutility, $u_i(\ell)$, of moving to the ℓ th LDL level will increase as the difference between ℓ_c and ℓ increases. Furthermore, the disutility of intervention is estimated to be proportional to a fraction f of the utility of health u_h minus the disutility of a cardiac event u_e . A plausible (though uncertain) model for the disutility of intervention would be:

$$\tilde{u}_i(\ell) = |\ell - \ell_c|u_0 \quad (5)$$

where u_0 is the following negative value:

$$u_0 = -\frac{(\tilde{u}_h - \tilde{u}_e)f}{4} \quad (6)$$

The '4' in the denominator is the greatest possible value of $|\ell - \ell_c|$. Note that if $f = 0$ then there is no disutility of intervention, while a large value of f implies large estimated disutility.

The function $\tilde{u}_i(\ell)$ in eq.(5) is plausible, but we don't have much actual evidence that the dependence is really linear, or for a specific value of u_0 . In short, the magnitude and shape of this disutility function is highly uncertain. We will now formulate an info-gap model for uncertainty in this disutility function.

An info-gap model expresses the unknown deviation of the true function, $u_i(\ell)$, from the plausible function $\tilde{u}_i(\ell)$. We are considering uncertainty in the actual shape of the function, not just in its parameters. We use a "slope-bound" model, in which all the functions are negative, reach zero when $\ell = \ell_c$, and the fractional error in the slope is unknown and unbounded. This implies that cost will increase with the magnitude of the intervention, though the slope (and magnitude) of the cost function is uncertain. $u'_i(\ell)$ is the slope of the disutility function, which is negative for $\ell > \ell_c$ and positive otherwise. Explicitly, the info-gap model is the following unbounded family of nested sets of functions:

$$\mathcal{U}_i(\alpha, \tilde{u}_i) = \{ u_i(\ell) : u_i(\ell_c) = 0, u_i(\ell) \leq 0, \forall \ell, \\ (1 + \alpha)u_0 \leq u'_i(\ell) \leq h(1 - \alpha)u_0, \ell > \ell_c \\ -h(1 - \alpha)u_0 \leq u'_i(\ell) \leq -(1 + \alpha)u_0, \ell < \ell_c \}, \quad \alpha \geq 0 \quad (7)$$

Recall that $u_0 < 0$, as defined in eq.(6).

4.2 Robustness and Opportuneness

We now define robustness and opportuneness functions, and explain how they assist patient and physician in choosing an LDL level.

Robustness. If we confidently knew $P_\ell(\beta)$, u_h , u_e and $u_i(\ell)$, then we could confidently choose the LDL level, ℓ , to maximize the expected utility, $E_\ell(\beta, u)$. However, $P_\ell(\beta)$, u_h , u_e and $u_i(\ell)$ are highly uncertain. Consequently we evaluate how reliably we can obtain an acceptable outcome with different ℓ 's. Conversely, what constitutes an acceptable outcome is influenced by how confident we are in attaining that outcome with a chosen LDL level, ℓ .

E_c denotes the lowest expected utility the patient would accept. Neither ℓ nor E_c are specified, and the patient may be unsure about what E_c value to require. We use a robustness concept [5] to choose ℓ and evaluate different E_c 's.

We have estimates—likely to be off the mark—of u_h , u_e , $u_i(\ell)$ and $P_\ell(\beta)$. We wish to choose an LDL level, ℓ , for which adequate utility, E_c , will be achieved even if these estimates err greatly.

The **robustness** of the ℓ th LDL level is the greatest horizon of uncertainty, α , up to which expected utility $E_\ell(\beta, u)$ is guaranteed to be no less than the critical utility, E_c :

$$\hat{\alpha}(\ell, E_c) = \max \left\{ \alpha : \left(\min_{\substack{\beta \in \mathcal{U}(\alpha, \tilde{\beta}) \\ u \in \mathcal{U}_i(\alpha, \tilde{u}) \\ u_i \in \mathcal{U}_i(\alpha, \tilde{u}_i)}} E_\ell(\beta, u) \right) \geq E_c \right\} \quad (8)$$

The robustness function $\hat{\alpha}(\ell, E_c)$ establishes preferences over the options. ℓ is preferred over ℓ' , at critical aspiration E_c , if we are more robust to the uncertainty with ℓ than with ℓ' . Succinctly:

$$\ell \succ_r \ell' \quad \text{if} \quad \hat{\alpha}(\ell, E_c) > \hat{\alpha}(\ell', E_c) \quad (9)$$

We show how to conveniently evaluate the robustness function in appendix A.

Interpreting robustness curves. We will use plots of robustness, $\hat{\alpha}(\ell, E_c)$, vs. expected utility, E_c , to choose therapeutic intervention. We now explain how to interpret these plots, and illustrate that a choice of ℓ can usually be made with only a rough idea of the required critical utility, E_c . Two points are characteristic of all robustness curves, illustrated in fig. 1.

First, the negative slope of the robustness curve in fig. 1 expresses the trade-off of robustness to uncertainty, against the expected utility which can be reliably anticipated. *Greater* expected utility is invariably associated with *lower* robustness to error in the underlying models. This intuitive idea—that high aspirations are more vulnerable to surprises or errors than low aspirations—is quantified by the negative slope.

Second, the robustness curve reaches the horizontal axis at some value of expected utility, as shown by the solid dot in fig. 1. The robustness is zero at this value of utility. Significantly, this value of expected utility is precisely the value obtained with the estimated models and data. In other words, the best-estimate of the expected utility has no robustness against error in the models and data upon which that estimate depends. Best-estimates exploit all available information, without regard to their potential error, so the estimated utility has no immunity against error in this information. Only less optimistic estimates—lower expected utility—have positive robustness, which returns us again to the previous point: the trade-off between robustness and utility.

We now examine figs. 2 and 3 to understand how robustness curves are used to evaluate and choose among alternative interventions.

Fig. 2 shows the robustness curves of two different therapeutic interventions, denoted ‘1’ and ‘2’. Option ‘1’ is more robust than ‘2’ at all levels of expected utility with positive robustness. Since more robustness is preferable over less, option ‘1’ is unambiguously favored over option ‘2’. Note that this is the same choice as the guideline recommendation based on the estimated utilities of these two options (represented by the points at which the curves meet the horizontal axis).

Fig. 3 shows a different situation, in which the robustness curves for two different therapeutic interventions intersect at some value of expected utility, E_x , and robustness, $\hat{\alpha}_x$. More robustness is better than less robustness. However, when utility is sacrificed for robustness, with it goes the aspiration for the result promised by the model. If utility in excess of E_x is needed, then option ‘2’ is preferred. This is the same choice as the guideline recommendation based on the estimated utilities of these two options. We must recognize, however, that the trade-off between robustness and utility implies that utility in excess of E_x will be obtained only with robustness in the lower part of the robustness scale, below robustness $\hat{\alpha}_x$. If greater confidence (greater robustness) is needed, and the patient and physician are willing to obtain this robustness premium by relaxing the aspiration for utility to a value below E_x , then alternative ‘1’ is preferred. In this case the crossing of the robustness curves has caused the decision maker to change preference from the guideline option. The decision maker does not need to choose a specific value of either critical utility, E_c , or robustness, $\hat{\alpha}_x$, in order to gain the advantage of this formulation. Only a choice of the required range of these values is needed.

Opportuneness. Robustness against failing to achieve acceptable utility is only one part of managing uncertainty. Uncertainty also entails opportunities for windfall, that is, a benefit or outcome better than anticipated [5]. A more opportune choice is preferred, though this may disagree with the robustness preferences.

E_w denotes a large and highly desirable level of utility, a windfall, larger than the critical utility E_c . The **opportuneness** of the ℓ th LDL level is the lowest horizon of uncertainty, α , at which expected utility $E_\ell(\beta, u)$ is possibly (though not necessarily) as large as the windfall value E_w :

$$\hat{\beta}(\ell, E_w) = \min \left\{ \alpha : \left(\max_{\substack{\beta \in \mathcal{U}(\alpha, \tilde{\beta}) \\ u \in \mathcal{U}_i(\alpha, \tilde{u}) \\ u_i \in \mathcal{U}_i(\alpha, \tilde{u}_i)}} E_\ell(\beta, u) \right) \geq E_w \right\} \quad (10)$$

The opportuneness function establishes preferences over the options. ℓ is preferred over ℓ' , at windfall aspiration E_w , if we are more prone to favorable uncertainty with ℓ than with ℓ' . Small $\hat{\beta}(\ell, E_w)$ implies that windfall is possible at small deviation from the estimates. Thus ℓ is preferred over ℓ' if $\hat{\beta}(\ell, E_w)$ is less than $\hat{\beta}(\ell', E_w)$:

$$\ell \succ_o \ell' \quad \text{if} \quad \hat{\beta}(\ell, E_w) < \hat{\beta}(\ell', E_w) \quad (11)$$

The preference rankings in eqs.(9) and (11) may or may not agree.

We show how to conveniently evaluate the opportuneness function in appendix A.

Interpreting opportuneness curves. Fig. 4 shows a typical opportuneness curve, illustrating the analog of the two robustness properties described in fig. 1. The opportuneness function, $\hat{\beta}(\ell, E_w)$, is the *immunity against windfall*, so a *small* value is desirable, the opposite of robustness. The positive slope in fig. 4 expresses the trade-off between opportuneness and certainty: high windfall aspiration (for larger-than-expected utility) is feasible only at great ambient uncertainty. Likewise, the opportuneness curve hits the horizontal axis precisely at the estimated utility: no surprise is needed in order to enable (though not guarantee) the expected outcome.

Since decision makers are usually risk averse, the opportuneness curves are usually used to resolve situations where robustness is ambiguous, as illustrated in fig. 5. The

decreasing curves on the left of the figure are the robustness curves for two alternative interventions. These curves intersect at expected utility E_{\times} . Consequently, if utility around E_{\times} is required, consideration of robustness does not resolve the choice between these options, since the two options are equally robust. The opportuneness curves—with positive slope—do not intersect one another in this case. Since a small value for $\hat{\beta}(\ell, E_w)$ is preferred, we see that option 2 is more opportune than option 1, suggesting a resolution of the robustness-ambiguity in favor of option 2.

5 Results: 4 Case Studies

In this section we illustrate the info-gap decision analysis with uncertainty in the probability of a cardiac event, the patient’s utility coefficients for disease and health, and the cost of intervention. We consider 4 hypothetical, but realistic, case studies.

Cases 1 and 2, sections 5.1 and section 5.2, compare the decision analysis for a middle-aged male with difference in HDL level, blood pressure, smoking and diabetes.

Case 3, section 5.3, looks at the effect of age, with other variables unchanged.

Case 4, section 5.4, considers a female of age 55.

5.1 Case 1

Example 1 is a male, aged 55, group-5 HDL, group-1 blood pressure (see table 1), non-diabetic non-smoker whose pre-intervention LDL level is group 5. The info-gap analysis examines various estimated (but uncertain) costs of intervention, together with uncertainty in the probability of a cardiac event and uncertainty in the patient’s utility coefficients for disease and health.

The disutility of intervention, $u_i(\ell)$, for moving to the ℓ th LDL level is estimated to increase as the difference between ℓ and the patient’s current LDL level, ℓ_c , increases. Furthermore, the disutility is estimated to be proportional to a fraction f of the utility of health u_h minus the disutility of a cardiac event u_e . These subjective estimates, however, are highly uncertain.

Figs. 6 and 7 show robustness and opportuneness curves for transition to various LDL levels ℓ . The left frame of fig. 6 is the case of no cost at any level of uncertainty ($f = 0$), while the right frame of fig. 7 shows an uncertain cost estimated as 40% of the benefit ($f = 0.4$). The other frames of figs. 6 and 7 show intermediate values ($f = 0.1$ and $f = 0.2$) for the estimated cost of intervention.

The robustness curves in the left frame of fig. 6 are for the case of no cost of intervention. The nominal preferences, based on the best-estimates—at which the robustness is zero as explained in connection with fig. 1—are for decreasing the LDL level as much as possible. Level 1 is preferred over level 2 (represented by “ \succ ”). Levels 2 and 3 are identical (represented by “ \sim ”), since their estimated β coefficients are essentially the same (table 6). However, they are both preferred over level 4, which is preferred over level 5. We can succinctly represent these preferences as:

$$1 \succ 2 \sim 3 \succ 4 \succ 5 \tag{12}$$

The robustness to uncertainty for each of these options, for attaining the corresponding estimated utility, is zero, as explained in fig. 1. Consequently these options can not be depended on to reliably result in the corresponding utilities. However, the preference ranking is the same at every level of robustness up to 100% ($\hat{\alpha} = 1$), since the robustness curves have not crossed up to robustness of 1. The situation here is like fig. 2, in which the robustness curves do not cross one another. It is noteworthy, though, that levels 4 and 5 have substantially less utility than lower LDL levels at robustness of 0.5 and greater. This is unlike the situation at zero robustness, in which the utility-margin between the

different options is small. At robustness of $\hat{\alpha} = 1$ the robustness curve for $\ell = 1$ crosses the curves for levels 2 and 3, thus reversing the preference among these levels if larger robustness is required, noting that the corresponding utility is quite low compared to the nominal utility.

The opportuneness curves in the lefthand frame of fig. 6 are ordered nominally, and rapidly converge. This indicates that considerations of opportuneness do not promote one intervention over another.

The situation is very different in the righthand frame of fig. 6, for which the estimated (though uncertain) cost of intervention is 10% of the estimated benefit, so $f = 0.1$. Now the nominal (zero-robustness) preferences are the reverse of the no-cost preferences in eq.(12):

$$5 \succ 4 \succ 3 \succ 2 \sim 1 \tag{13}$$

The curve for $\ell = 5$ has not shifted between the two frames of fig. 6 because the patient's pre-intervention LDL level is $\ell_c = 5$. However the other curves have shifted to the right, and changed in shape, as a result of the cost of intervention. These nominal, zero-robustness preferences are weak. However, there is substantial crossing of robustness curves at low robustness (around $\hat{\alpha} \approx 0.2$), causing preference-reversal among the interventions as explained in connection with fig. 3. At 50% robustness ($\hat{\alpha} = 0.5$) there is strong preference against level 5 in fig. 6, despite the intervention cost, while the preferences among the other levels is not large. More precisely, the preferences at 50% robustness are:

$$(3 \succ 1) \succ 2 \succ 4 \succ 5 \tag{14}$$

where the parentheses indicate that the preferences between levels 3 and 1 are weak.

A similar picture emerges when we consider higher estimated cost of intervention, $f = 0.2$ and $f = 0.4$ in fig. 7. The results of these 4 figures are summarized in table 2.

Before examining table 2, consider the righthand frame of fig. 7 at moderate robustness ($\hat{\alpha} = 0.5$). The robustness curves for the two most attractive interventions, levels 4 and 5, cross at $\hat{\alpha} = 0.5$, indicating indifference between these two options, where level 5 implies no intervention since this is the patient's pre-intervention LDL level. However, examining the opportuneness curves in this figure shows that remaining at level 5 is more opportune for windfall outcome than moving to level 4. This is an instance where the opportuneness analysis can be used to resolve a robustness-tie between options, as discussed in connection with fig. 5.

A clear picture emerges from table 2 for this individual, whose pre-intervention LDL concentration is at level 5. If there is no cost for intervention ($f = 0$), then the nominal, zero robustness ($\hat{\alpha} = 0$), preference is for reducing the LDL concentration to level 1. If there is any cost to intervention ($f \geq 0.1$), then the nominal (no-robustness) preferences call for no intervention. However, requiring moderate robustness to uncertainty ($\hat{\alpha} = 0.5$) changes the picture, and intervention to lower the LDL to the 3rd level is indicated at moderate cost ($f = 0.1$ or $f = 0.2$). At high cost, $f = 0.4$, levels 4 and 5 are equivalent in robustness, and opportuneness mitigates for no intervention (level 5). The enhanced robustness resulting from these decisions is obtained at the expense of guaranteeing lower utility, as understood from the trade-off between robustness and utility (fig. 1). The picture remains the same at high robustness ($\hat{\alpha} = 1$), and correspondingly low utility.

5.2 Case 2

Let's consider a case whose prognosis is quite different from the case in section 5.1: a male, aged 55, group-1 HDL, group-5 blood pressure, diabetic smoker whose current (pre-intervention) LDL level is group 5. We will again consider the info-gap analysis for various

estimated (but uncertain) costs of intervention, together with uncertainty in the probability of a cardiac event and uncertainty in the patient’s utility coefficients for disease and health.

Results for 4 different estimated costs of intervention are shown in figs. 8 and 9. The nominal best-estimated utilities of the options—at zero robustness—are lower than in case 1 (section 5.1, figs. 6 and 7) at all estimated costs. Likewise, at any given level of utility, the robustnesses are lower in case 2 than in case 1 for all estimated costs. The crossing of robustness occurs as in case 1, though at lower robustness and lower utility.

The picture which emerges for this case, in table 3, is somewhat different than for case 1 in table 2. In case 2, as in case 1, if there is no cost for intervention ($f = 0$), then the nominal, zero robustness ($\hat{\alpha} = 0$) preference is for reducing the LDL concentration to level 1. However, the robustness curves rapidly converge at $f = 0$, so that at moderate and high robustness, $\hat{\alpha} = 0.5$ and $\hat{\alpha} = 1$, there is no preference among the options in terms of robustness, and very little preference based on opportuneness, though the opportuneness curves are separated and do not cross one another. If there is no cost of intervention, then one presumably would not intervene in the absence of additional considerations. At low or moderate cost of intervention, $f = 0.1$ or $f = 0.2$, the nominal, zero-robustness preference is for minimizing the LDL level. At high cost, $f = 0.4$, the zero-robustness preference is indifferent between all levels except $\ell = 2$ which is less preferred; again one would presumably not intervene. However, at moderate or high robustness ($\hat{\alpha} = 0.5$ or $\hat{\alpha} = 1$) and positive cost ($f \geq 0.1$), the preference is for $\ell = 5$, which is the patient’s current state, so intervention is not indicated here either.

We see here, as in case 1, the strong effect considering robustness to uncertainty in cost and the other factors of the estimated decision model.

5.3 Case 3

In this example we explore the effect of age and estimated cost of intervention. Case 3 is a non-smoking non-diabetic male with group-5 HDL and group-1 blood pressure, at pre-intervention LDL level 5. We compare ages 35, 55 and 75.

Consider first the robustness curves without intervention cost, fig. 10 (ages 35 and 75), and the left frame of fig. 6 (age 55). The main effects of advancing age are to reduce the zero-robustness nominal utility, which shifts the curves to the left, and to substantially reduce the robustness at any lower utility, which lowers the robustness curves.

Similar conclusions hold at moderate estimated cost of intervention, $f = 0.2$, as seen in fig. 11 and the left frame of fig. 7. Furthermore, the curves have moved with respect to one another sufficiently so that the preference rankings are different at the different ages, as illustrated in table 4, part of which (age 55) is reproduced from table 2. The nominal, zero-robustness recommendation is the same for all three ages: no intervention. At moderate robustness, $\hat{\alpha} = 0.5$, the recommendations are: no intervention at age 35, lower LDL to level 3 at ages 55 and 75. At high robustness, $\hat{\alpha} = 1$, the young and mid-age groups move to LDL level 3, while the oldest age group does not mandate intervention. We see in this example, as before, the strong effect of considering uncertainty in the underlying data and models.

5.4 Case 4

This example is a non-smoking non-diabetic aged-55 woman with HDL level 5, blood pressure group 1, and pre-intervention LDL level 5. This is the same as the case in section 5.1 except for the sex of the patient, so the figures for comparison are figs. 6 and 7 and table 2.

Figs. 12 and 13 shows results for four different estimated costs of intervention. The most striking result is the far lower robustness than for the similar male patient, figs. 6

and 7.

We summarize the results of figs. 12 and 13 in table 5, which should be compared to table 2. ‘Moderate’ and ‘High’ robustnesses are lower for female than male patients, but the interventions are roughly similar. At zero robustness, both male and female cases call for no intervention if there is even low cost of intervention ($f \geq 0.1$), and lowering LDL to level 1 if $f = 0$. At moderate robustness ($\hat{\alpha} = 0.08$) the recommendation for females is for no intervention at high cost ($f = 0.2$ or $f = 0.4$), and lowering to level 1 at zero or low cost ($f = 0$ or $f = 0.1$). At high robustness ($\hat{\alpha} = 0.2$) the recommendation for females is strong intervention at zero cost, and no intervention otherwise.

6 Discussion

Clinical guidelines have become central to medical practice. The physician is charged with evaluating a guideline’s relevance for each patient, and knowing when and how to recommend a deviation from the guideline. Furthermore, the patient should be able to evaluate the guideline and express individual preferences. Missing from the process of considering clinical guidelines is the diverse and partly non-probabilistic uncertainty facing both physician and patient. Info-gap analysis explicitly incorporates this severe uncertainty into the decision making process thus respecting individual judgment, variation in preference, and autonomy. A methodology is presented here for employing guidelines, in light of uncertain relevance of population studies to individual patients, uncertainty in patient preferences among outcomes, and uncertain cost of intervention. The uncertainties represented by info-gap models are both in the *values* of parameters and in the *shapes* of functions.

Info-gap robustness and opportuneness functions are useful for evaluating and selecting therapies. Robustness is defined as the greatest uncertainty at which acceptable outcomes will occur. Large robustness is preferred over small robustness, generating preferences among available therapies. Opportuneness is defined as the lowest uncertainty which is needed in order to enable a windfall outcome. Small values for the opportuneness function are preferred over large values, also generating preferences among options which need not agree with robustness-based preferences. The opportuneness-preferences can be used to resolve ambiguous robustness-preferences.

We have illustrated the use of robustness and opportuneness for selecting LDL levels in conjunction with guidelines, for plausible clinical situations. The following conclusions are suggested.

- Decisions using guidelines and best-estimates of expected utility are sometimes supported by analysis of robustness to, and opportuneness from, uncertainty. That is, ranking the options in terms of estimated expected utility is sometimes the same as ranking the options in terms of robustness and opportuneness. When this occurs, the robustness and opportuneness analysis provides additional support for the guideline-based decision.
- Combined with guidelines, info-gap analysis can increase confidence in their treatment choices. The degree of confidence in attaining an outcome is quantified by robustness: the numerical evaluation of the robustness indicates how wrong the estimates can be without jeopardizing one’s aspiration for quality of outcome. When the robustness is low, as occurs in some cases, the decision maker will perhaps look further before deciding. Or, less risk-averse decision makers may use the opportuneness function to identify opportune therapies.
- The analysis helps resolve ambiguity. In some situations the best-estimated outcome is essentially the same for several therapies (righthand frame of fig. 6 or fig. 9, or the left hand frame of fig. 10). One may choose the most robust option, which

may differ from the guideline recommendation. For example, the nominal, guideline, recommendation in the righthand fig. 6 is for no intervention ($\ell = 5$), but the nominal preference for this choice is weak. The robustness curves cross one another at low robustness in this figure and the $\ell = 5$ option rapidly becomes substantially less robust than the other options, suggesting that the nominal recommendation is not suited to this case.

- The opportuneness function can be used to resolve situations where robustness does not establish unambiguous preferences. The left hand frame of fig. 13 is a case in point. The robustness curves are very close to one another over much of the utility-range, resulting in ambiguous robustness-preferences. However, the opportuneness curves are well separated, indicating strong opportuneness-preference for LDL level 5. The decision makers may choose to resolve the robustness-ambiguity by selecting the greater opportuneness of non-intervention (level 5) in this situation.
- The analysis provides guidance when judgment suggests deviation from the guideline. The left hand frame of fig. 9 illustrates this. The best-estimates indicate guideline-based preference for the lowest LDL level. However, as always, best-estimated outcomes have zero robustness against uncertainty (fig. 1). The left hand frame of fig. 9 shows that LDL level 5 has far greater robustness than level 1, over much of the utility range. When the decision makers feel substantial uncertainty, they may opt for level 5, rather than 1, due to greater robustness of this option. Additionally, exogenous considerations of collateral medical impacts may be folded into preferring level 5, supported by greater robustness of this option.

Conventional application of clinical guidelines is often appropriate. A robust approach expands the usefulness of guidelines to individual patients and provides increased confidence in outcomes when dealing with diverse and substantial uncertainty. Further, coupling opportuneness to robustness reveals potential for better-than-expected outcomes. Additionally, uncertainty-analysis may provide support when the physician's judgment indicates deviation from the guidelines. Finally, the value of clinical guidelines is enhanced by the availability of quantitative decision-theoretical tools, suggesting that guidelines are amenable to computer-based decision-support technology.

We make no claim of optimality for the info-gap analysis developed here. For decisions of such complexity, and with uncertainties of such diversity, we know of no feasible criterion for optimality of a decision methodology. We claim only that diverse and clinically realistic information and uncertainty can be efficiently and meaningfully managed with info-gap theory. Furthermore, just as we have combined non-probabilistic info-gap tools with probabilistic ones (expected utility theory) our contention is that the combination of tools can prove useful in situations such as clinical decision making. Finally, the search for criteria of optimality of a decision tool is of prime importance. We suggest that methodological pluralism is a possible guide in this search.

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7 References

1. Hacking, Ian, 1975, *The Emergence of Probability: A Philosophical Study of Early Ideas About Probability, Induction and Statistical Inference*, Cambridge University Press.

2. Ekeland, Ivar, 1988, *Mathematics and the Unexpected*, University of Chicago Press.
3. Klir, George J., 2006, *Uncertainty and Information: Foundations of Generalized Information Theory*, Wiley Publishers.
4. John A. Wheeler, quoted in *Scientific American*, Dec. 1992, p20.
5. Ben-Haim Y. Info-Gap Decision Theory: Decisions Under Severe Uncertainty, 2nd edition. London: Academic Press; 2006.
6. Klir, George J., 2004, Generalized information theory: aims, results and open problems, *Reliability Engineering and System Safety*, 85: 21–38.
7. NGC. 2007, National Guideline Clearinghouse, http://www.guideline.gov/browse/guideline_index.aspx.
8. Mehta RH, Peterson ED, Califf RM. Performance measures have a major effect on cardiovascular outcomes: A review. *Am. J. Med.* 2007;120:398–402.
9. Frei CR, Restrepo MI, Mortensen EM, Burgess DS. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. *Am. J. Med.* 2006;119:865–871.
10. Cabana MD, Rand CS, Powe NR *et al.* Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA*, 1999;282:1458–1465.
11. Hening WA. Current Guidelines and Standards of Practice for Restless Legs Syndrome. *Am. J. Med.* 2007;120:S22–S27.
12. Greenfield S, Kravitz R, Duan N, Kaplan SH. Heterogeneity of treatment effects: Implications for guidelines, payment, and quality assessment. *Am. J. Med.* 2007;120:S3–S9.
13. Feinstein AR, Horwitz RI. Problems in the “evidence” of “evidence-based medicine”. *Am. J. Med.* 1997;103:529–535.
14. Morimoto T, Fukui T, Lee TH, Matsui K. Application of U.S. guidelines in other countries: Aspirin for the primary prevention of cardiovascular events in Japan. *Am. J. Med.* 2004;117:459–468.
15. McLaughlin MJ, for the members of the HTE Policy Roundtable Panel. Healthcare policy implications of heterogeneity of treatment effects. *Am. J. Med.* 2007;120:S32–S35.
16. Lobach DF, Hammond WE. Computerized decision support based on a clinical practice guideline improves compliance with care standards. *Am. J. Med.* 1997;102:89–98.
17. Burgman M. *Risks and Decisions for Conservation and Environmental Management*. Cambridge: Cambridge University Press; 2005.
18. Regan HM, Y. Ben-Haim, B. Langford, W.G. Wilson, P. Lundberg, S.J. Andelman, M.A. Burgman, Robust decision making under severe uncertainty for conservation management. *Ecological Applications*. 2005;15:1471–1477.
19. McCarthy MA, Lindenmayer DB. Info-gap decision theory for assessing the management of catchments for timber production and urban water supply. *Environmental Management*. 2007;39:553–562.

20. Carmel Y, Ben-Haim Y. Info-gap robust-satisficing model of foraging behavior: Do foragers optimize or satisfice? *American Naturalist*. 2005;166:633–641.
21. Fox DR, Ben-Haim Y, Hayes KR, McCarthy M, Wintle B, Dunstan P. An info-gap approach to power and sample size calculations. *Environmetrics*. 2007;18:189–203.
22. Moffitt LJ, Stranlund JK, Field BC. Inspections to Avert Terrorism: Robustness Under Severe Uncertainty. *Journal of Homeland Security and Emergency Management*. 2005. <http://www.bepress.com/jhsem/vol2/iss3/3>
23. Kanno Y, Takewaki I. Robustness analysis of trusses with separable load and structural uncertainties. *International Journal of Solids and Structures*. 2006;43:2646–2669.
24. Kanno Y, Takewaki I. Sequential semidefinite program for maximum robustness design of structures under load uncertainty. *Journal of Optimization Theory and Applications*. 2006;130:265–287.
25. Pantelides CP, Ganzerli S. Design of trusses under uncertain loads using convex models, *ASCE J. Structural Engineering*. 1998;124:318–329.
26. Ganzerli S, Pantelides CP. Optimum structural design via convex model superposition. *Computers and Structures*. 2000;746:639–647.
27. Lindberg HE. Dynamic response and buckling failure measures for structures with bounded and random imperfections. *ASME Journal of Applied Mechanics*. 1991;58:1092–1094.
28. Pierce SG, Ben-Haim Y, Worden K, Manson G. Evaluation of neural network robust reliability using information-gap theory. *IEEE Transactions on Neural Networks*. 2006;17:1349–1361.
29. Ben-Haim Y, Laufer A. Robust reliability of projects with activity-duration uncertainty. *ASCE Journal of Construction Engineering and Management*. 1998;124:125–132.
30. Regev S, Shtub A, Ben-Haim Y. Managing project risks as knowledge gaps. *Project Management Journal*. 2006;37:17–25.
31. D. Berleant, L. Andrieu, J.-P. Argaud, F. Barjon, M.-P. Cheong, M. Dancre, G. Sheble and C.-C. Teoh, 2008, Portfolio management under epistemic uncertainty using stochastic dominance and information-gap theory, *International Journal of Approximate Reasoning*, vol.49, issue #1, pp.101–116.
32. Ben-Haim Y, Hipel KW. The graph model for conflict resolution with information-gap uncertainty in preferences. *Applied Mathematics and Computation*. 2002;126:319–340.
33. Wilson PWF, D’Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel, WB. *Circulation*. Prediction of Coronary Heart Disease. 1998;97:1837–1847. See also: <http://www.nhlbi.nih.gov/about/framingham/riskabs.htm>
34. Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt, GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: A prospective study. *British Journal of General Practice*. 2005;55:838–845.
35. Kostis JB. A New Approach to Primary Prevention of Cardiovascular Disease. *Am. J. Med*. 2007;120:746–747.

36. Robson J. Information needed to decide about cardiovascular treatment in primary care. *British Medical Journal*. 1997;314:277–283.
37. Gómez M, Bielza C, Fernández del Pozo JA, Ríos-Insua, S. A graphical decision-theoretic model for neonatal jaundice. *Medical Decision Making*. 2007;27:250–265.
38. Chan PS, Nallamothu BK, Gurm HS, Hayward RA, Vijan S. Incremental benefit and cost-effectiveness of high-dose statin therapy in high-risk patients with coronary artery disease. *Circulation*. 2007;115:2398–2409.
39. Davie AP, McMurray JJV. Editorial. *European Heart Journal*. 1996;17:974–975.
40. Mark DB, Hlatky MA. Medical Economics and the Assessment of Value in Cardiovascular Medicine: Part II. *Circulation*. 2002;106:626–630.

A Evaluating the Robustness and Opportuneness Functions

Robustness. Let $\mu(\alpha, \ell)$ denote the inner minimum in the definition of the robustness function, eq.(8). The robustness is the greatest horizon of uncertainty, α , up to which $\mu(\alpha, \ell) \geq E_c$. The uncertainty sets, $\mathcal{U}(\alpha, \beta)$, $\mathcal{U}_u(\alpha, \tilde{u})$ and $\mathcal{U}_i(\alpha, \tilde{u}_i)$, become more inclusive as α increases. This means that $\mu(\alpha, \ell)$ (which is a minimum on the uncertainty set at horizon α) decreases monotonically as α increases. Hence the robustness is the greatest value of α at which $\mu(\alpha, \ell) = E_c$. Finally, this implies that $\mu(\alpha, \ell)$ is the inverse of the robustness function: a plot of $\mu(\alpha, \ell)$ on the horizontal axis, versus α on the vertical axis, is identical to a plot of E_c horizontally versus $\hat{\alpha}(\ell, E_c)$ vertically. This is the basis for evaluating the robustness function.

One can readily derive the following expression for $\mu(\alpha, \ell)$:

$$\mu(\alpha, \ell) = \left[1 - S e^{-G + c^T \tilde{\beta} + \alpha c^T b} \right] (1+\alpha) \tilde{u}_e + S e^{-G + c^T \tilde{\beta} + \alpha c^T b} h(1-\alpha) \tilde{u}_h + (1+\alpha) |\ell - \ell_c| u_0 \quad (15)$$

The dependence of the righthand side on the chosen LDL level, ℓ , arises through c . b is the vector whose elements are $b_i = |\tilde{\beta}_i| \rho_i$.

Opportuneness. Let $M(\alpha, \ell)$ denote the inner maximum in the definition of the opportuneness function in eq.(10). By an argument analogous to the one about $\mu(\alpha, \ell)$ we conclude that $M(\alpha, \ell)$ is the inverse of the opportuneness function. That is, a plot of $M(\alpha, \ell)$ on the horizontal axis versus α on the vertical axis, is identical to a plot of E_w horizontally versus $\hat{\beta}(\ell, E_w)$ vertically. This is the basis for evaluating the opportuneness. One finds:

$$M(\alpha, \ell) = \left[1 - S e^{-G + c^T \tilde{\beta} - \alpha c^T b} \right] h(1-\alpha) \tilde{u}_e + S e^{-G + c^T \tilde{\beta} - \alpha c^T b} (1+\alpha) \tilde{u}_h + h(1-\alpha) |\ell - \ell_c| u_0 \quad (16)$$

Group	HDL-C, mg/dL	Blood pressure	LDL-C, mg/dL
1	< 35	Optimal	< 100
2	35–44	Normal	100–129
3	45–49	High normal	130–159
4	50–59	Stage I hypertension	160–189
5	≥ 60	Stage II–IV hypertension	≥ 190

Table 1: HDL-C, blood pressure and LDL-C groups. The systolic and diastolic pressures defining the blood pressure groups are defined in table 1 of Wilson [33].

Cost f	No robustness $\hat{\alpha} = 0$	Moderate robustness $\hat{\alpha} = 0.5$	High robustness $\hat{\alpha} = 1$
0.0	1 \succ 2 \sim 3 \succ 4 \succ 5	1 \succ 2 \sim 3 \succ 4 \succ 5	1 \sim 2 \sim 3 \succ 4 \succ 5
0.1	5 \succ 4 \succ 3 \succ 2 \sim 1	(3 \succ 1) \succ 2 \succ 4 \succ 5	3 \succ 2 \succ 1 \succ 4 \succ 5
0.2	5 \succ 4 \succ 3 \succ 2 \succ 1	3 \succ 4 \succ (2 \succ 1 \succ 5)	3 \succ 2 \succ 4 \succ (1 \succ 5)
0.4	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \sim 4 \succ 3 \succ 2 \succ 1	3 \sim 5 \succ 4 \succ 2 \succ 1

Table 2: Preference ranks of LDL options for case 1, based on robustness, from figs. 6 and 7.

Cost f	No robustness $\hat{\alpha} = 0$	Moderate robustness $\hat{\alpha} = 0.5$	High robustness $\hat{\alpha} = 1$
0.0	1 \succ 2 \sim 3 \succ 4 \succ 5	1 \sim 2 \sim 3 \sim 4 \sim 5	1 \sim 2 \sim 3 \sim 4 \sim 5
0.1	1 \succ (3 \succ 2) \succ 4 \succ 5	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ 4 \succ 3 \succ 2 \succ 1
0.2	1 \succ 3 \succ 2 \sim 4 \succ 5	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ 4 \succ 3 \succ 2 \succ 1
0.4	1 \sim 3 \sim 4 \sim 5 \succ 2	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ 4 \succ 3 \succ 2 \succ 1

Table 3: Preference ranks of LDL options for case 2, based on robustness, from figs. 8 and 9.

Age (y)	No robustness $\hat{\alpha} = 0$	Moderate robustness $\hat{\alpha} = 0.5$	High robustness $\hat{\alpha} = 1$
35	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ 4 \succ 3 \succ 2 \succ 1	(3 \succ 4) \succ (2 \succ 5) \succ 1
55	5 \succ 4 \succ 3 \succ 2 \succ 1	3 \succ 4 \succ (2 \succ 1 \succ 5)	3 \succ 2 \succ 4 \succ (1 \succ 5)
75	(5 \succ 4 \succ 3) \succ (1 \succ 2)	1 \sim 3 \sim (2 \succ 4) \succ 5	5 \succ 4 \succ 3 \succ 2 \succ 1

Table 4: Preference ranks of LDL options for case 3, based on robustness and figs. 10 and 11, and the left frame of fig. 7. Results for $f = 0.2$.

Cost f	No robustness $\hat{\alpha} = 0$	Moderate robustness $\hat{\alpha} = 0.08$	High robustness $\hat{\alpha} = 0.2$
0.0	1 \succ 2 \sim 3 \succ (4 \succ 5)	1 \succ 2 \sim 3 \succ (4 \succ 5)	1 \sim 2 \sim 3 \sim 4 \sim 5
0.1	5 \succ 4 \succ 3 \succ 2 \succ 1	1 \succ 3 \succ (2 \succ 5 \succ 4)	5 \succ 4 \succ 3 \succ 2 \succ 1
0.2	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ (3 \succ 4) \succ 1 \succ 2	5 \succ 4 \succ 3 \succ 2 \succ 1
0.4	5 \succ 4 \succ 3 \succ 2 \succ 1	5 \succ 4 \sim 3 \succ 2 \succ 1	5 \succ 4 \succ 3 \succ 2 \succ 1

Table 5: Preference ranks of LDL options for case 4, based on robustness and figs. 12 and 13.

Symbol	Variable	Men	Women
$\tilde{\beta}_1$	Age, y	0.04808	0.33994
$\tilde{\beta}_2$	Age squared, y ²	0 [‡]	−0.0027
	HDL-C, mg/dL		
$\tilde{\beta}_3$	< 35	0.48598	0.88121
$\tilde{\beta}_4$	35–44	0.21643	0.36312
$\tilde{\beta}_5$	45–49	0*	0.19247
$\tilde{\beta}_6$	50–59	−0.0471	0*
$\tilde{\beta}_7$	≥ 60	−0.3419	−0.35404
	Blood Pressure		
$\tilde{\beta}_8$	Optimal	−0.02642	−0.51204
$\tilde{\beta}_9$	Normal	0*	0*
$\tilde{\beta}_{10}$	High normal	0.30104	−0.03484
$\tilde{\beta}_{11}$	Stage I hypertension	0.55714	0.28533
$\tilde{\beta}_{12}$	Stage II–IV hypertension	0.65107	0.50403
$\tilde{\beta}_{13}$	Diabetes	0.42146	0.61313
$\tilde{\beta}_{14}$	Smoker	0.54377	0.29737
	LDL-C, mg/dL		
$\tilde{\beta}_{15}$	< 100	−0.69281	−0.42616
$\tilde{\beta}_{16}$	100–129	0*	0*
$\tilde{\beta}_{17}$	130–159	0.00389	0.01366
$\tilde{\beta}_{18}$	160–189	0.26755	0.26948
$\tilde{\beta}_{19}$	≥ 190	0.56705	0.33251

Table 6: Estimated β coefficients, $\tilde{\beta}$, for predicting cardiac event using LDL-C categories, based on Wilson *et al* [33]. The values marked ‘*’ are “referent” values which are zero by definition. The value marked ‘‡’ is zero by definition: the age-squared term is not included in the regression for men.

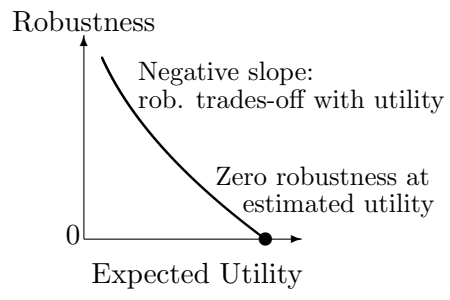


Figure 1:

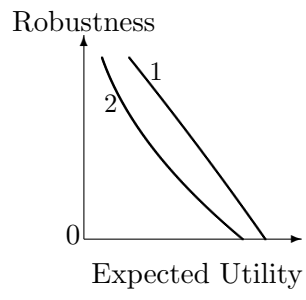


Figure 2:

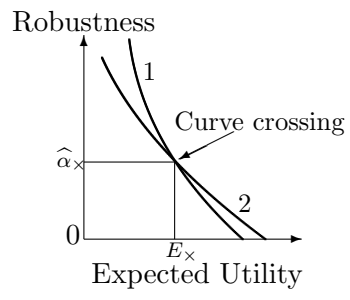


Figure 3:

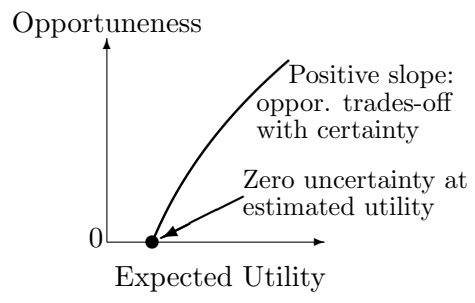


Figure 4:

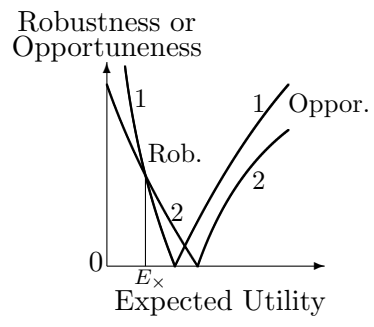


Figure 5:

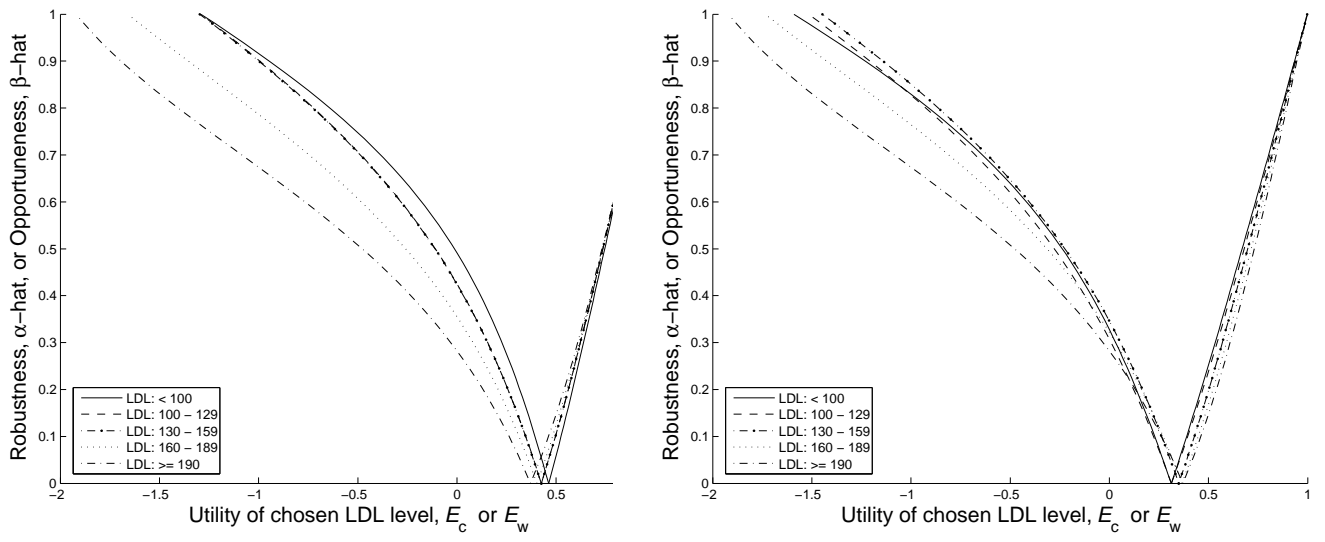


Figure 6:

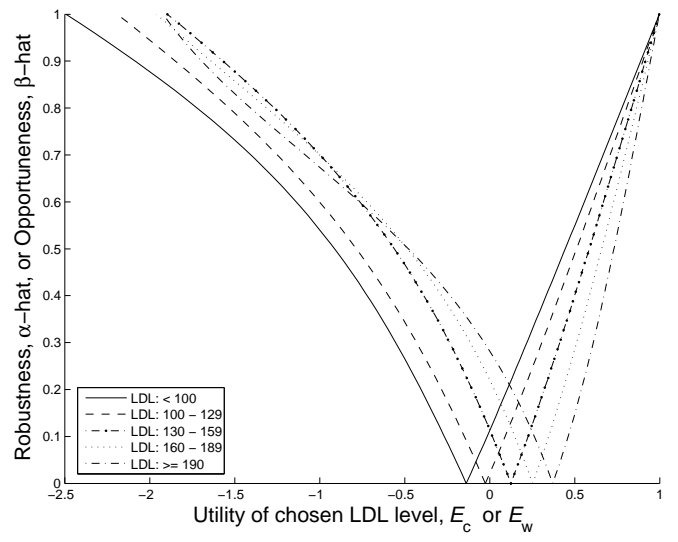
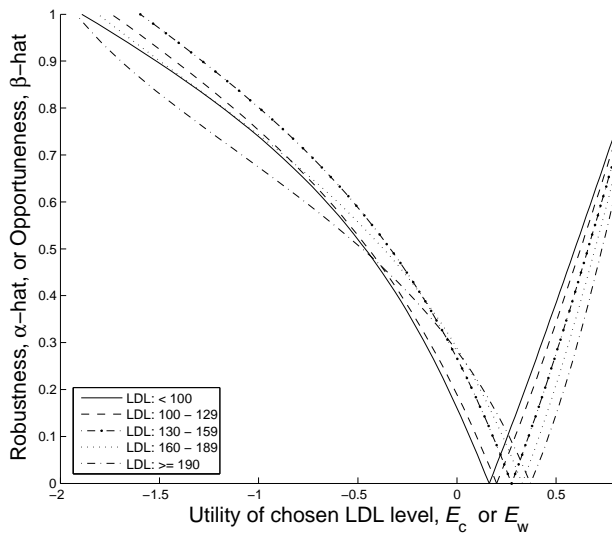


Figure 7:

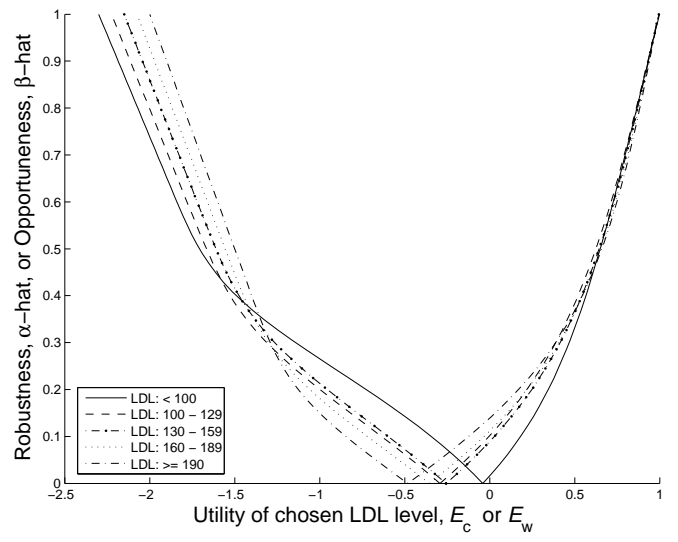
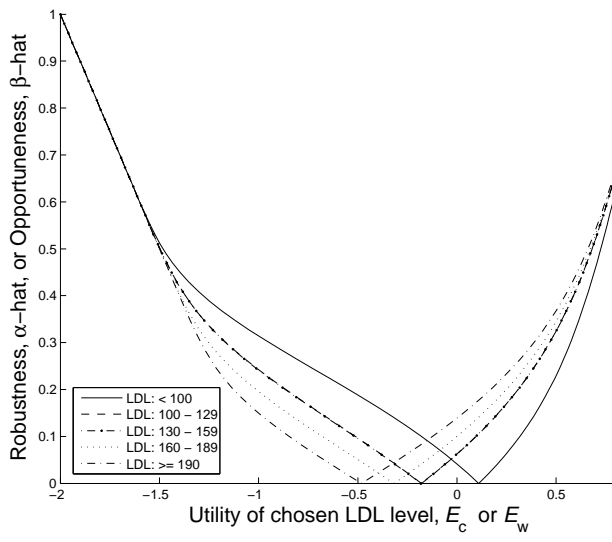


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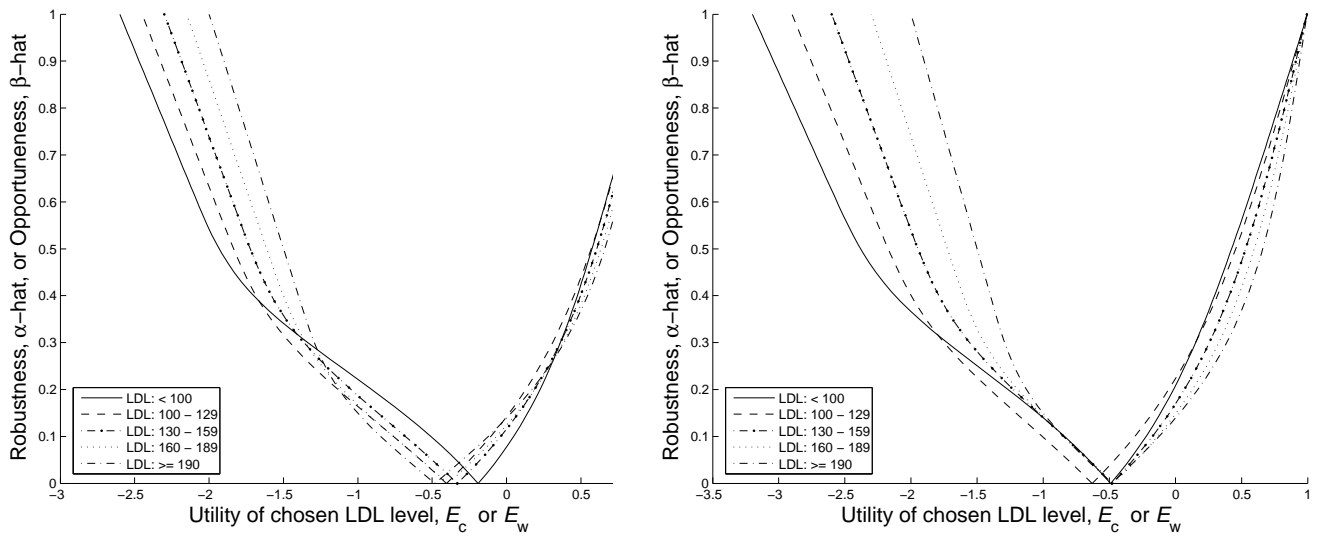


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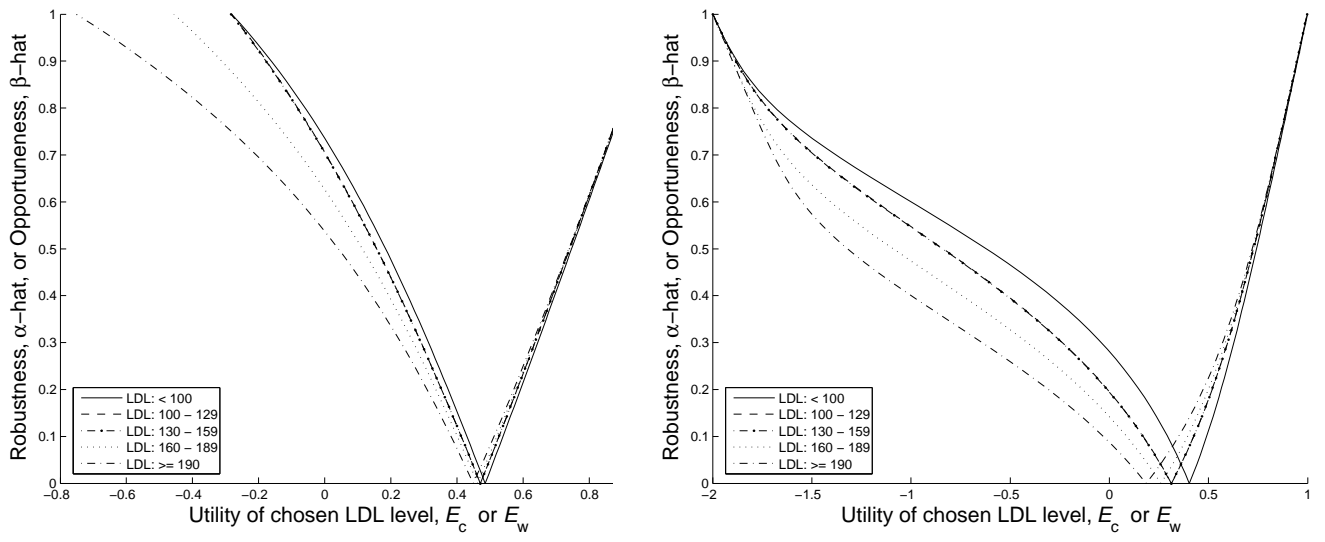


Figure 10:

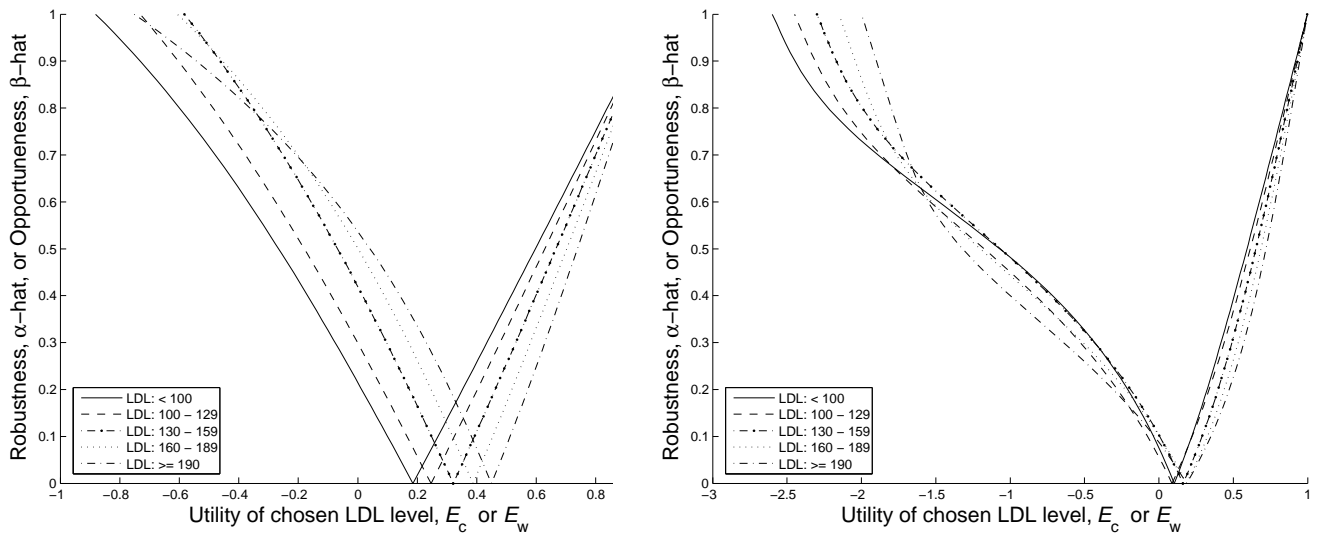


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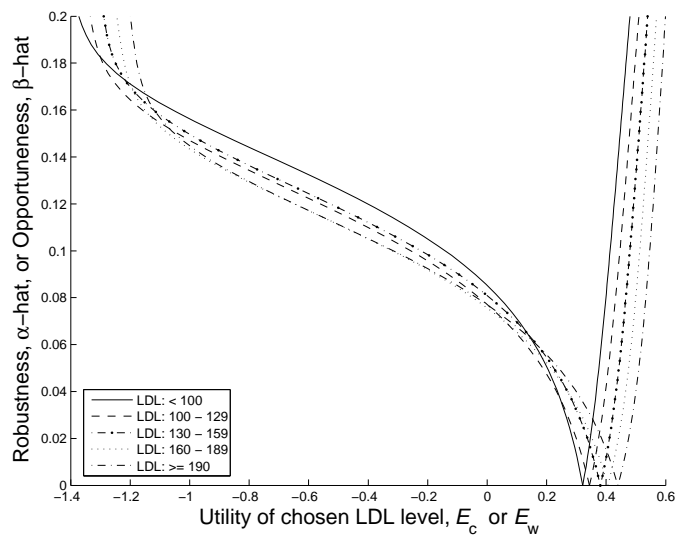
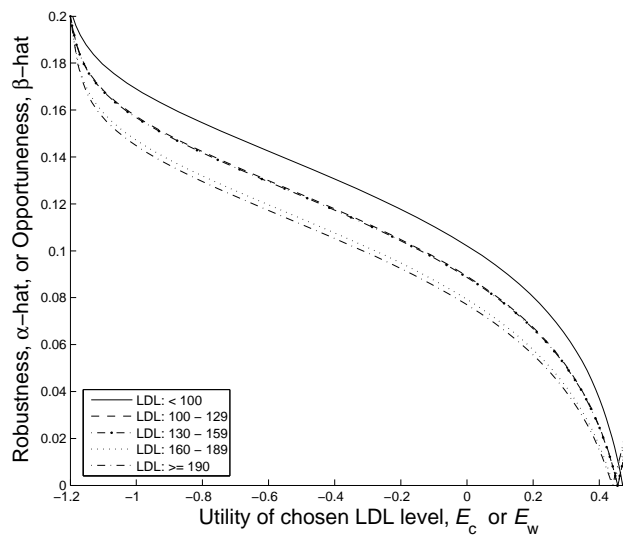


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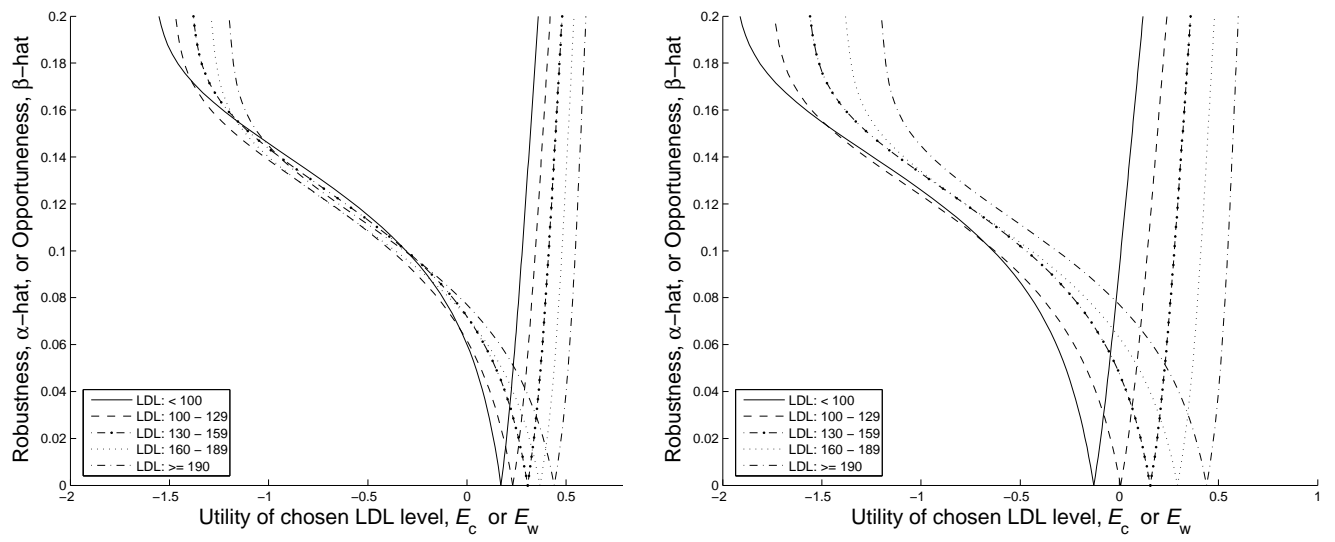


Figure 13:

Fig. 1. Properties of robustness curves.

Fig. 2. Preference for intervention 1.

Fig. 3. Preference reversal between therapies.

Fig. 4. Properties of opportuneness curves.

Fig. 5. Using opportuneness and robustness.

Fig. 6. Case 1. Robustness and opportuneness vs. desired utility for case in section 5.1. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$. $f = 0$ (left), $f = 0.1$ (right).

Fig. 7. Case 1. Robustness and opportuneness vs. desired utility for case in section 5.1. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$. $f = 0.2$ (left), $f = 0.4$ (right).

Fig. 8. Case 2. Robustness and opportuneness vs. desired utility for case in section 5.2. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$. $f = 0$ (left), $f = 0.1$ (right).

Fig. 9. Case 2. Robustness and opportuneness vs. desired utility for case in section 5.2. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$. $f = 0.2$ (left), $f = 0.4$ (right).

Fig. 10. Case 3. Robustness and opportuneness vs. desired utility for case in section 5.3. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$, $f = 0$. Age 35 (left), age 75 (right).

Fig. 11. Case 3. Robustness and opportuneness vs. desired utility for case in section 5.3. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$, $f = 0.2$. Age 35 (left), age 75 (right).

Fig. 12. Case 4. Robustness and opportuneness vs. desired utility for case in section 5.4. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$, $f = 0$ (left), $f = 0.1$ (right).

Fig. 13. Case 4. Robustness and opportuneness vs. desired utility for case in section 5.4. Patient's estimated utilities are $\tilde{u} = [-1, 0.5]$. ρ is the unit vector. $\ell_c = 5$, $f = 0.2$ (left), $f = 0.4$ (right).