Linking Clinical Variables With Health-Related Quality of Life

A Conceptual Model of Patient Outcomes

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HEALTH-related quality of life (HRQL) is increasingly used as an outcome in clinical trials, effectiveness research, and research on quality of care. Factors that have facilitated this increased usage include the accumulating evidence that measures of HRQL are valid and "reliable," the publication of several large clinical trials showing that these outcome measures are responsive to important clinical changes, and the successful development and testing of shorter instruments that are easier to understand and administer. Because these measures describe or characterize what the patient has experienced as the result of medical care, they are useful and important supplements to traditional physiological or biological measures of health status.

Given this improved ability to assess patients' health status, how can physicians and health care systems intervene to improve HRQL? Implicit in the use of measures of HRQL in clinical trials and in effectiveness research is the concept that clinical interventions such as pharmacologic therapies can affect parameters such as physical function, social function, or mental health. However, there has been relatively little research to date that either explicitly conceptualizes the relationships of clinical variables to measures of HRQL or attempts to determine the intervening variables that mediate these effects. We believe that a clear understanding of these causal relationships will facilitate the design of optimally effective clinical interventions. As therapeutic efforts focus more on improving patient function and well being, the need to understand these relationships will increase.

One problem that has hampered progress in this area is the lack of conceptual models that specify how different types of patient outcome measures interrelate. Such a conceptualization involves the integration of two different paradigms or models of health: one held by clinicians and basic science researchers, and the other by social scientists. The models of these two academic traditions differ in purpose, methods, and intellectual history, and it is useful to compare them.

In the clinical paradigm, the "biomedical" model, the focus is on etiologic agents, pathological processes, and biological, physiological, and clinical outcomes. The principal goal is to understand causation in order to guide diagnosis and treatment. Controlled experiments are its principal methodology, and current biomedical research is directed at fundamental molecular, genetic, and cellular mechanisms of disease. Its intellectual roots are in biology, biochemistry, and physiology.

In contrast, the social science paradigm, or the "quality-of-life" model, focuses on dimensions of functioning and overall well-being, and current research examines ways to accurately measure complex behaviors and feelings. Experimental research designs are rarely possible since the focus of social science is on the way numerous social structures and institutions influence individuals. These models of health have their foundations in sociology, psychology, and economics and use concepts and methodologies often foreign to physicians and clinical researchers.

Researchers have proposed a number of conceptual models of the relationships among the components of HRQL. The development of several of these models was prompted by the observation that commonly used measures of functional status frequently include conceptually distinct constructs of disease, functional limitations, and self-rated health. However, none of these models include the full range of variables that now typically are included in HRQL assessments, most do not specify the links between biological and other types of measures, and generally, they have not been tested empirically. Although some modeling work has been done, the principal goal of the field has been to validly and comprehensively describe health status.

In this article, we present a conceptual model, a taxonomy of patient outcomes, that categorizes measures of patient outcome according to the underlying health concepts they represent and proposes specific causal relationships between different health concepts, thereby integrating the two models of health described. Because our model focuses on relationships among aspects of health, the taxonomy that we develop is not necessarily related to other classifications of health status measures. There is a conceptual difference between identifying the dimensions of health that are necessary to comprehensively and validly describe health and specifying a series of critical con-
cepts on a causal pathway. Since the latter is our goal, some existing measures of HRQL will fit at one level in our model, and other measures at different levels. Some existing measures contain concepts from multiple levels. It is not possible to create a one-to-one relationship between our levels and existing measures because our causal model and the numerous existing measures have fundamentally different, though complementary, goals.

A useful model should be relatively simple, intuitively reasonable to clinicians and researchers, and empirically testable, and these principles have guided the model's design. The ultimate promise of the ability to measure HRQL will not be fulfilled until it has clear applications to clinical care. We believe that this conceptual model is a useful step toward that goal.

A CONCEPTUAL MODEL

Definitions

The concept of quality of life is distinct from health, though related to it.\textsuperscript{5,24} Economic, political, cultural, and spiritual factors may affect overall quality of life, but are generally not considered to fall under the purview of physicians and health care systems.\textsuperscript{25,26}

Clinicians and clinical researchers are usually interested in HRQL, or the aspects of quality of life that relate specifically to a person's health.\textsuperscript{27,28} Health status and HRQL can refer to different concepts,\textsuperscript{31,32} but in this article we use the terms interchangeably.

Most conceptualizations of HRQL include the dimensions of physical functioning, social functioning, role functioning, mental health, and general health perceptions.\textsuperscript{29,30} with important concepts such as vitality (energy/fatigue), pain, and cognitive functioning subsumed under these broader categories.\textsuperscript{30,36} Clinical data, such as measures of biological and physiological function, tissue diagnoses, and patient-reported symptoms, are only occasionally included in conceptualizations of HRQL.\textsuperscript{17,24,30,36}

When we use the phrase "traditional clinical variables," we are referring to data that come from medical histories and physical examinations, supplemented by what Feinstein\textsuperscript{36} has called "paraclinical" data, such as pathology reports and results of laboratory tests.\textsuperscript{36}

Description of the Model

Measures of health can be thought of as existing on a continuum of increasing biological, social, and psychological complexity. At one end of the continuum are biological measures such as serum albumin levels and hematocrit, and at the other are more complex and integrated measures such as physical functioning and general health perceptions. These relationships, as we conceptualize them, are displayed schematically in the Figure and described in detail herein. The arrows in the Figure do not imply that there are not reciprocal relationships. Neither does the absence of arrows between nonadjacent levels imply that there are not such relationships. The main purpose of the Figure is to distinguish among conceptually distinct measures of HRQL and to make explicit what we think are the dominant causal associations.

The following five subsections of the paper will describe each of the five levels in the model: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. Included in each will be a description of the health concepts represented by each level and a justification for their inclusion, a description of what is known about the relationships of concepts at that level to levels preceding it in the model, suggestions about what important determinants of the concepts at that level might be, and comments about what future empirical work might show, where relevant. Because the relationship of emotional or psychological factors to each of the levels in the model is quite important, particularly complex, and not fully shown in the Figure, it will be discussed separately.

Biological and Physiological Factors

The most fundamental determinants of health status are molecular and genetic factors, but we begin our model with biological and physiological factors because these are commonly conceptualized, measured, and applied in routine clinical practice. The assessment of biological and physiological factors focuses on the function of cells, organs, and organ systems. Examples include the following: diagnoses such as pulmonary tuberculosis, inflammatory bowel disease, or small cell lung cancer; laboratory values such as serum hemoglobin or creatinine; measures of physiological function such as pulmonary function tests; and physical examination findings such as a systolic ejection murmur, pulmonary wheezes, or splenomegaly. Also included at this level in the model are factors whose effects on health are principally mediated by changes in cell, organ, or organ system function.

Symptoms

When symptoms are assessed, the focus shifts from specific cells and organs to the organism as a whole. Several different classes of symptoms have been described. Physical symptoms have been
defined as "a perception, feeling or even belief about the state of our body." Psychophysical symptoms have been referred to as symptoms "primarily associated with mental health" or symptoms not clearly physical or psychological in origin. Less clearly conceptualized are emotional or psychological symptoms such as fear, worry, and frustration. Emotions and physical symptoms tend to be related when studied empirically, and causal relationships clearly can go in both directions. To include all of these different phenomena, we define a symptom as a patient's perception of an abnormal physical, emotional, or cognitive state.

A number of processes usually have occurred by the time a patient with a symptom sees a physician. The patient has perceived some sensation, a judgment has been made about the origin, importance, and meaning of the sensation, and finally, the decision to seek medical attention has been made. These processes, and the patient symptom reports that result, are influenced by a number of demographic and cultural factors. Symptom reports, therefore, are expressions of subjective experiences that summarize and integrate data from a variety of disparate sources.

To what extent are symptom reports determined by biological or physiological factors? The relationship between biological or physiological variables and symptoms is complex. Certain critical biological and physiological variables can be profoundly abnormal without the patient having any symptoms. For example, the pulmonary function of a patient with chronic obstructive lung disease as assessed by forced expiratory volume in 1 second (FEV1) may have decreased to 30% of normal before the patient complains of respiratory compromise, and a left main coronary artery may be 70% occluded without the patient having symptoms of cardiac ischemia.

The other extreme is represented by conditions such as depression, for which no biological or physiological abnormalities may be clinically identifiable, but a wide variety of symptoms are present. In clinical practice, anywhere from 30% to 80% of patients who see a physician may have conditions for which no physiological or organic cause is found after routine investigation. Empirical studies illustrate the complexity of the relationships of biological and physiological factors to symptom reports. In a study of benign prostatic hypertrophy, there was no association between urodynamic indices of obstruction and obstructive symptoms. In a controlled, double blind, crossover trial of plasmapheresis for rheumatoid arthritis, there were statistically significant reductions in the erythrocyte sedimentation rate, the rheumatoid factor titer, the hemoglobin level, and serum IgM and C3 in the active treatment groups. However, this was not accompanied by improvements in any of seven measures of clinical improvement, including a subjective assessment of general status and joint symptoms, morning stiffness, grip strength, and walking time.

A recent study of chronic obstructive pulmonary disease showed little or no correlation between dyspnea and FEV1 at base-line, and several other studies have shown poor correlations between changes in dyspnea and changes in FEV1. Studies of patients seeking care for cardiac palpitations have shown that there is little correspondence between documented arrhythmias and patients' symptom reports. In a randomized controlled trial of large-dose antacids for duodenal ulcer, endoscopic healing correlated poorly with symptom relief. Studies of radiological imaging show that there is little correlation between radiological abnormalities and back pain, whether the imaging modality is plain x-ray films, computed tomographic scanning, or magnetic resonance imaging. These results emphasize the need for caution in the way measures of biological and physiological function are interpreted and applied.

Patient-reported symptoms not only cause patients to enter the medical system, they also may affect subsequent use and the costs of medical care. Given that biological and physiological factors have an inconsistent relationship to symptoms, it is unlikely that treatments directed at biological and physiological factors alone, even if they can be identified, will be fully effective in the relief of symptoms. Research that explores other likely determinants of patient-reported symptoms such as psychological factors, patient expectations, social factors, and aspects of the physician-patient relationship may help clinicians to address better both the clinical and nonclinical factors related to reported symptoms.

Functioning
The next level in our model is functional status, and like symptom status, it is an important point of integration. Measures of function assess the ability of the individual to perform particular defined tasks. Symptom status is one important determinant of functioning. For example, an older woman with painful hip arthritis may have reduced ability to bathe herself, walk up stairs, or do her own shopping. Other patient-specific factors will also be important, such as personality and motivation. Given two older women with similar hip conditions, the one who is more determined to be self-sufficient may function at a higher level. Many aspects of an individual's social environment also may have an important effect on functioning. A supportive family, a first-floor apartment, friends who drive her to the grocery store, and access to medical care are all examples of environmental factors that may improve this same woman's physical, social, and role functioning.

Four domains of functioning that are commonly measured are physical function, social function, role function, and psychological function. These are not the only domains that might be of interest to a patient, physician, or researcher, but there is general consensus that these four are a minimum required.

A number of studies have included biological and physiological, symptom, and functional status measures among the outcomes examined. These studies, many of which are clinical trials, demonstrate convincingly that measures of HRQL can be as sensitive to clinically important changes as traditional clinical variables and can detect important differences not assessed by such endpoints. But what are the intervening variables that mediate the effects that pharmacologic therapies have on measures of HRQL? Although there are many studies that have assessed the association between clinical measures of disease severity and measures of HRQL, only a few of these studies have explicitly modeled the relationships among biological and physiological measures, symptoms, psychological measures, social factors, and measures of function.
In a study of human immunodeficiency virus (HIV)-positive patients, the combination of symptoms and several sociodemographic variables explained from 25% to 39% of the variability in a series of measures of function and well-being. In a study of patients with the acquired immunodeficiency syndrome (AIDS), fatigue and a physical symptom score explained 55% of the variability in physical functioning.

In summary, studies analyzing the relationships between symptoms and specific dimensions of functioning suggest that symptoms and biological and psychological variables are indeed correlated with functioning, but also that variations in functioning cannot be fully explained by these variables. As expected, measures of functioning represent conceptually distinct aspects of health status. We believe that comprehensive, disease-specific measures of symptoms will prove to be excellent predictors of function, and that much of the effect of biological and physiological factors on functioning will be demonstrated to be mediated by symptoms.

This may not be the case, however. There may be important effects of clinical conditions on functioning that cannot be explained by measured mediating variables. Such relationships between nonadjacent levels that are not mediated by measured intervening variables may highlight important measurement and/or clinical issues. For cases in which there is a relationship between a condition and functional impairments that is not mediated by biomedical markers or measured symptoms, this would indicate the need to understand better the ways in which the condition affects functioning.

General Health Perceptions

Two salient characteristics of general health perceptions are that they represent an integration of all of the health concepts that we have previously discussed, as well as others such as mental health, and they are by definition a subjective rating. This and related concepts have been reviewed in detail recently. The importance of general health perceptions arises from the observation that they are among the best predictors of the use of general medical and mental health services, as well as strong predictors of mortality, even after controlling for clinical factors.

Functional status has been shown to be associated with general health perceptions, as have emotional distress and dysphoria and social factors. One recent study examined a population of medical outpatients and found that measures of hypochondriasis and somatization were the strongest predictors of general health perceptions in a model that included sociodemographic characteristics, several indices of medical and psychiatric morbidity, and functional status. We think studies that explicitly examine the association of symptoms to general health perceptions may yield important findings. General health perceptions have been shown to be related to biological and physiological factors, but because of the numerous factors affecting health perceptions, there almost inevitably will be large variations within each stratum of clinical severity.

Overall Quality of Life

Researchers frequently assess respondents' subjective well-being with general measures of how happy and/or satisfied they are with their life as a whole. Numerous typologies of well-being constructs and theories of subjective well-being have been developed and tested. A review of these theories is beyond the scope of this article, but in most theories these measures are assumed to represent a stable synthesis of a wide range of experiences and feelings that people have. As such, they should be related both to HRQL and to other salient life circumstances and experiences and can be thought of as a summary measure of quality of life. Interestingly, however, general measures of life satisfaction or happiness are not as strongly related to objective life circumstances as might be anticipated, lower levels of functional status are not necessarily related to lower levels of satisfaction, and measures of life satisfaction tend to be unstable. This may be due partially to the fact that people change their expectations and aspirations as circumstances change. Questions about satisfaction with specific aspects of a person's health, on the other hand, may be more sensitive to such changes.

The Role of Patient Preferences

Patients' preferences or values play an important role at several points in the model and are particularly important in understanding the last two levels in the model—general health perceptions and overall quality of life. For any individual, certain symptoms are more burdensome than others, and those individuals will prefer not to have those symptoms even if they may have to put up with others. For example, in a study of patients undergoing prostatectomy, it was found that among patients with "severe" symptoms, 32% reported no day-to-day limitations because of their prostate condition, and 19% reported no worry about their health because of their prostate. Among patients who had already had an episode of acute retention, 47% reported no day-to-day limitations, 19% no discomfort from the prostate, and 42% no worry about health because of their prostate. Among older men with similar prostate symptomatology, both levels of worry and limitations because of their prostate were considerably, presumably because each patient valued these symptoms differently.

Utility assessment is a methodology that elicits patients' values for particular states of health, and utilities are often used as an overall measure of HRQL. Whereas most HRQL measures assess particular health states, utility measures assess the value that individuals assign to different states. There are practical and conceptual problems with using utility assessment to measure HRQL. One of the conceptual problems is that because of the way utilities are measured, they may reflect factors other than health status, such as the value patients place on life, their risk averse, or their attitudes toward certain types of medical intervention. Probably because of such potential influences, the correlations between utility measures and measures of health status are generally only modest. The sensitivity of utilities to important clinical changes may have been good in some studies but poor in others.

The Role of Emotional or Psychological Factors in the Model

The distinction between a physical symptom and physical function is relatively clear. Hip pain in an elderly woman is a symptom, and the inability to walk up stairs is an impairment of function. Although it certainly is the case that patients who attempt to do more experience more pain, it is likely that the more consequential causal pathway is that the pain and other factors) is causing the functional impairment. Using similar logic, a psychological symptom is a feeling such as depression or anxiety, and impairment of psychological functioning would be the inability to accomplish a task that requires psychological health such as making difficult decisions or handling stressful situations.

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However, many scales that measure mental health or psychological well-being actually assess symptoms of emotional or psychological distress, not how these symptoms impair the performance of particular tasks.  

Depending on how it is conceptualized and measured, an emotional or psychological factor such as depression could be classified three different ways. Some would argue that depression has a strong biological component and would, therefore, classify it as a biological or physiological factor. A scale that specifically assessed emotional symptoms associated with depression might classify depression as a measure of symptom status. Finally, a scale that focused on the behavioral impairment associated with depression might classify it as a measure of psychological functioning.

Regardless of how emotional or psychological factors are classified, these factors can have causal relationships with variables at every level of the model, although they are not represented in the Figure. Furthermore, most of these relationships can be bidirectional. Consider the case of a diabetic with depression. Depression may cause serum glucose to rise if it makes the patient unable or unwilling to comply with an effective fingerstick and insulin regimen. Lack of interest in self-care or in seeing friends may cause measures of physical and social function to deteriorate. Finally, the effect of depression on general health perceptions and overall quality of life can be profound. Similar arguments can be made for other psychological symptoms such as anxiety, fear, and hopelessness. Reasoning in the opposite direction, worsening physical symptoms, functional impairments, and low overall quality of life all cause depression, anxiety, and fear.

Measures of psychological health and many other measures of patient outcome are empirically related to each other, defying simple unidirectional models of causation. We know, for example, that pain can cause depression, and that depression can worsen pain. Further, treatment of each can improve the other. Therefore, the causal relationships between emotional or psychological phenomena and many of the other factors in the model should be considered potentially bidirectional.

We think this issue is most salient for emotional and psychological factors, but it also is relevant for the other associations in the model. As mentioned in the introduction, the arrows in the Figure identify what we hypothesize are the dominant associations; there also may be reciprocal associations in many cases.

**SUMMARY**

Our model proposes a taxonomy or classification scheme for different measures of health outcome. We divide these outcomes into five levels: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. In addition to classifying these outcome measures, we propose specific causal relationships between them that link traditional clinical variables to measures of HRQL. As one moves from left to right in the model, one moves outward from the cell to the individual to the interaction of the individual as a member of society. The concepts at each level are increasingly integrated and increasingly difficult to define and measure. At each level, there are an increasing number of inputs that cannot be controlled by clinicians or the health care system as it is traditionally defined.

**IMPLICATIONS**

The principal goal of clinical care is improvement of patient outcomes. The optimal design of interventions to improve patient outcome requires identification of causal pathways that link different types of outcome to each other. To use an analogy from the biomedical model, clinicians and researchers would benefit from a thorough understanding of each step in the pathogenesis of impairments in specific dimensions of HRQL. The relationships between traditional clinical variables and health status measures have not been adequately conceptualized in much of the research done to date, and we present a model that we believe facilitates the understanding of these associations. This model should be useful in the formulation of strategies to improve function and HRQL.

For clinicians, this model has diagnostic and therapeutic implications. Although good clinicians have always recognized the importance of diagnosing functional impairments, empirical studies show that physicians do not assess patient-perceived health status accurately. Also, physicians may overestimate the impact of biological and physiological variables on symptoms and functioning. Part of the reason for this may be that most physicians have little training in the assessment of functional disorders. These findings emphasize the importance of measuring HRQL using standardized instruments and the need for further studies that quantify these relationships.

Currently, there is no clear linkage between the diagnosis and treatment of HRQL "problems," though there are considerable efforts in this area. Several studies suggest that assessment of HRQL can lead to improvements in HRQL. However, these studies were all done in structured geriatric evaluation unit settings where comprehensive medical, social, and functional evaluations were performed, and deficiencies were clearly linked to specific interventions. Other studies in which clinicians were provided with HRQL data without any linkage of this diagnostic data to therapeutic solutions did not demonstrate improvements in health status.  

A study by Rubenstein and colleagues is an example of how HRQL can be measured and used in clinical practice. In that study, HRQL in ambulatory patients was evaluated using a scale that assessed physical, psychological, and social functioning and general health perceptions. A randomly selected half of the physicians in the study received four reports describing the HRQL of each of their patient studies over a 1-year period. The goal of the study was to evaluate whether providing such information to physicians would improve their patients' outcomes. Unfortunately, there were no significant differences between experimental and control group patients on any health outcome measured. For physicians to embrace the concept of measuring HRQL, it must be clear how they will be able to use this data to design therapeutic interventions. The conceptualization and measurement of the relationships of clinical variables to measures of HRQL described herein should facilitate the establishment of this important linkage between diagnosis and therapy.

The implication and challenge for researchers is to measure these various outcomes and to develop statistical models that explicitly estimate the size of the effects specified in the model. Only by having a clear, quantitative understanding of the determinants of HRQL can we hope to develop rational and cost-effective strategies to remedy HRQL problems. The development of treatment strategies requires not only that we identify the key factors that combine to determine function and quality of life, but also that we understand their relative importance and the degree to which they can be altered or modified. We need to identify risk factors for poor health status that can be modified by physicians and health care systems. If we succeed in this effort, the measurement of health status is likely to become an increasingly useful clinical tool.

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