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# MEDICAL PROGRESS

## DECISION ANALYSIS

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EXCELLENT clinical judgment requires optimal decision making. Many of the decisions that physicians make in their practices involve little uncertainty and little risk: these rote or routine choices need no special contemplation because they are "tried and true" practices. But for each routine problem there are several for which no easy solution is at hand. To deal with these, the tough problems, a physician can search for a properly designed, double-blind controlled study that examined patients of the same age, sex, and race and with the same conditions in the same stage; use an algorithm developed for such patients; use the problem-oriented approach to data gathering and hope that the solution to the problem will emerge; or ask for the help of one or more consultants. The frustrations encountered with all these approaches are familiar to all.

For 15 years we and others have been developing and applying decision analysis to difficult clinical problems,[1-6] and after experience with several hundred such analyses tailored to individual patients,[7] we are convinced that this quantitative approach warrants careful consideration as a tool for making decisions not only for individual patients but also for classes of clinical problems. This actively evolving field provides insights not available from clinical studies or expert opinion.

In this review we provide a few examples of some advances in the methods and the application of decision analysis. We consider both the advantages of the method and its limitations and offer our thoughts about the extent of the dissemination of decision analysis in medicine.

### BAYES' RULE

The modern physician is inundated by data — both clinical information that has been obtained intentionally and unanticipated results of screening tests and imaging procedures. In most circumstances, clinical information does not establish diagnoses with certainty; instead, each finding allows the physician to revise the probability of various diagnostic alternatives. In this sequential, iterative process, three sets of probabilities are defined: (1) the probabilities of the diagnoses *before* the presence of a new finding is revealed (prior probabilities); (2) the probabilities that a given finding can be observed in each disorder diagnosed (conditional probabilities); and (3) the probabilities of the diagnoses *after* the presence of a new finding is revealed (posterior or revised probabilities). The terms "prior" and "posterior" are defined with respect to a given diagnostic finding. In the sequential diagnostic process, the posterior probabilities for one finding become the prior probabilities for the next. Thus, the diagnostic implications of a given test result vary from patient to patient, depending on the presence of other findings.

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A mathematical combination of prior and conditional probabilities produces posterior probabilities. The relation among the three sets of probabilities — Bayes' rule — has been understood for two centuries, but this formulation has been applied to clinical reasoning only in the past several decades. Initial applications of Bayes' rule presented the physician with an equation* or with a computer program[8-12] that had the characteristics of a "black box." Other popular alternatives to the formal equation have been introduced, including nomograms[13-15] and tables.[16] Unfortunately, these latter approaches are practical only when a single disease is considered to be either present or absent and when the test result can be considered to be binary — i.e., either positive or negative. Recently, two different tabular formulations of Bayes' rule have appeared: a two-by-two table,[5,17] best used for calculating measures of test performance in a given study, and a posterior-probability calculator, designed to provide the interpretation of test information in a given clinical setting.[18,19] The latter technique can be used when several alternative diagnoses are possible and when test results lie along a continuum — e.g., serum enzyme levels. The calculation is performed easily with pencil and paper or with a handheld calculator. With the almost ubiquitous availability of personal computers and spreadsheet programs, templates for this calculation are easily created. Table 1 demonstrates the use of a spreadsheet to interpret the results of preoperative dipyridamole–thallium perfusion scanning in a 67-year-old man with peripheral vascular disease. This formulation of Bayes' rule uses a table with five columns: Column A, a list of mutually exclusive and exhaustive diagnoses; Column B, the prior probability of each diagnosis; Column C, the conditional probability of the observed finding, given each diagnosis; Column D, the product of Columns B and C — after each product is calculated, the products are added up; and Column E, the posterior probability, which is calculated by dividing each product in Column D by the sum of the products. A negative dipyridamole–thallium test diminishes the likelihood of critical coronary disease in this patient from 10 percent to less than 2 percent (Table 1), but almost half of comparable patients with such a test result will nonetheless have clinically important disease.

This simple technique can help the physician avoid the common reasoning error of neglecting the base rate.[20-22] In fact, because of the availability of probabilistic data in the medical literature and because clinicians are taught to quote and rely on the literature, this type of reasoning error is quite prevalent. Such errors are most likely to arise when the diagnostic test provides an unexpected result; the unwary clinician may rely too heavily on a highly "accurate" diagnostic test, neglecting the critical influence of disease prevalence.

Table 1. Spreadsheet Template Using Bayes' Rule to Interpret a Negative Thallium Test.*

| A — Diagnosis: Coronary Artery Disease | B — Prior Probability | C — Conditional Probability of Negative Scan | D — Product (B × C) | E — Posterior Probability (100 × D/Sum) |
|---|---|---|---|---|
| | *percent* | *percent* | | *percent* |
| Critical | 10 | 5 | 50 | 1.6 |
| Noncritical | 70 | 20 | 1400 | 43.6 |
| Negligible | 20 | 88 | 1760 | 54.8 |
| | | | 3210 | |

*This template can be easily built on any standard spreadsheet program and is available on request to the authors.

## Decision Trees

Decision analysis, a derivative of operations research and game theory, involves identifying all available choices and the potential outcomes of each and structuring a model of the decision, usually in the form of a decision tree. Such a tree consists of nodes, which describe choices, chances, and outcomes. The tree is used to represent the strategies available to the physician and to calculate the likelihood that each outcome will occur if a particular strategy is employed. The relative worth of each outcome is also described numerically, as a utility, on an explicitly defined scale — e.g., a life expectancy of 17 years or a score of 50 on a scale on which immediate death is defined as 0 and normal life expectancy in good health is defined as 100. The utility of a chance node is calculated as the weighted average of the utilities of its possible outcomes, where the weights are the probabilities that each outcome will occur. For example, a chance node describing a 5 percent chance of immediate death (with a life expectancy of 0), a 20 percent chance of survival with disabling angina (with a life expectancy of 7 years), and a 75 percent chance of survival free of angina (with a life expectancy of 15 years) would represent a life expectancy of 12.65 years, i.e., (5% × 0) + (20% × 7) + (75% × 15). The utility of a decision node is the maximum of the utilities of its component strategies, since the rational decision maker should choose the alternative that, on average, provides the highest value. Even when objective data are not available from the literature or from local experience, probabilities and utilities nevertheless must be quantified to preserve the logic of the decision process and to make optimal use of whatever data are available.

## Structuring Problems with Subtrees

A decision-analysis model is used to provide insight about real-world problems. Because the real world of clinical medicine is complex, such models often must be rather complex. The insights and conclusions that a

$$* \quad P_{dis|find} = \frac{P_{dis} \times P_{find|dis}}{\sum_{i=1}^{n} P_{dis\ i} \times P_{find|dis\ i}},$$

where $P_{dis\ i}$ denotes the prior probability of disease $i$, $P_{find|dis\ i}$ the conditional probability of the finding in patients with disease $i$, and $P_{dis\ i|find}$ the posterior probability of disease $i$, given the presence of the finding. The particular disease, among the $i$ possible diseases, is denoted as dis.

decision model provides can be helpful only if the model represents the clinical problem with sufficient fidelity. To create realistic models, the analyst needs a notation that is compact and that helps avoid certain mistakes. These seemingly contradictory demands can be resolved because most decision trees contain many repetitive structures. Even when management plans are vastly different, the prognosis is often described by the same series of chance events but with different frequencies of occurrence. These homologous structures can often be represented by a common tree fragment, called a subtree, that can be shared among different strategies and events. Figure 1 shows a rather complex decision tree representing alternative strategies for treating a patient whose thyroid was irradiated in childhood. Figure 2 shows the same model with subtree notation. Not only is the representation in Figure 2 readily understood, but it emphasizes analogies among events. When a common subtree appears in different places within a decision model, the likelihoods and the values of the outcomes may differ. For example, the probability of a benign lesion with a defect on a scan is somewhat lower than the probability of a benign lesion in a palpable nodule. On the other hand, the chance of recurrence of a cancer in a palpable nodule is 10 times higher than the chance of recurrence of a cancer found on scanning. Thus, the features of a subtree are often represented as variables, which assume different values when the same subtree is used in different contexts.

Subtree notation emphasizes relations among factors in a decision model. For example, when considering whether or not to perform surgery in a patient with unstable coronary disease, the analyst might be tempted to consider as separate variables the likelihoods of survival with and without such therapy, estimating likelihood from either a single report in the literature or several reports. In fact, survival in both circumstances often reflects the underlying state of the patient: patients with more severe coronary disease or poorer ventricular function survive less well under either plan. Thus, these two factors are linked, either to each other or to a common underlying factor. For example, if the efficacy of by-

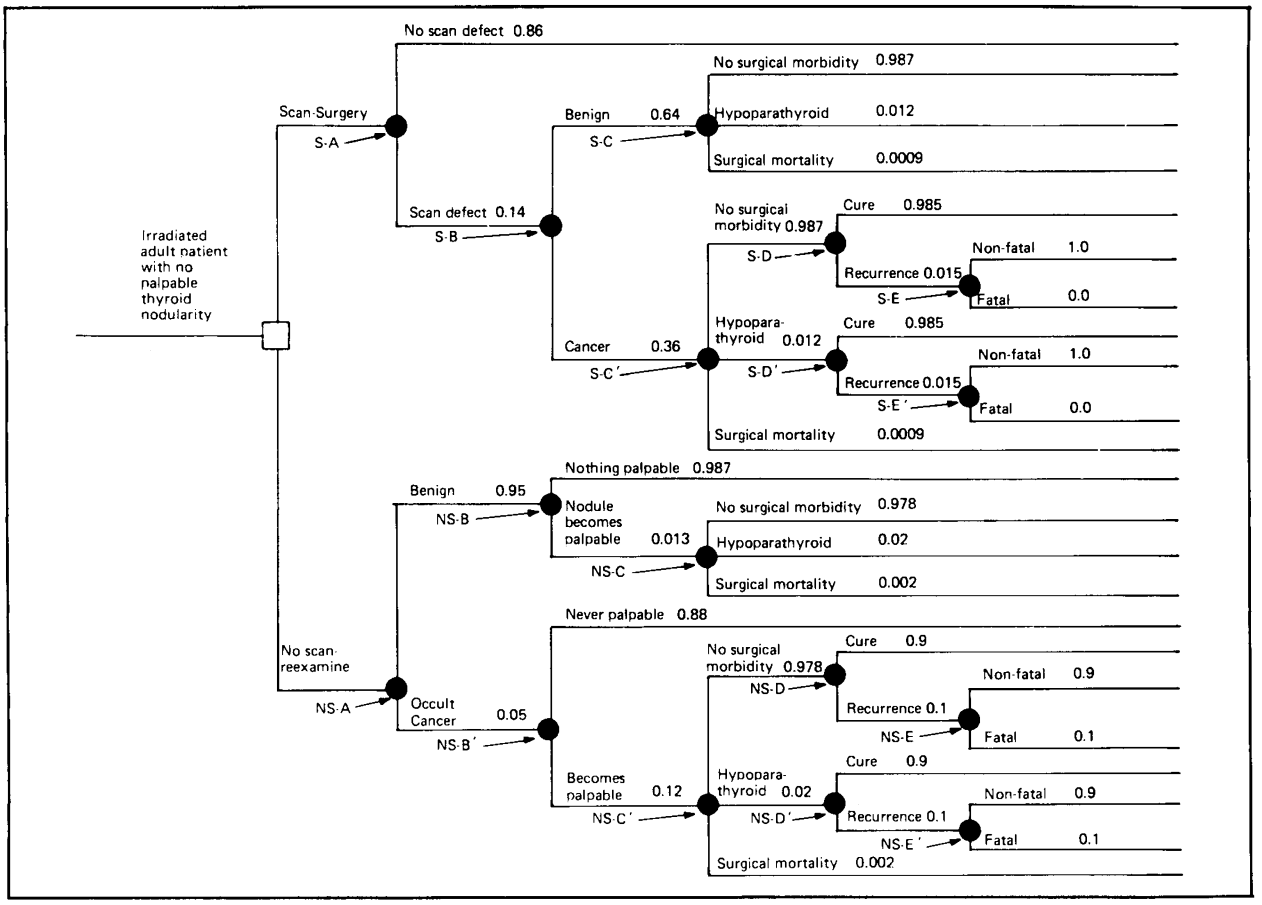


Figure 1. Decision Tree for Treating an Adult Who Received Thyroid Irradiation during Childhood (Reproduced from Stockwell et Al.,[23] with the Permission of the Publisher).

The decision, represented by the node (open square) at left, is between obtaining a thyroid scan, with surgery if a defect is found, and not obtaining a scan, with a plan to reexamine the patient for palpable thyroid nodules. Each chance event is represented by a node shown as a solid circle. A nodule or a defect may represent either benign disease or cancer, surgery may be complicated by hypoparathyroidism or death, and a cancer may or may not recur. This tree contains 17 chance nodes and 23 outcomes. S denotes scan, and NS no scan. The numbers on each branch are probabilities.

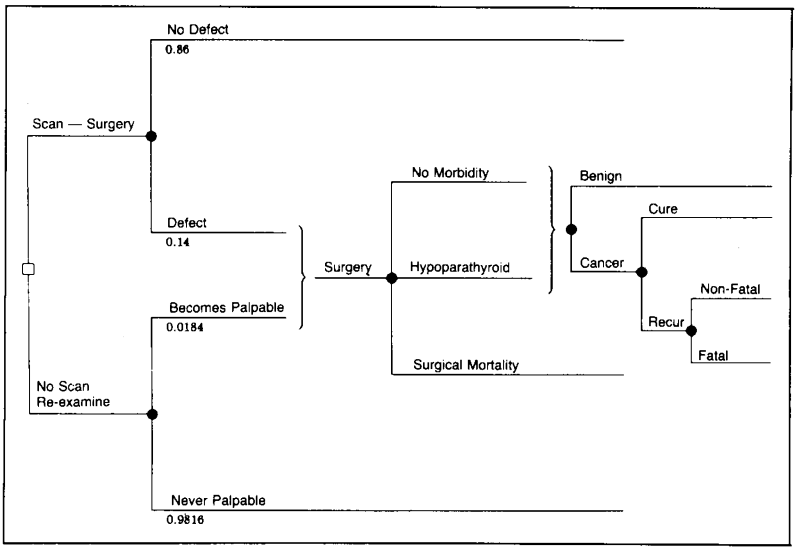


Figure 2. Subtree Representation for Childhood Thyroid Irradiation.

This tree is equivalent to the one shown in Figure 1, but contains only six chance nodes and seven outcomes.

pass surgery in lowering the annual mortality rate from coronary artery disease is denoted by e, and the mortality rate among patients with coronary artery disease (CAD) by $\mu_{CAD}$, then the annual mortality rate among patients in whom surgery is successful can be expressed as $\mu_{CAD} \times (1 - e)$. Because subtree notation encourages the analyst to look for symmetries in a decision problem and to express probabilities and values symbolically, it provides a new language and technique for expressing and examining such relations.

Occasionally, using subtree notation can suggest additional strategies. For example, certain treatments are traditionally given only after a diagnosis is considered to have been confirmed. As an alternative, the decision analyst might consider whether such therapy might be given "empirically" — before a diagnosis has been established definitively. In our experience, empirical therapy is a viable alternative when one is considering issues such as steroids for idiopathic nephrotic syndrome,[24,25] amphotericin for unexplained fever in a patient receiving immunosuppressants,[26] or radiation for a new pulmonary nodule in an octogenarian with anorexia.[27]

## Presenting Sensitivity Analyses

The full benefit of the effort required to design and implement a decision tree is not obtained if the model is used simply to determine the optimal management strategy. One of the principal benefits of a decision model is the capacity to ask "What if?" — "What if the disease is really more likely?" "What if the test is actually less accurate?" "What if the risk of surgery is greater?" Such questions are answered by performing sensitivity analyses — varying the values assigned to one or several variables in a systematic fashion and repeating the calculations to determine whether the optimal decision changes.

The simplest sensitivity analysis involves changing the value of a single variable and recalculating the expected utility of each strategy. Such a univariate examination of the model is called a one-way sensitivity analysis. It can be presented as a table of values or, often more informatively, as a graph. An example of such a graph, shown in Figure 3, reveals an interesting and frequent phenomenon — namely, that strategy lines may intersect. These intersections are called decision thresholds[29,30]: if a given variable (in this case, the probability of herpes simplex encephalitis) has a value less than a threshold value, then one action is optimal (in this case, brain biopsy); if the variable has a value greater than a threshold, then another action is optimal (in

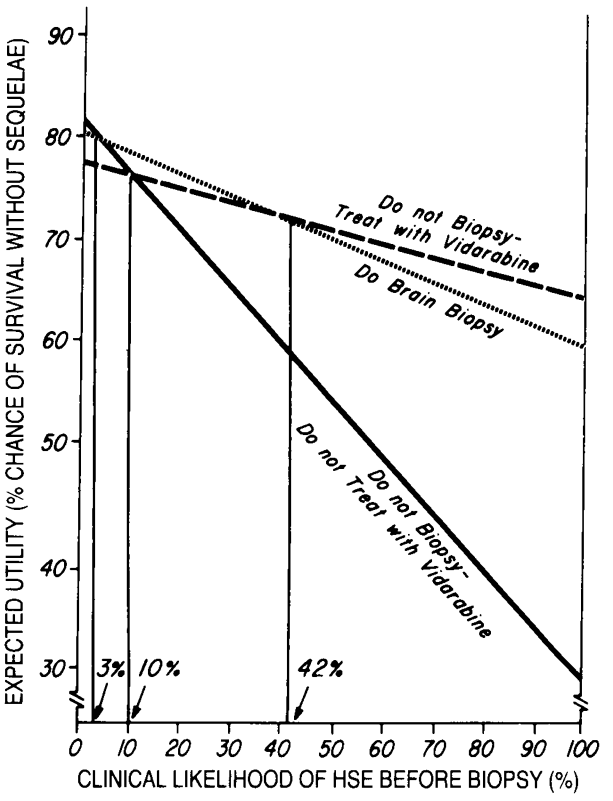


Figure 3. One-Way Sensitivity Analysis (Reproduced from Barza and Pauker,[28] with the Permission of the Publisher).

This analysis examined whether or not to administer vidarabine or perform a brain biopsy in a patient with suspected herpes simplex encephalitis (HSE). The variable being examined is the probability that the patient has the disease (horizontal axis); the expected utilities are shown on the vertical axis. Each strategy under analysis corresponds to a single line. The vertical lines at 3 percent, 10 percent, and 42 percent indicate diagnostic and therapeutic thresholds at which the optimal strategy changes.

this case, empirical drug therapy). In fact, the threshold values summarize the results of the one-way sensitivity analysis. Threshold values can tell the analyst whether a change in a given variable would change the optimal decision, but they do not indicate how much would be gained or lost by choosing a given strategy. That insight requires knowledge of the expected utilities of each strategy and the differences among them. Such differences are readily identified by examining Figure 3.

Of course, one-way sensitivity analyses provide only limited insight because they examine only changes in a single variable; the other variables are held to base-line values. The clinician, on the other hand, must sometimes explore the best strategy for a combination of factors — e.g., what if both the risk associated with lung biopsy and the probability of pneumocystis pneumonia are increased in a particular patient? Such complex yet important questions can be addressed by performing two-way sensitivity analysis — varying the values of two variables independently over broad ranges and determining the best strategy for all combinations. The calculational demands of such an analysis are only the first hurdle; once performed, the analysis must be presented in a format that provides the physician with clinical insight.

Two somewhat different formats have been developed for summarizing such analyses. The one shown in Figure 4 demonstrates how thresholds and expected utilities vary, and is useful in displaying the differences between options. Such formats, however, can only compare two strategies. A more compact and understandable representation is shown in Figure 5, in which every combination of the two variables corresponds to a unique point on the graph. In the left panel, the graph is divided into two regions that specify which strategy is optimal for each combination of values. If the point lies within the shaded area, administering amphotericin empirically is optimal; if the point lies within the unshaded area, avoiding amphotericin administration is optimal. In contrast to the representation in Figures 3 and 4, however, the graphs in Figure 5 do not indicate how strongly one strategy should be preferred over another.

A format similar to the one in the left panel of Figure 5 can be used to summarize the results of a so-called three-way sensitivity analysis, in which three clinically relevant factors are varied simultaneously and independently, shown in the middle and right panels of Figure 5. In both these panels, a family of curves depicts how the optimal strategy for each combination of the first two variables might be altered by changes in a third, independent factor. For example, in the middle panel the region bounded by the curves $P = 0.1$ and $P = 0.3$ represents the circumstances in which the optimal strategy would be to administer amphotericin if the probability of fungal infection was greater than 0.3, but to withhold such therapy if the probability was less than 0.1.

## Automation

As should be evident from the discussions of tree representation and sensitivity analysis, clinical applications of decision analysis impose substantial calculational burdens. If even a moderately complex problem is examined manually, even with the help of a calculator, the analyst must devote many hours to multiplications and additions. In fact, the questions that an analyst wishes to ask of a decision-tree model are severely limited by the time required to calculate the answers. If a sensitivity analysis requires 20 or 30 hours of computation, even the most ardent analyst may turn to other tasks.

Over the past several years, many microcomputer programs, developed in the medical arena[32-35] and elsewhere,[36] have become available, allowing the experienced analyst to explore decision-tree models efficiently. These programs are cumbersome to use, however; they require substantial time to learn; and they cannot teach the inexperienced physician how to design and interpret a decision tree or identify or avoid errors in a model.

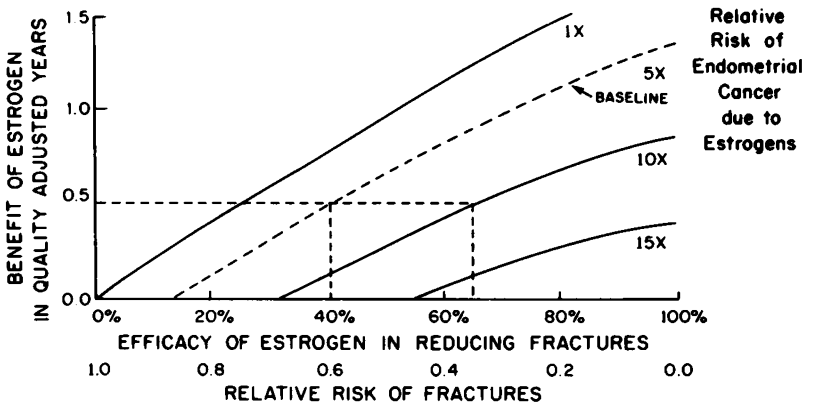


Figure 4. Two-Way Sensitivity Analysis (Reproduced from Hillner et Al.,[31] with the Permission of the Publisher).

This analysis examined whether or not to administer estrogens to postmenopausal women to prevent osteoporosis. The efficacy of postmenopausal estrogens in reducing fractures is shown on the horizontal axis, and the benefit of estrogen therapy (i.e., the difference between the calculated expected utilities of two strategies) is shown on the vertical axis. Each line corresponds to a different relative risk of endometrial cancer induced by estrogen therapy.

## Assigning Values to Outcomes

Some major criticisms of decision analysis have focused on the assignment of utilities to various outcome states. Early models used arbitrary scales[3,4]; it was difficult to understand the meaning of the scales and to determine whether small differences had any clinical

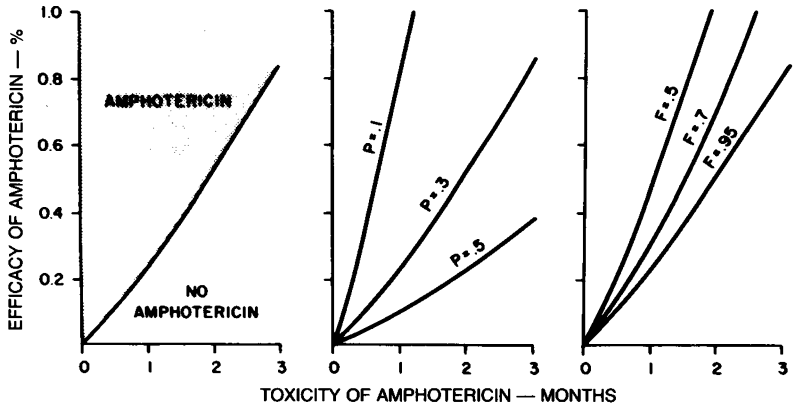


Figure 5. Two-Way and Three-Way Sensitivity Analyses (Reproduced from Gottlieb and Pauker,[26] with the Permission of the Publisher).

This analysis examined whether or not to administer amphotericin to an immunosuppressed patient with persistent fever. The toxicity of amphotericin is shown on the horizontal axis, and its efficacy on the vertical axis.

The left panel contains a two-way sensitivity analysis, and the middle and right panels contain three-way sensitivity analyses in which each line corresponds to a different value of a third variable. In the middle panel, the probability of fungal infection (P) has been varied from its base-line value of 30 percent: the lower the probability of fungal infection, the smaller the set of circumstances in which empirical amphotericin is indicated — i.e., the smaller the region above the curve. In the right panel, the mortality rate for fungal infection (F) is varied from the base-line assumption of 95 percent. Again, the lower the risk of fungal infection, the smaller the set of circumstances in which empirical therapy is indicated.

importance. Recently, clinical decision analysts have begun to use meaningful utility scales — e.g., quality-adjusted life expectancy.[37] Several techniques have also been developed for helping patients assess their attitudes toward alternative health outcomes and to express these attitudes quantitatively so that their preferences can be explicitly incorporated into decision analyses.

### Life Expectancy

The literature typically summarizes the prognosis of patients with a single disease process — i.e., a select and fairly "clean" population or, at best, average patients. The clinician, however, cares for individual patients, who often differ in important ways from patients described in the literature — e.g., in age or coexisting diseases. Thus, one of the clinician's central tasks is to identify the experience reported in the literature and tailor it to the individual patient. Such "massaging" of data is always somewhat arbitrary and empirical, but it is an essential part of traditional, implicit decision making. For quantitative decision making, an approximation of life expectancy has been developed to provide a mechanism for calculating and understanding how independent mortality risks operate.[38] According to this method (the declining exponential approximation of life expectancy), the mortality rate is viewed as the exponent in a declining exponential curve, similar to a drug half-life in the familiar single-compartment model of pharmacokinetics. Independent "forces of mortality" can be combined by addition, yielding an overall mortality rate.

When an average rate is known, life expectancy or average survival can be approximated by the reciprocal of the rate. For example, the life expectancy of a 70-year-old man with three-vessel coronary artery disease and Dukes' stage B carcinoma of the colon can be approximated by adding together the average mortality rate among patients of his age, sex, and race ($\mu_{ASR}$) and the independent excess mortality rates associated with these diseases ($\mu_{CAD}$ and $\mu_{ColonCa}$). As shown in Table 2, this technique can approximate life expectancy under various management strategies that might be specified in a decision tree. One must be careful, however, to notice that the disease-specific mortality rates are excess rates and not crude rates.

### Quality of Life

Increased participation by patients in making decisions about their medical care requires not only that they be informed about alternatives and given the opportunity to express their wishes but also that they be guided in assessing their attitudes; these results need to be incorporated into the decision-making process.[39] When using decision analysis, the physician's role as *a* decision maker (as opposed to being *the* decision maker) is not abdicated to the patient; instead, patient and physician work as a team. The physician's expertise clearly consists of knowledge of the medical facts; the patient's expertise often consists of conceptualizing the effects of a potential outcome on him and his family.

Table 2. Calculation of Life Expectancy.

| Step | Action | Result |
|---|---|---|
| 1 | Life expectancy of 70-year-old man | 8 yr |
| 2 | Reciprocal of Result 1 yields $\mu_{ASR}$* | 0.125/yr |
| 3 | Excess mortality† for coronary disease | 0.080/yr |
| 4 | Excess mortality for colon cancer | 0.090/yr |
| 5 | Total average mortality (sum of Results 2 through 4) | 0.295/yr |
| 6 | Reciprocal of Result 5 yields life expectancy | 3.39 yr |
| | *If surgery has 50% efficacy, then* | |
| 7 | Excess mortality of coronary disease | 0.040/yr |
| 8 | Total average mortality (sum of Results 2, 4, and 7) | 0.255/yr |
| 9 | Reciprocal of Result 8 yields life expectancy | 3.92 yr |

*$\mu_{ASR}$ denotes average mortality among patients of the same age, sex, and race as the patient under evaluation.

†If the point survival at a given time is known, then the average mortality rate for a period can be calculated with the equation $\mu_{Crude} = -(1/n) \ln S_n$, where $S_n$ is the probability of surviving n years. For example, if a series reports that the five-year survival among 56-year-old men with three-vessel coronary artery disease is 55 percent, then the crude mortality rate would be $-(1/5) \ln 0.55$, or 0.12 per year. The excess mortality rate is defined as the force of mortality over and above the rate among average patients of the same age, sex, and race. In this case, the series described 56-year-old men, whose life expectancy is approximately 25 years; thus, $\mu_{ASR}$ is 1/25 year, or 0.04 per year. The excess mortality rate for three-vessel coronary artery disease treated medically is then 0.12 per year minus 0.04 per year, or 0.08 per year.

Several approaches are available to help patients understand the dynamics of a decision and to help them formulate ideas about the relative merits of its outcomes. With most techniques, the patient is presented with a limited set of scenarios and is asked to choose between pairs of alternatives. For example, a prospective parent, informed in advance of the medical terms, might be asked[40] whether a pregnancy in which there is a 20 percent risk that the fetus has trisomy 21 should be aborted or carried to term. By presenting a sequence of such choices in which the probability of an outcome in one scenario is varied — e.g., from 20 percent to 50 percent to 80 percent — the physician can help assess in what circumstances the patient would be indifferent to choosing between two scenarios — i.e., when both scenarios would be perceived as equally bad. That point of indifference can then be used to create a utility scale. Presenting a sequence of scenarios involving chance events is called the lottery technique.

Another common technique for assessing attitudes is the time trade-off approach,[41] in which the patient is asked to consider two scenarios that differ not in the probabilities of their outcomes but in their duration. For example, a patient with carcinoma of the larynx might be asked,[42] "Would you rather live for 8 years with normal speech or live for 10 years after a laryngectomy?" The duration of life with normal speech is varied in a sequence of questions until the patient recognizes his or her indifference point, which can then be used to create a utility scale.

## The Markov Process

Prognosis can often be described as a series of chance events for which the patient is at risk. For example, a patient with silent gallstones may have an episode of acute cholecystitis in any given year.[43] If an episode occurs and the patient requires cholecystectomy, the risks of surgery depend on how old the patient is at the time. If this sequence of events were modeled as a simple decision tree with a set of chance nodes describing the events that might occur each year (i.e., acute cholecystitis, death due to surgery, or death due to other causes), the tree would double in breadth each year. After a mere 30 years (a reasonable time frame for clinical events in such a patient), the tree would contain more than 1 billion branches and would be impossible to evaluate by hand and even cumbersome to assess by computer.

Fortunately, a vast segment of the tree structure is repetitive, describing the same events year after year. In recent years it has become increasingly popular and convenient to use state-transition, or Markov-process, models in such decision problems.[44] These models define a small set of "health states" and specify the allowed transitions between the states. For example, a patient in the "silent gallstones present" health state may, in any given year, move to the state "cholecystectomy" and then to the state "post-cholecystectomy" or to the state "dead." The likelihood that a patient will move from one health state to another in any given period is called the transition probability for such a change. Each state of health is also assigned an incremental value when a patient remains in the state for a given period. For example, a patient who has silent gallstones for a year might be credited with 1 quality-adjusted year, whereas a patient who has an episode of cholecystitis and undergoes cholecystectomy in a given year might be credited with only 0.9 quality-adjusted year.

Table 3. Markov Simulation of Prognosis of Cholelithiasis.

| Year* | Patient Age | Patients with Silent Gallstones | Patients Surviving Cholecystectomy This Year | Patients Post-Cholecystectomy | Patients Dead |
|---|---|---|---|---|---|
| 0 | 30 | 100,000 | 0 | 0 | 0 |
| 1 | 31 | 98,838 | 994 | 0 | 168 |
| 2 | 32 | 97,676 | 982 | 992 | 349 |
| 3 | 33 | 96,516 | 970 | 1,971 | 544 |
| 4 | 34 | 95,356 | 958 | 2,934 | 752 |
| 5 | 35 | 94,198 | 945 | 3,883 | 974 |
| 10 | 40 | 90,698 | 452 | 6,600 | 2,251 |
| 20 | 50 | 83,936 | 206 | 8,582 | 7,277 |
| 30 | 60 | 71,403 | 171 | 9,246 | 19,180 |
| 40 | 70 | 50,509 | 114 | 7,906 | 41,472 |
| 50 | 80 | 27,785 | 53 | 5,061 | 67,100 |
| 60 | 90 | 867 | 1 | 178 | 98,954 |
| 70 | 100 | 0 | 0 | 0 | 100,000 |
| Total | | 3,788,787 | 13,571 | 380,022 | |
| **Quality adjustment** | | 1.0 | 0.9 | 1.0 | |
| **Quality-adjusted total** | | 3,788,787 | 12,213 | 380,022 | |
| **Total quality-adjusted years for cohort** | | | | | 4,181,025 yr |
| **Average quality-adjusted survival for member of cohort** | | | | | 41.8 yr |

*Although the actual calculation was done for each year, to conserve space the table shows only the results for years 0 through 5 and for each 10th year after year 10.

The model is used by placing a hypothetical cohort of patients in one or more states at the beginning of the horizon of analysis (e.g., placing 100,000 patients in the silent-gallstones state) and following their course year by year. As shown in the simplified example in Table 3, after a sufficiently long time horizon, all patients will have died. The number of quality-adjusted years of life in the cohort is added up and then divided by the size of the original cohort, yielding the expected quality-adjusted survival for a member of the cohort. Such decision models, quite feasible with computer support, provide important insights into clinical disorders that evolve over time.

## Some Expectations

Over the 15 years during which decision analysis has been evolving in medicine, many of the principal concerns of its critics[45-51] have been satisfied: the time-consuming calculational burden has been eliminated by automation[32-36]; arbitrary utilities have been replaced by meaningful scales; and the threat to physicians of a mathematical approach to medical decision

making simply has not materialized. Despite critically important and substantive advances in the application of decision analysis to clinical problems, most physicians faced with a difficult clinical problem do not immediately reach for a sketch pad or a microcomputer to create a decision tree. Why not? First, expertise in using the method is limited. Second, formal decision analysis takes time — time to construct a model (the tree) properly, time to gather and tailor the data, and time to interpret the model and decide which assumptions to test with sensitivity analysis. In short, it is often impractical in the hectic arena of clinical practice. Beyond these serious problems are several that aficionados worry about: the necessarily simplified models do not always reflect the real problems of the patient; the results are often distorted because the data available are stretched to the extreme to fit the problem; the utilities used to reflect patients' feelings about the quality of life associated with various outcomes are "soft" and inconstant over time; and the methods available to examine the effect of the data used in the analysis are still in need of considerable refinement.

Are these problems so immense that decision analysis will be relegated to a footnote in medical history? Not from our vantage point. Any assessment of decision analysis must be made against the "usual" approach to medical decision making; in that traditional mode, when we encounter a difficult problem for which no controlled study has provided a solution, we either contemplate the decision ourselves, implicitly, or we gather the opinions of consultants, hoping to build a consensus. Whether or not consensus is reached, the decision is usually made implicitly, a tacit approach that may or may not consider all reasonable alternatives or weigh the outcomes of competing choices appropriately. Implicit decision making almost never identifies situations in which the choice simply does not matter, despite the clear existence of such situations.[52] Alternative strategies of solving problems, such as the problem-oriented record, algorithms, flow charts, and the new discipline of clinimetrics, have not yet proved advantageous over the traditional approach. In contrast to the traditional approach, decision analysis is explicit; it forces us to consider all pertinent outcomes, it lays open in stark fashion all our assumptions about a clinical problem, including numerical representations of the chances and values of outcomes; it forces us to consider how patients feel about the quality of outcomes; and it allows us to come to grips precisely with the reasons why colleagues differ about actions to be taken.

We believe that applying decision analysis to individual and generic clinical problems is worth the effort but that it will require further investment in methodologic research and expanded effort to teach quantitative problem solving to a generation of students and house officers. As we delve deeper and deeper into the molecular nature of the diseases we battle, so should we dissect the day-to-day medical decisions that so critically influence the quality of the care we deliver.

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# MEDICAL INTELLIGENCE

## GLUCOSE PHOSPHATE ISOMERASE DEFICIENCY AS A CAUSE OF HYDROPS FETALIS

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ERYTHROCYTE enzymopathies are well-recognized causes of hemolytic anemia in newborn infants, but have rarely been implicated etiologically in hydrops fetalis or immediate neonatal death. Death occurred within a few hours of birth in only 4 of 260 cases recently reviewed by Matthay and Mentzer.[1] One patient was deficient in glucose phosphate isomerase (D-glucose-6-phosphate ketol-isomerase, E.C. 5.3.1.9),[2] two others in pyruvate kinase,[3,4] and another in triosephosphate isomerase.[5] Hydrops fetalis is also rare in association with the more common deficiencies of glucose-6-phosphate dehydrogenase. In two cases, severe anemia and hydrops in an infant were attributed to maternal ingestion of oxidants (sulfisoxazole,[6] fava beans, and ascorbic acid[7]).

This report describes a consanguineous family from southern India in which five of six pregnancies resulted either in stillbirth or in early neonatal death (one with hydrops). The sixth child was delivered early, noted to have hydrops fetalis, and successfully treated with exchange transfusion in the immediate postnatal period. The hemolytic anemia was subsequently shown to be due to glucose phosphate isomerase deficiency and was clinically ameliorated by splenectomy at the age of three years.

### METHODS

Venous blood was anticoagulated with heparin and transported under refrigeration by air express for processing within 24 to 48 hours. Suspensions of erythrocytes in saline were freed of leukocytes by cellulose filtration and assayed for glucose phosphate isomerase activity and other enzyme activities according to standard techniques.[8,9] Leukocytes were isolated by flotation in Ficoll–Paque (Pharmacia Fine Chemicals, Piscataway, N.J.), washed thoroughly with isotonic saline, and lysed by ultrasonication before enzyme assays. Electrophoresis was performed with the method of Detter et al.,[10] and thermostability at 48°C was assessed as described by Blume et al.[11]

### RESULTS

The proband was a girl delivered by cesarean section (performed at the All India Institute for Medical Sciences, New Delhi) at 35 weeks of gestation because of suspected hydrops fetalis. Her birth weight was 2.25 kg, and peripheral edema, ascites, and hepato-

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