Short-Term Mortality Predictions for Critically Ill Hospitalized Adults: Science and Ethics

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Modern life-sustaining therapy often succeeds in postponing death but may be ineffective at restoring health. Decisions that influence the time and circumstances of an individual's death are now common and require an accurate and comprehensive characterization of likely outcome. Evaluation of alternative outcomes requires acknowledgment that most patients find some outcomes to be worse than death. Improved understanding of major predictors of patient outcome, combined with rapidly expanding technical abilities to collect and manipulate large amounts of detailed clinical data, have created a new intellectual and technical basis for estimating outcomes from intensive medical care. Such objective probability estimates, such as the system described here, can reduce uncertainty about difficult clinical decisions and can be used by physicians, patients, and society to reorient health care toward more scientifically and ethically defensible approaches.

"Another property that sets the genuine sciences apart is . . . their predictive capability" (*1*).

Because of powerful pharmacological interventions and mechanical devices, physiologic abnormalities that were once uniformly fatal can now be reversed. In many cases the patient lives longer with chronic disease, sometimes with severe disability, and a few depend on intensive therapy to stay alive. Sometimes life with treatment is clearly not better than the outcome without therapy, but medicine has not devoted much effort to characterizing or evaluating the outcomes of different plans of care (*2*).

Medical decision-making has also recently been influenced by three major social trends: the public demand that patients have authority to make a broad range of choices, the pressure to reshape health care financing to limit the growth in health care expenditures, and the need to allocate access and burdens more fairly (*3*). Patients and their families want the ability and authority to choose among the full range of therapeutic alternatives. Society, facing economic constraints, is increasingly limiting insurance coverage for some therapeutic options, especially those that offer small returns at substantial costs. To address these conflicting goals and priorities, adequate descriptions of the likely outcomes of alternative courses of care are needed. These descriptions must allow predictions comprehensive enough to address the concerns of all involved. They must be valid and reliable and have estimates of their own uncertainty.

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In this article, we review the development of objective probability estimates for severely ill patients and the clinical applications, and ethical implications of such estimates. We describe the improved understanding of patient outcome determinants, progress in analytic capabilities, and new technical capability to collect and manipulate large amounts of detailed clinical data. The objective probability estimates produced from these procedures can provide a reproducible and accurate empiric basis for difficult but increasingly common decisions to forgo treatment and could serve as the basis of more informed discussions by clinicians and patients about the desirability of alternative plans of care. These prognostic estimates could also inform revisions in health care financing and structure.

Methods and Definitions

The development of objective probability estimates generally requires (i) the specification of the factors thought to be related to the outcome of interest, (ii) the collection of a database with information on these predictive variables and outcome, and (iii) the analysis of the relations among the predictive variables and patient outcome. A variety of methods is used to select and weight predictive variables and to present the relationship (for example, multivariate or summary scores) (*4*). Although large databases collected for other purposes have important shortcomings in regard to reliability and completeness of data, they can be used to explore relations between predictive variables and patient outcomes. Validation of the specifications of a model is best done on a new group of patients; but resampling schemes, such as bootstrapping, can be applied in some situations to obtain an estimate of predictive accuracy (*5*).

Prediction science in clinical medicine has relied heavily on regression analysis to weight predictive variables (*6*). The empiric models for which these methods are used have been most highly developed in regard to predicting mortality for acutely ill hospitalized patients, especially those within intensive care units, persons for whom the risk of death is substantial. Our discussion will concentrate on that application.

Let us first define the key terms that we use. A probability or prognostic estimate is a number ranging from 0 to 1 that measures an individual patient's expected risk of dying or of having another defined outcome within a specified period of time. An objective probability estimate is one estimated for an individual patient from a database derived from experience with previous patients. A subjective probability estimate is one given for an individual patient that is based on the personal knowledge and experiences of the prognosticator (for example, a physician's own judgment). Both objective and subjective probability estimates can be expressed numerically or in qualitative terms (such as, unlikely, likely, probable, improbable, and so on). The overall explanatory power of probability estimates relates to two major constructs, discrimination and calibration. Discrimination measures the ability of a prognostic estimate to separate patients into groups—for example, those who will live from those who will die. Calibration refers to the relation of the probability estimate to the observed frequency of the outcome in a set of similar subjects.

Probability Estimates and Medical Practice

Historically, one of the most valued services of a physician was the foretelling of the future course of disease (*2*). As medical practice became more effective this service became more difficult and less valued. The greatly expanded possibilities for treatment gave rise to extraordinary therapeutic optimism and engendered insecurity in prediction. Most new treatments have not been fully evaluated, and the emphasis in research has been on uncovering the next new treatment rather than evaluating current capabilities.

Physicians have also been hesitant to apply probability estimates to a particular patient. The physician always knows elements of the patient's condition that are not in the predictive model, and rarely is there evidence to show that the additional information is irrelevant. Knowledgeable physicians are also concerned over whether current patients and treatments are truly comparable to those in the predictive model and whether the identical therapies were used for patients in the database. For all of these reasons and, perhaps, more self-serving ones (such as maintaining authority and prestige), physicians have been reluctant to employ objective probability estimates, relying instead on clinical judgment.

There have been three rather simple developments that have radically reshaped predictive science in recent years: the use of multiple continuous variables to describe severity of illness; the implementation of multivariable analysis; and the development of large databases and the computer technology to manipulate them (*7*). These methodologic innovations have granted current predictive estimates of the power and precision necessary to have a role in shaping clinical decisions.

Continuous variables and the basic model. Until quite recently, the most common quantification of severity used to estimate prognosis for patients with infection was a three-category descriptive scale (rapidly fatal, ultimately fatal, or nonfatal) based on the physician's assessment (*8*). Many individual categorical variables, such as a third heart sound in congestive heart failure, have also been associated with outcome (*9*). Observer error is common with such subjective or categorical variables, however, often nullifying their reliable use. A number of continuous physiologic variables, such as pulse rate and blood pressure, are now recognized to be more reliable and accurate and to reflect better the underlying severity of physiologic derangement (*10, 11*). These measurements, used directly or as weighted scoring systems incorporating multiple variables can generate a continuous measure of the underlying severity of the patient's condition (*12*). Recording changes in the physiologic variables over time may be especially powerful in assessing response to therapy (*13*).

Physiologic abnormalities are correlated most strongly with hospital mortality, but the relation is modified by certain co-variables. As chronologic age increases, the influence of any degree of physiologic abnormality increases. Co-morbid conditions decreasing immunity such as metastatic cancer or severe cirrhosis have a similar impact. Which disease created the acute physiologic abnormalities also has an impact (*14*). Some diseases, for example, drug overdoses, generate substantial physiologic disturbances but a low probability of death. For other diseases, such as septic shock, smaller variations from normal mean substantial death rates (Fig. 1). This variation is probably largely explained by the effectiveness of treatment in correcting the underlying pathophysiology of the disorder. Creating these predictive models also requires attention to the circumstances under which the patient was selected for study—for example, whether they were admitted directly to the intensive care unit from the emergency room—as a control for lead time and selection biases.

Multivariable analysis. The applicability of objective probability estimates to individual decision-making has also been advanced by the development of multivariable approaches, such as regression methods to probability estimation (*10*). Bivariate analyses have not been powerful enough for prognostic guidance. Multivariable analyses simultaneously use many predictive variables from a large number of individuals to establish an unusually precise and reliable probability estimate. Because the two major sources of error in regression analyses are the predictive variables chosen and their measurement reliability, the wide availability and reliable measurement of the continuous physiologic variables predicting hospital mortality for intensive care patients is encouraging.

Large databases. Much of the patient data required for prognostication, particularly the acute physiologic measures, are now available in electronic form, and their storage and manipulation is increasingly common and inexpensive (*15*). Thus, an individual clinician could have the collective experience of having treated thousands of similar patients when considering treatment of a new patient. Because the dependent variable (whether it is hospital mortality, survival time, or quality of survival) is frequent within the databases of severely ill patients, models of patient outcomes have substantial explanatory power. Databases from thousands of patients are now common and those from hundreds of thousands are under development (*16*). The linkage between databases necessary to reflect specific episodes of treatment and subsequent outcomes is under way (*17*). These databases also now can be updated to reflect therapeutic capabilities. Because these are observational databases, caution must be used in directly inferring specific treatment effect.

The capacity to weight and quantify key predictive variables and to create automated databases have recently been combined to provide real-time estimates of short-term mortality for patients within intensive care units. Figure 2 illustrates a computer display from one such system providing daily updated risk estimates of hospital mortality for simulated patients in a six-bed intensive care unit (ICU). The system is based on a series of predictive regression equations that used the APACHE III (acute physiology, age, chronic health evaluation) prognostic scoring system (*18*), which contains information on prognostic variables for a nationally representative database of 17,440 adults admitted to medical and surgical

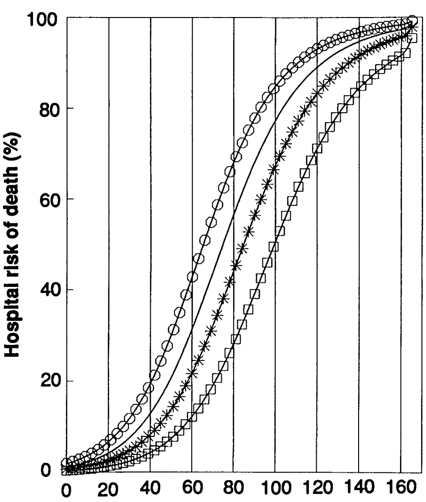

Fig. 1. Relations between APACHE III score on initial day of intensive care treatment and subsequent risk of hospital death for two medical diseases [acute myocardial infarction (——) and congestive heart failure (*)] and two surgical diseases [subdural hematomas (○) and peripheral vascular surgery (□)]. As the degree of acute physiologic abnormalities increases, importance of disease in estimating risk first increases and then decreases once the degree of physiologic abnormalities becomes severe.

intensive care units.

The APACHE III equation uses a continuous weighting scheme for physiology, age and co-morbid conditions. These variables (the APACHE III score) are combined with weighted coefficients for disease and selection criteria to predict (at the initiation of intensive care) probability of death before hospital discharge. Then, changes in physiology update the estimates throughout the course of the patient's intensive care stay (*25*). APACHE III has its origins in the detailed monitoring of acute physiologic abnormalities made routine in ICUs (*19–21*). A number of such prognostic systems are currently under development (*22–24*) and have been reviewed (*4*).

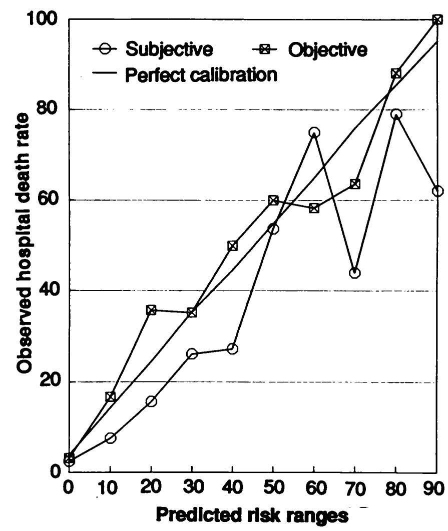

Fig. 3. Calibration curve contrasting subjective and objective hospital mortality risk estimates for 850 ICU admissions on the basis of information available during initial day of ICU treatment. Subjective risk estimates were made by 13 physicians from nine medical centers. The objective estimates were derived from the APACHE III prognostic scoring system.

Objective Versus Subjective Probability Estimates

Most comparisons of objective and subjective probability estimates use the total area under a receiver operator characteristic (ROC) curve (*26*). The total area under the curve is an expression of overall discrimination across the range of risks. An area of 1.0 would be perfect discrimination and 0.5 is no better than random chance. ROC areas obtained from a variety of algorithms for the objective prediction of hospital mortality and produced at the time patients are admitted for treatment to an intensive care unit average from 0.78 to 0.90 (*12, 18, 22–24*). Recent surveys of subjective probability estimates indicate total ROC areas of 0.82 to 0.85, which are roughly similar to those obtained by objective methods (*27–30*).

In Fig. 3 calibration of physicians' subjective probability estimates are compared with objective probability estimates derived from the APACHE III database (*18*). Thirteen experienced ICU clinicians in 11 ICUs within nine tertiary care centers were asked to record, during the initial day of ICU treatment, their best numerical estimate of the patient's probability of survival to hospital discharge. Estimates were attempted on 1100 patients and obtained on 850 within the prescribed 24 hours, then compared to the objective probability estimates independently calculated by the APACHE III system with data from the same time period.

Both approaches discriminated survivors from nonsurvivors reasonably well: The objective estimates had an ROC area of 0.88 compared to 0.85 for the subjective estimates. The objective estimates, however, were much better calibrated. This sample had 20.7% in-hospital deaths; the objective estimates averaged 19.7% ($\chi^2 = 1.1$); and the subjective estimates averaged 25.5% ($\chi^2 = 14.7$, $P < 0.001$). The 45 patients the clinicians identified as being at or over a 90% mortality risk of hospital death actually had only a 62% death rate ($\chi^2 = 73$, $P = 0.001$). The 16 patients APACHE III estimated at a 90% or higher mortality all died ($\chi^2 = 0.8$). These findings are in agreement with previous studies that analyzed smaller numbers of patients in individual hospitals as well as with findings in other disciplines comparing objective and subjective estimates (*31*).

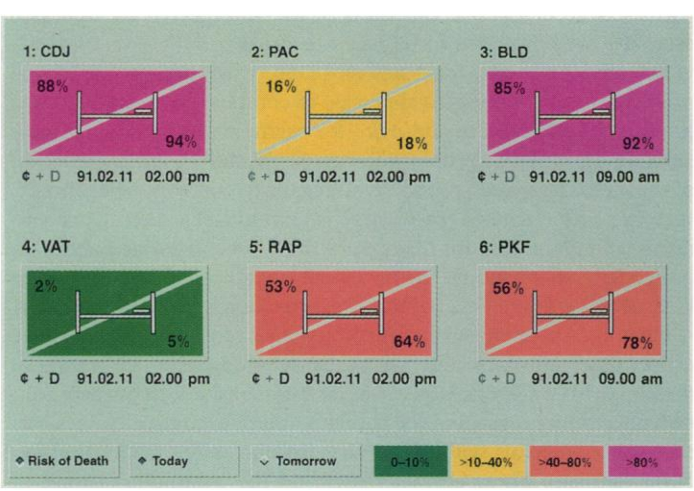

Fig. 2. Clinical decision support computer screen from APACHE III management system providing risk estimates for ICU and hospital mortality. This risk of death display designates a stylized bed space with patient's initials along with the date and time the system last received information to update estimates. The percentage in the upper triangle is the risk of death in the ICU; the lower percentage, risk of death during entire hospitalization. Each estimate is based on a predictive equation that uses disease, treatment location prior to ICU admission, and most recent APACHE III score.

Objective probability estimates on later days do not, as might be expected, increase the overall explanatory power of the predictions for the group as a whole, because patients at low and high probabilities of death often are either discharged or die early in hospitalization. Objective probability estimates of more complex outcomes or of mortality risk over a longer time period have not yet been developed fully enough to have confidence in their predictive accuracy. One would want to combine into one summary measure the elements that describe, for each plan of care, the impact on the patient—a combination of length and nature of life as well as the impact on close family (*32*). Pursuit of this objective is complicated by many measurement problems including the fact that, although most individuals find some outcomes (such as a vegetative state) to be worse than death, they vary in the specific ordering of preferences. Analytic approaches to model complex outcomes and qualities of life need to be developed (*33*).

Scientific Aspects of Objective Probability Estimates

The physician's first obligation in medical decision-making is to discern the likely effects of each major alternative plan of care. The major scientific contributions of objective probability estimates are the reduction of interphysician variation and the improvement in overall calibration and discrimination in prognostications. A reference database and a predictive algorithm can yield both an objective probability estimate expressed as a continuous risk measure and a confidence band around that point estimate, thus quantifying its uncertainty. The former is essential for scrutinizing thresholds for specific plans of care, whereas the latter quantifies the risk of error in relying on the estimate. Both tasks are very difficult for individuals to perform accurately (*34*).

Because objective probability estimates are reliable and standardized, they also provide an excellent method for judging the incremental efficacy of new therapy. In contrast to categorical estimates, a continuous probability estimate, by summarizing variation in a unitary measure, can reduce the number of observations necessary for research even while enhancing statistical confidence (*35*). This reduction of otherwise unexplained variation among patients is essential in evaluating most new therapies, which have a much narrower comparative therapeutic efficacy than earlier breakthroughs.

Objective probability estimates can assist clinicians in making decisions in four distinct ways: (i) by providing greater certainty about the expected effects of treatment, (ii) by improving understanding of specific prognostic elements and their relative influence on outcomes, (iii) by reducing reliance on commonly used clinical rules that may be biased, and (iv) by providing an explicit opportunity to review and compare explicit probability thresholds for important clinical decisions.

A physician treating an acutely ill patient ordinarily applies therapy, expecting improvement in the patient's physiologic condition and thereby improvement in the likelihood of survival. The simultaneous application of multiple therapies (respirator, dialysis, vasoactive drugs, for example) makes it difficult to determine whether any one treatment is effective. Objective probability estimates provide a summary measure of the composite efficacy of therapy over time.

With the increasing prevalence of elderly persons, the physician's ability to estimate the incremental contribution of age to prognosis is especially important. Although advanced age correlates with decreased physiologic reserve and a decreased likelihood to survive serious acute illness despite advanced medical care, individuals vary substantially. Without an adequate measure of physiologic reserve, however, physicians often rely on chronologic age in determining the likely efficacy of therapy. Objective probability estimates incorporate age as a predictive variable, assigning an appropriate coefficient relative to other more influential predictive variables such as physiologic instability, and thereby ensuring that chronologic age is not disproportionately influential. Within the APACHE III prognostic system, for example, chronologic age only accounts for 3% of total explanatory power; acute physiologic abnormalities account for 86% (*18*).

Medical decision-making is distorted in the same ways as other human decisions (*36*). The most recent experience disproportionately influences probability estimates for current patients. Clinicians with substantial experience with critical illness will be influenced differently by prior probabilities for an event than less experienced physicians. The clinician's recall of rare cases often introduces a highly biased estimate. Objective probability estimates help mitigate these effects.

Physician thresholds vary in choosing to undertake potentially dangerous therapy; these thresholds may also differ when used for individuals as compared to determining practice guidelines for groups (*37*). For an individual patient, the threshold for action is conditioned on the probability and value of the potential net benefit offered by the treatment for this individual alone. For groups, the impact on others and the total cost to society may are also be important. In practice, however, neither physicians nor society can readily quantify these thresholds. Objective probability estimates allow scientific examination of thresholds for specific therapeutic actions and education to expand clinical experience and to improve calibration and discrimination. Determinations of comparative entitlements at times of triage should also use objective probability estimates to avoid bias and ensure equity (*38*). In all these applications, a confidence estimate and sample size should be provided.

Ethical Aspects of Objective Probability Estimates

Objective probability estimates have profound impacts on two central arenas of ethical concern in medical care: decision-making for individuals and social justice in allocating fairly the benefits and burdens of the health care system.

Decision-making. Society's growing protection of the patient's authority to control his or her life, the increasing prevalence of chronic disease, and the explosive growth in the number and power of partially effective treatments have encouraged more collaborative decision-making rather than decisions based on professional standards or the physician's own predilections (*39*). Collaborative decision-making requires a shared undertaking of the likely futures for the patient under available plans of care (*40*). Anchoring such estimates with valid and reliable morbidity and mortality estimates would be especially useful in mitigating the individual physician's subjective bias or inexperience. Objective probability estimates can also help the patient and family accept reality.

In 1983, nearly half the deaths occurring within ICUs followed formal limits on therapy (*41*). Objective probability estimates could support making these decisions appropriately, especially when patients, family members, and clinicians initially have differences about the appropriateness of therapy. Variations in background, experience, emotions, and expectations among these individuals can be expected sometimes to create discord. Indeed, considering how fundamental probability estimation is in any discussion of alternative therapies for the critically ill, it is remarkable that society has not made the necessary research a priority. In relying solely on human judgment, many severely ill patients and their families may have been harmed by pursuing normalization of physiology or by precipitating confrontation, at times when compassion and relief of suffering would have been a higher priority.

Although professionals seldom employ objective probability estimates now, use of these in numerical estimates certainly would increase the precision of communication by reducing reliance on emotional, poorly calibrated, and routinely misunderstood qualitative descriptors such as "hopeless," "unsalvageable," and "terminal" (*42*). Currently available, numerical mortality estimates must be supplemented with mostly subjective estimates of quality of life. Increased accuracy and precision is to be expected as objective estimates are developed for all key outcomes.

Directly combining measures of quality with measures of length of life requires adopting a value scale to combine outcomes (various levels of both disability and pain, for example) and including early death in the ranking. People will, very likely, differ in their valuation of these characteristics, especially in regard to controversial concepts such as productivity. Even if there is enough societal consensus to justify a single scaling for many purposes, decision-making about an individual patient should, to the extent possible, adopt the patient's view of the relative desirability of various outcome states (*39, 40*).

Defining futility regarding future therapy requires both objective probability estimates and an evaluative judgment in setting a threshold (*43*). Objective probability estimates will frequently confirm uncertainty regarding the patient's ability to survive. Sometimes confidence intervals will be too large to encourage reliance on the point estimate. These characteristics and the continuous nature of the estimates must be emphasized, lest objective estimates be misunderstood as decision rules, which might restrict rather than enhance clinical reasoning.

Objective probability estimates will not resolve most ethical controversies. Objective probability estimates should also not be expected to overwhelm deeply held personal or religious beliefs regarding the appropriateness of the individual influencing the time and circumstances of their dying. Physicians should, however, recognize the potential of objective probabilities to differentiate the symbolic uses of medical care from its clinical effects and to reduce the human tendency to be awed by coincidence.

Social justice. Objective probability estimates can also form the basis of more equitable comparative entitlement determinations in response to scarce resources. Because the proportion of the United State's national wealth allocated to medical care is the largest in the world and because at least some of that investment is not efficacious, it would be ethically appropriate to set as a priority the reduction of treatment that provides marginal or negative benefits. Society should want to make widely available those courses of care that yielded substantial improvements for patients and had relatively low societal costs. Objective probability estimates could provide powerful guidance for such an effort. As the expected benefits from a treatment decrease or costs increase, the treatments should be more difficult to obtain. Some treatments, established to be of no net benefit, ordinarily should not be available. The concept of medical futility must rest upon probability estimates, though the threshold for limiting or barring access will be political questions as well.

Within institutions facing resource limits, an approach based on objective data would also be a practical and preferable alternative to current practices. For example, when intensive care services are limited relative to demand, access is frequently denied to patients with a low severity of illness and to those who present for treatment later (*44, 45*). Because the anticipated efficacy of therapy is much less obvious, it has not been readily incorporated into decision-making. As a result, severely ill patients with immediate requirements for life-sustaining treatment are given preference for admission even if the likelihood of benefit is extremely small. A measure of the probability of benefiting from advanced medical treatment and the magnitude of the benefit expected could radically reshape this heuristic.

Objective Probability Estimates and Health Policy

Despite growing disillusion with the current health care system on both a national and individual level, efforts at reform and experimentation have concentrated in the financing, legal, and insurance sectors rather than on the scientific or ethical foundations for the delivery of care. Recent efforts to control the growing demand for medical services have concentrated on major procedures, such as selected surgeries, or on particularly vulnerable portions of the population, such as the poor relying on Medicaid (*46*). This has contributed substantial limitations of access to primary health care for the poor, aged, and disabled and has increased disparities in health status within the U.S. population (*47*). The reforms have limited the clinical freedom of individual physicians. These efforts are also increasing the administrative burden and the total cost of providing care (*48*). The United States now has the largest proportion of uninsured persons of any developed country and the highest per capita cost of medical care.

The largest proportion of expenditures for medical care ($255 billion out of $540 billion in 1988) were for acute in-patient services (*49*). In addition, a substantial proportion (28%) of Medicare program expenditures are for patients within 6 months of their deaths (*50*). Overall, approximately 5% of the U.S. population accounts for 50% of total medical care expenditures each year. Some of these individuals suffer an unexpected catastrophe; more are both chronically and acutely ill (*51*). The current emphasis on experience rating in health insurance exploits the concentration of expensive care on a few members of society and makes financial considerations (preexisting medical condition or the current insurance coverage of an individual) a determining factor in decisions about access to care.

Increased research and development on predictive methods in medical science could counterbalance these trends by encouraging priority determinations based on the relative ability to benefit from medical services (*52*). Objective probability estimates offer the promise of more equitable and ethically appropriate delivery of advanced medical care to individuals as well as to populations.

Wider use of objective probability estimates depends on addressing several practical issues. Most important is the current unfamiliarity of physicians with such estimates and their origins and manipulation. Physicians need to understand the conceptual origins and practical limitations to the use of objective probability estimates as a new intellectual basis of critical decision-making (*53*). Evaluations will detect the impact of these estimates. Experiments with new approaches to formats and displays of probability estimates, including confidence intervals, are required. Clinically accurate and comprehensive databases need to be collected, made available, and extended beyond intensive care units. There must be a better understanding of the role of patient preferences and values to ensure that increased availability of numerical probabilities does not allow them to dominate other considerations. Finally, no matter how sophisticated they became, objective probability estimates represent substantial simplifications of very complex systems. Opportunities to exercise human discretion must be kept open.

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Quantum Mechanical Calculations to Chemical Accuracy

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Full configuration-interaction (FCI) calculations have given an unambiguous standard by which the accuracy of theoretical approaches of incorporating electron correlation into molecular structure calculations can be judged. In addition, improvements in vectorization of programs, computer technology, and algorithms now permit a systematic study of the convergence of the atomic orbital (or so-called one-particle) basis set. These advances are discussed and some examples of the solution of chemical problems by quantum mechanical calculations are given to illustrate the accuracy of current techniques.

THE YEAR 1970 HAS BEEN CITED (*1*) AS THE STARTING DATE for the "third age of quantum chemistry," as theory began obtaining quantitative solutions to chemical problems. Since that time, the number of problems for which theory has contributed has grown dramatically. See, for example, the review by Schaefer (*1*) where the success of theory is demonstrated on problems ranging from aiding in the identification of interstellar microwave lines to the prediction of ground-state structures, such as the $^3B_1$ state of CH_2. We contend that another large enhancement in the utility of theory for solving chemical problems occurred in about 1987, as a result of benchmark calculations that considerably enhanced our understanding of the fundamental approximations used in standard quantum mechanical approaches (*2*). This led to the observation that the largest shortcoming of the theoretical treatment was often the incompleteness of the atomic orbital (AO) basis, as opposed to limitations in the treatment of electron correlation.

In this review, we present several examples of theoretical calculations that illustrate the accuracy of present-day molecular structure calculations. It is, of course, impossible to describe all of the approaches in use today. Instead we limit the discussion to two approaches. First is the coupled-cluster singles and doubles (CCSD) method (*3*) with a perturbational estimate (*4*) of the contribution of connected triple excitations [CCSD(T)]. Because the FCI method (*5–7*) is not feasible for most systems, this is probably the most accurate, practical single-reference approach in use today. Second, we consider the multireference configuration-interaction (MRCI) approach to the correlation problem. Size-extensive modifications, such as the averaged-coupled pair functional (ACPF) approach (*8*), further extend the applicability of the MRCI approach. Multireference correlation treatments are generally the most accurate approaches, because they account for both dynamical and nondynamical correlation. These approaches have been shown (*2*) to reproduce FCI results for both the energy and molecular properties for a wide range of molecular systems.

New Insight from Benchmark Calculations

Most quantum mechanical methods attempt to solve the time-independent Schrödinger equation

$$\hat{H}\Psi = E\Psi \qquad (1)$$

where Ψ is the wave function, E is the energy, and $\hat{H}$ is the Hamiltonian. Because the electrons are much lighter than the nuclei, the electronic and nuclear motions are generally treated separately (the Born-Oppenheimer approximation). Relativistic effects are also neglected as they contribute little to valence properties. Although theoretical work (*9, 10*) directed at understanding the limitations of these two approximations has been reported, this is outside the scope of this article. With these approximations the Hamiltonian operator (in atomic units) can be written as

$$\hat{H} = -\frac{1}{2}\sum_{i=1}^{n}\nabla_i^2 - \sum_{A=1}^{N}\sum_{i=1}^{n} Z_A r_{Ai}^{-1} + \sum_{i>j=1}^{n} r_{ij}^{-1} + \sum_{A>B=1}^{N} Z_A Z_B R_{AB}^{-1} \qquad (2)$$

where Z is the nuclear charge, r_{ij} is the electron-electron distance, r_{Ai}

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