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Quality of Life in Rare Genetic Conditions: A Systematic Review of the Literature

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Abstract

Quality of life (QoL) refers to an individual's sense of overall well-being encompassing physical, psychological, emotional, social, and spiritual dimensions. Although genetics healthcare providers strive to promote patient well-being, and the term QoL is often invoked to refer to this outcome, there is lack of clarity as to what actually constitutes QoL from the patient's perspective. This systematic literature review aims to summarize and integrate research findings to help elucidate how healthcare providers can more effectively enhance the QoL of patients affected with rare genetic conditions. Eligible studies were those that measured QoL as a primary outcome variable using a validated, multi-dimensional scale. Detailed criteria were used to rate quality of design, methodology, and analytic rigor. Fifty-eight studies were selected for inclusion in the review, and a narrative synthesis of the data was performed. A central theme emerging from the literature is that, although genetic conditions have the potential to have significant negative consequences for individuals' lives, having a genetic condition does not necessarily entail poor QoL. Evidence demonstrates that factors beyond the physical manifestations of the disease, such as psychological well -being, coping, and illness perceptions, influence QoL and may serve as potent targets for intervention. The field of research on QoL in rare genetic conditions will be advanced by uniting around a clear conceptualization of QoL and using more rigorous methodology with comprehensive measures of global QoL.†

Keywords

quality of life; genetic diseases; genetic counseling; psychological adaptation

Introduction

The experience of living with a rare genetic condition is vastly more complex than its medical features. Any aspect of an individual's life may be affected. Quality of life (QoL) refers to an individual's sense of overall well-being encompassing physical, psychological, emotional, social, and spiritual dimensions. Although genetics healthcare providers strive to promote patient well-being, and the term QoL is often invoked to refer to this outcome, there is a lack of clarity as to what actually contributes to QoL from the patient's perspective. Historically, research into genetic conditions has been limited to natural history and descriptions of clinical features. In recent years, QoL has increasingly been studied in genetic conditions. Findings from this research have begun to illuminate the subjective

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experience of living with a genetic condition and the complex, often profound effects on individuals' QoL. However, progress in this emerging area of research has been hindered by conceptual and methodological issues, and the medical literature remains limited in fully representing the perspective of those affected with these conditions.

The goal of the next frontier in healthcare for individuals living with rare genetic conditions is to improve QoL, not only by advancements in medical treatment, but with interventions aimed at modifying psychosocial and contextual factors that influence QoL. Research thus far has revealed promising opportunities; yet improvements in overall well-being resulting from targeted QoL interventions are far from being realized.

Objectives

A systematic review of the literature of studies examining QoL in rare genetic conditions was conducted. The aims of this paper are to:

1. Explicate the concept of QoL.
2. Evaluate approaches to measurement and strategies in QoL research.
3. Summarize and integrate research findings to help elucidate how healthcare providers can more effectively enhance the QoL of patients living with rare genetic conditions.
4. Discuss clinical implications and directions for future research on QoL in rare genetic conditions.

Background

QoL has been defined as “a person's sense of wellbeing that stems from satisfaction or dissatisfaction with areas of life that are important to him/her” [Ferrans and Powers, 1992]. QoL encompasses all major aspects of an individual's life, including physical health and functioning, social, psychological, emotional, spiritual, and family dimensions. Importantly, QoL is not a representation of health per se. Although one's health may influence QoL, and indeed the impact of a health condition is often reflected in poorer QoL, the concept in its truest sense represents the global picture of well-being [Ferrans and Powers, 1992; Leventhal, 1997].

Theoretical Framework

Theories of adaptation are useful to framing an understanding of QoL. In the context of chronic illness and disability, adaptation is “the process of coming to terms with the implications of a health threat and the observable outcomes of that process” [Biesecker and Erby, 2008]. QoL can be conceptualized as an outcome of the adaptation process [Leventhal, 1997; Stanton et al., 2001]. Theoretical models based on stress and coping theory are especially well-suited for QoL research, because they feature concepts that clinicians can influence [Biesecker and Erby, 2008]. Stress and coping models postulate that in response to a stressor, such as having a genetic condition, individuals make cognitive and emotional appraisals of the stressor. These appraisals include perceptions of “the personal significance of the stressor, including susceptibility to the stressor and its causes, severity, and relevance to their lives,” as well as perceptions of “one's ability to cope with the problems and emotions generated by the stressor” [Lazarus and Folkman, 1984]. These appraisals direct coping behaviors, and the coping process leads to adaptation. As individuals adapt to living with the genetic condition, they gradually attain or restore optimal QoL.

Yet despite the availability of useful theoretical models in which to frame research, most QoL studies ignore theory, making it difficult to interpret the relationship of QoL to other highly correlated variables. Lack of a theoretical foundation leaves the literature without a coherent framework within which to integrate existing data into our understanding of QoL. Moreover, factors that contribute to positive QoL and greater adaptation to living with a genetic condition are largely unexamined. Facilitating adaptation to the medical, psychological, and familial implications of the condition is a fundamental goal of genetic counseling [Resta et al., 2006].

Historical Challenges in QoL Research

The lack of conceptual clarity in QoL research poses a major hurdle towards advancement of the field. Throughout the literature, the term QoL has been inexactly used to refer to a variety of related but *conceptually distinct* constructs, including functional health status, level of physical disability, clinical symptoms, psychological well-being, and mood [Anderson and Burckhardt, 1999]. The introduction of the term “health-related quality of life,” intended to distinguish QoL in health status from QoL in the broader context, has only served to exacerbate this confusion. The conceptualization of QoL-as-health is problematic, because it implies that “people make distinctions between some part of life that is influenced by health, and some other parts of life that are not so influenced” [Anderson and Burckhardt, 1999] and that QoL is merely the absence of pathology. This also assumes that individuals' perceived QoL correlates neatly with their objective or clinical health status. Objective assessments often do not accurately reflect subjective perceptions of health and well-being; therefore, it is important to capture QoL from the individual's perspective and employ patient-centered outcome measures to do so [Stevenson and Carey, 2009].

A related problem in the literature occurs when authors do not explicitly define QoL, but rather imply its meaning by the constructs measured. These omissions have led to inconsistencies and imprecision in QoL conceptualization and research. See a commentary by Anderson and Burckhardt [1999] for more in-depth discussion of the historical development and pitfalls of the conceptualization of QoL in health research.

Measurement of QoL

An ongoing challenge in the field of QoL research has been its measurement. There is debate about how to accurately assess QoL. The approach to measurement and selection of a particular instrument stem largely from the way one defines QoL. A wealth of distinct and discrepant scales have been created to measure QoL. Most consist of several subscales that encompass, at a minimum, the physical, psychological, emotional, and social domains. Although the particular subscales vary among measures, they can be grouped into physical and psychosocial domains. Broadly, there are two main approaches to measuring QoL: generic scales and disease-specific scales.

Generic Scales

Generic scales are designed to study to any health condition, and accordingly, they are most useful for making comparisons across populations. Thanks to the widespread use of these scales, normative data on healthy populations are readily available, thereby allowing comparison of affected patients to unaffected individuals. Generic scales can also be used to compare to other illness populations, assess within-group differences, and examine associations with other variables. An example of a generic QoL scale is the Medical Outcomes Study Short Form (SF-36) [Ware and Sherbourne, 1992]. This 36-item scale has eight domains that encompass physical and psychosocial components of QoL. Physical functioning, role-physical, bodily pain, and general health subscales make up the physical

component; mental health, role-emotional, social functioning, and vitality make up the mental (psychosocial) component.

Although widely used, generic QoL scales are biased for two reasons. First, most generic scales measure *status* (i.e., level of impairment or satisfaction) in the various domains of QoL, without assessing *importance* of each domain. This is a crucial weakness because it overlooks the relative meaning of the various components of QoL to each individual. In effect, by asking only about status, this imposes an objective standard of ideal QoL. This notion was articulated by Ferrans [1996], who stated that "individuals personally define what QoL is for them;" therefore, because "different people value different things… there is no single QoL for all people with the same life condition." The second weakness is that most generic scales specifically assess the impact of one's health condition on the aspects of one's life primarily related to physical functioning. This limited approach to measurement is incongruent with the definition of QoL as a global construct that includes psychological, spiritual, and social well-being.

A newer generation of generic QoL scales address these issues by incorporating importance ratings along with satisfaction ratings and by moving away from the health-related focus. An example of such a scale is the Ferrans and Powers Quality of Life Index (QLI), which consists of four domains: health and functioning, social and economic, psychological and spiritual, and family [Ferrans and Powers, 1992]. The 32 paired items assess these aspects of life in general, not specifically oriented to a health condition. For each item, respondents rate their degree of satisfaction and the level of importance, and the scale is scored weighting corresponding items against one another.

Disease-Specific Scales

More recently, disease-specific QoL scales have been developed for a number of health conditions, including a few genetic conditions, such as cystic fibrosis and sickle cell anemia. These scales resemble generic QoL scales in that they assess multiple domains. In addition, some or all of the questions relate to potential direct effects of the particular condition. For example, cystic fibrosis scales ask about the impact of pulmonary symptoms on the major domains of QoL. By their very nature, these are health-related scales, and thus do not measure QoL as a global construct. Disease-specific QoL scales may be useful for making within-group assessments but not normative comparisons. These scales also may be useful in evaluating outcomes of clinical trials specific to the condition.

Measuring QoL in Pediatric Populations

There are numerous challenges around measuring QoL in children and adolescents. Although the concept of QoL is the same regardless of age, the domains that constitute QoL differ across the lifespan. Therefore, it is necessary to employ either a pediatric QoL instrument or a QoL instrument with age-specific versions. In either case, the instrument must be validated in the age group. A controversial issue is reporting method. The underlying assumption is that the child is the best judge of his or her QoL, so a self-report scale is ideal. Indeed, a number of pediatric QoL scales are available for children as young as 5 years of age. However, self-report may not be feasible for some children, particularly those who are very young or cognitively impaired, so the parent or primary caregiver serves as a proxy. There is debate as to whether parents can "accurately" assess their child's QoL. Studies yield discrepant results between parents and children even within the same cohort. This begs the question: who is (more) correct? Do parents tend to overestimate the impact of disease on their children, and/or do children underestimate the impact? We refer the reader to a comprehensive review and commentary on the subject of QoL studies in pediatric populations by De Civita et al. [2005].

Other Approaches to Measurement

Although this systematic review focused on quantitative research, qualitative studies into QoL can yield rich data. Interview-based studies are often important as the first step in understanding affected individuals' perspectives on QoL, and, more importantly, specific factors that they consider critical to defining their QoL. Qualitative data are also important to supplement quantitative findings by aiding in the interpretation of results.

Due to the above-described limitations, many of the published studies yield incomplete data for designing interventions aimed at enhancing the QoL of patients with rare genetic conditions. There are, however, a number of excellent, valuable studies that serve as models. This review aims to summarize and integrate available high-quality research on QoL in rare genetic conditions, in order to provide a launching point for future research that will advance our understanding of QoL, both as a concept and as an important clinical outcome.

Methods

Search Strategy

Reports of original research studies on the QoL of individuals affected with rare genetic conditions were identified. Specifically, a “quality of life study” was defined as a study in which QoL, consistent with the previously described conceptual definition of the construct, was measured as a primary outcome variable using a validated, multi-dimensional scale. For the purposes of this review, a “rare genetic condition” was defined as a single-gene disorder (i.e., a condition characterized by a Mendelian pattern of inheritance) with a general population frequency of less than 1 in 2,000. This frequency threshold was selected based on the National Organization for Rare Disorders definition of a rare disease as one that affects fewer than 200,000 individuals in the United States.

Articles published through January 1, 2009 in peer-reviewed journals were identified by searches of PubMed, Scopus, and Web of Science. Database searches were conducted using the keyword combinations including “quality of life,” “genetic disease,” “congenital disease,” and related MeSH terms. Additional reports were identified by hand-searching the references of the retrieved articles.

Selection Criteria

Detailed selection criteria were defined by the authors prior to embarking on the systematic review. The criteria, which comprised basic inclusion criteria as well as quality criteria, were developed based on a preliminary review of a random subset of relevant QoL studies and informed by theoretical and conceptual literature.

The three basic inclusion criteria are summarized in Table I. First, the population under study was individuals *affected* with *rare genetic conditions*. Familial cancer syndromes (e.g., hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, and hereditary breast and ovarian cancer) were excluded from this review, as there is an extensive body of literature on QoL among cancer patients. Studies with mixed populations including genetic and non-genetic conditions that did not report subgroup analyses (i.e., a subgroup consisting only of individuals affected with the rare genetic condition) were also excluded. Studies located in developing countries, as designated by the International Monetary Fund, were excluded, because it is reasonable to expect that the inherent disparities in overall population health would preclude accurate comparison and generalizability with studies from developed countries. Second, only articles reporting *original research studies* were included. The third inclusion criterion related to the purpose of the study; *at least one primary aim was to describe QoL and/or predictor variables or factors associated with QoL for rare genetic*

conditions. Clinical trials of a drug, surgery, or medical intervention on a clinical outcome were excluded from this review, because those studies were designed to evaluate the effectiveness of the medical intervention, rather than to understand QoL.

Articles that met basic inclusion criteria were further evaluated for quality based on criteria summarized in Table II. Each article was evaluated for the quality of the study itself (design, methodology, and analytic rigor), as well as for specificity in reporting the research methods and results.

Study Selection

The literature searches and reference mining yielded a total of 1,099 titles. The authors independently sorted and evaluated the articles based on standardized selection criteria, with disagreements resolved by discussion. The selection process consisted of three rounds of examination, culminating in the final body of literature selected for inclusion. The flow of literature through the selection process is depicted in Figure 1.

Data Extraction

The first author extracted data from the selected studies. Information was extracted on: study population, recruitment source, study design, QoL instrument, key predictor variables, and measures. Each study was analyzed for the primary outcome variable of QoL. Topics of interest were: statistical comparisons with healthy controls/population norms, statistical comparisons with other disease populations, and analysis of associations with key disease-related and psychosocial predictor variables. Frequencies of data were tabulated. Articles were grouped by condition and by topic categories. Summary and evidence tables were created. Because the studies were too heterogeneous to permit statistical pooling, a narrative synthesis of the findings was performed, taking into account methodological quality and analytic rigor in the examination and reporting of findings.

Results

Fifty-eight QoL studies of 30 distinct rare genetic conditions were selected for inclusion in the review and analysis. Because several of the studies were reported in more than one article, the body of literature covered in this review consisted of 72 articles in total. Details of each study and selected findings are presented in Table III.

Genetic Conditions

The 30 rare genetic conditions represent a diverse spectrum of disorders (Table IV). Although it is difficult to categorize each condition precisely, the groupings include neuromuscular and neurologic, metabolic, dermatologic, chromosomal, connective tissue, blood and vascular disorders, and skeletal dysplasias. The conditions also vary in illness typology; that is, age of onset, disease course, morbidity and mortality. Cystic fibrosis and neurofibromatosis type 1 were the most frequently studied conditions, with seven studies each.

Participant Characteristics

Forty studies focused on adults, whereas 12 studies focused exclusively on pediatric populations (children and adolescents) using a pediatric-specific QoL instrument or an instrument with age-appropriate versions. Six studies assessed QoL across the lifespan, with participants ranging in age from childhood through adulthood. In the eight studies that assessed children's QoL by both proxy- and self-report, there was some agreement between parents' assessments and their children's self-reported QoL; however, in several studies, the parents rated the QoL of their children significantly lower (poorer).

Recruitment

The majority of study populations were comprised of patients from clinical or hospital settings. Nine studies recruited participants from support organizations, such as the National Marfan Foundation [Peters et al., 2002]. These two recruitment methods each have their advantages and disadvantages regarding recruitment/selection bias. One could argue that the clinic-based studies oversampled more severely affected individuals, since they are more likely to seek medical care from a specialized clinic than less severely affected individuals. On the other hand, members of support organizations may differ from non-members in relevant ways; for example, individuals who are having difficulty coping with their disease may be more likely to seek support than individuals who are coping well. Interestingly, two studies perhaps overcame the threat of recruitment bias by identifying participants directly from the general population, thereby reaching a spectrum of affected individuals in the geographic region. Walsh attempted to include all males with hemophilia from a distinct Canadian kindred who share the same founder mutation [Walsh et al., 2008], and Ahlstrom et al. [1994] identified all eligible individuals with neuromuscular disorders in one county; both studies achieved high response rates.

Sample Size

Sample sizes varied widely, ranging from 20 to 568. Eighteen studies included less than 50 participants, 6 of these studies had less than 30 participants. Twenty-two studies had at least 100 participants. The average sample size was 108, median sample size was 77. In total, 6,270 subjects were reported. Most articles did not report power analyses; therefore, it was difficult to judge the whether these studies had sufficient power to detect statistically significant differences. Caution must be used in interpreting the findings of the smaller studies, likely underpowered to detect small or even moderate effects.

Study Design and Objectives

All of the studies were descriptive in nature. Broadly, the descriptive aims can be summarized as: *quantification* (what is the QoL of affected individuals?), *comparison* (how does the QoL of affected individuals compare to unaffected individuals and/or patients with other chronic health conditions?), and *correlation* (what factors are associated with QoL?). The studies were infrequently hypothesis-driven. The vast majority were cross-sectional in design. The five longitudinal studies had follow-up periods ranging from 1 to 10 years. Three studies utilized a case–control design, with healthy matched control individuals. In two of these studies, unaffected first-degree relatives served as the matched controls [Gollust et al., 2003a; Walsh et al., 2008]. Disappointingly, none of the 58 studies were of counseling interventions aimed at enhancing QoL.

QoL Instruments

An array of QoL scales were used (Table V). By far, the most popular instrument was the SF-36, which was employed in 30 studies. A number of pediatric QoL scales, such as the Child Health Questionnaire, were used in studies of children. Of the studies included in our review, cystic fibrosis was the only condition that had its own disease-specific QoL scale. Dermatologic-specific QoL scales (i.e., designed for use in any condition that affects the skin) were used in studies of neurofibromatosis type 1 and porphyria. Despite the variety of different QoL scales used, each with its own set of domains and scoring system, it is possible to make comparisons of the findings across studies that used different scales by grouping the QoL domains into two general categories: physical and psychosocial aspects of QoL.

Overall Synthesis of Findings

Genetic conditions have the potential to have major negative impact on individuals' lives. Many of the studies found that QoL of affected individuals was significantly poorer than their unaffected counterparts. An important pattern emerged: physical and psychosocial aspects are perceived differently. Some studies found no impairment in physical domains of QoL, but significantly poorer psychosocial QoL compared to unaffected individuals. This demonstrates that individuals who are objectively “healthy” may still experience lower QoL. Factors beyond the physical manifestations of the disease influence QoL. Overall, the findings highlight the subjective nature of individuals' perceptions of their QoL.

Importantly, several studies found that individuals with genetic conditions experienced *higher QoL* than their unaffected peers. For example, patients with hemophilia had significantly more positive psychosocial QoL than healthy controls [Solovieva, 2001; Solovieva et al., 2004]. Even more remarkable is the finding by Grootenhuis et al. [2007] on adolescents with muscular dystrophy, whose perceived QoL in the physical functioning domains was significantly better than that of their unaffected peers. The authors posited that living with a progressive disease changed patients' values in such a way that they respond differently than healthy children. In the health psychology literature, this concept of reframing to adjust expectations and thus satisfaction is referred to as response shift. It remains inadequately studied in living with rare genetic conditions.

Predictors of QoL: Disease-Related Factors

Of the 41 studies that investigated relationships between QoL and other variables in order to identify predictors or determinants of QoL, 38 examined disease-related factors, such as clinical severity, degree of disability or impairment, and frequency of medical complications. As expected, many of these studies found that disease-related factors have a negative impact on QoL among individuals with genetic conditions. Typically, these factors are strongly correlated only with physical dimensions of QoL. Clinical variables appear to have much less of an impact on psychosocial QoL, even among individuals with poor psychosocial QoL. Many studies found that clinical variables explained a relatively small or insignificant amount of the variance in psychosocial QoL. Furthermore, several studies found that clinical severity was not significantly related to any domains of QoL. Individuals with more severe disease do not necessarily have poor QoL. The converse is also true; individuals who are mildly affected physically may experience poor QoL. The data highlight the importance of studying non-clinical factors that affect QoL.

Predictors of QoL: Psychosocial Factors

Thirteen studies examined associations between psychosocial factors and QoL. These factors included: psychological well-being (6), coping (5), illness perceptions (3), family functioning (2), and self-esteem (1). Overall, these studies reveal strong correlations of each with QoL and demonstrate the importance of psychosocial factors in determining an individual's QoL.

All six studies that measured psychological well-being found strong negative associations with QoL [Piccininni et al., 2004; Carel et al., 2005; Szyndler et al., 2005; Antonini et al., 2006; Riekert et al., 2007; Havermans et al., 2008]. Individuals with symptoms of depression, anxiety, and psychological distress generally had poorer QoL in physical as well as psychosocial domains. Self-esteem and illness perceptions were also strong predictors of QoL [Helder et al., 2002; Gollust et al., 2003a; Geisthoff et al., 2007]. The matched case–control study on achondroplasia by Gollust [2003a] is particularly noteworthy, because it showed that self-esteem and perceived seriousness were the strongest predictors of QoL,

independent of affected status. This supports the notion that it is an individual's feelings and beliefs that determine their QoL—more than having a genetic condition.

In the stress and coping theoretical framework, coping is posited to be the mediator between the stressor (having a genetic condition) and QoL. Indeed, coping strategies were found to be significant predictors of QoL [Ahlstrom and Sjoden, 1996; Natterlund et al., 2000; Helder et al., 2002; Berglund et al., 2003; Szyndler et al., 2005; Abbott et al., 2008]. Although a particular coping strategy is not inherently good or bad (i.e., adaptive or maladaptive), some strategies appear to be more effective than others in adapting to living with a genetic condition. The use of avoidance, distraction, and disengagement techniques were associated with lower QoL in some studies. Individuals with more fatalistic or helpless attitudes also tended to have lower QoL. On the other hand, acceptance, optimism, and hopefulness were associated with higher QoL. Results from the study on adults with Ehlers–Danlos syndrome [Berglund et al., 2003] are especially compelling. Using validated instruments, they explored “Acceptance of Disability,” a construct similar to psychological adaptation, and “Sense of Coherence,” which encompasses one's life orientation and ability to cope with stressors. Both constructs were found to be robust predictors of positive QoL.

Family functioning also appears to significantly influence QoL among children and adolescents with genetic conditions. In a study on neurofibromatosis type 1, affected children/adolescents from families with greater cohesion and lower conflict had significantly better QoL [Graf et al., 2006]. Szyndler [2005] found similar results regarding family cohesion and conflict for teens with cystic fibrosis; in addition, teens with greater independence within the family had significantly higher QoL on some domains than their less-independent peers.

Discussion

The large number of quality studies aimed at assessing QoL among individuals affected with rare genetic conditions is heartening. They help to enhance understanding of the broader experience of living with a genetic condition. Yet there remains in the literature an emphasis on the bio-medical model that fails to encompass a more comprehensive and subjective self-assessment. In the health psychology literature, comprehensive measures of QoL as described are used more routinely. Thus, studies of rare genetic conditions would benefit from following suit.

Of the studies that examined predictors of QoL, most focused on disease-related variables and resulted in mixed evidence regarding the importance of factors such as clinical severity in influencing QoL. Far fewer studies explored the impact of psychosocial factors, but those that did revealed strong correlations of these variables with QoL. They reveal promising opportunities to enhance QoL. Clearly, there is more to QoL than physical health and functioning. For the majority of genetic diseases, there is no cure and medical treatments are limited in their ability to ameliorate the physical effects and medical complications. Certainly we, as genetics healthcare providers and researchers, should still strive to find effective treatments, and QoL is an important outcome measure to include in clinical trials [Stevenson and Carey, 2009]. Yet, we must also attend to factors that are potentially and more readily modifiable: psychosocial factors.

Interventions aimed at enhancing QoL by adjusting psychosocial factors need to be designed and tested. For children and adults living with rare genetic conditions, the stress and coping theoretical framework can inform the research. Interventions might aim to adjust appraisals of the stress evoked by the threat of the condition. One approach might be to enhance feelings of control over the condition or its implications and/or to enhance self-efficacy

(confidence in one's ability to do something about the condition or its implications). Another approach might be to enhance the effectiveness of the coping strategies used by patients. An example would be to assist patients in recognizing what aspects of their lives have been directly affected by the condition and what aspects have not. Past studies show that, in living with a chronic condition, it is common to perceive that many more aspects of one's life are negatively affected than truly are [Navon, 1999]. An exercise in distinguishing the two can help patients to see important areas of their lives untouched by disease. Re-engaging in these aspects of one's life can enhance QoL.

Scales that focus primarily on physical aspects will not sufficiently capture QoL and may fail to uncover potentially important associations with psychosocial factors. A more comprehensive measure of global QoL can be used to determine the impact of disease in a number of ways.

One resource for validated items that can be used to measure QoL is the Patient-Reported Outcomes Measurement Information System (PROMIS), an NIH Roadmap Initiative (http://www.nihpromis.org). One of the objectives of PROMIS is to standardize the measures that are used to assess outcomes such as QoL, while still allowing for tailoring of measures to a specific population. The measures can be used in a wide variety of chronic diseases and conditions. They should be re-validated in the new populations but will help to facilitate comparisons across conditions. The measures are publicly available on the PROMIS website for use in studies of genetic conditions.

The importance of conceptual clarity, rigorous methodology with appropriate QoL scales, and theoretically grounded research cannot be overemphasized. The field of research on QoL in rare genetic conditions will be advanced by uniting around a clear conceptualization of QoL and using more rigorous methodology. This research will yield more potent evidence for clinical applications and interventions to facilitate improvements in the healthcare and counseling for individuals living with rare genetic conditions, and, ultimately, to enhance patients' QoL.

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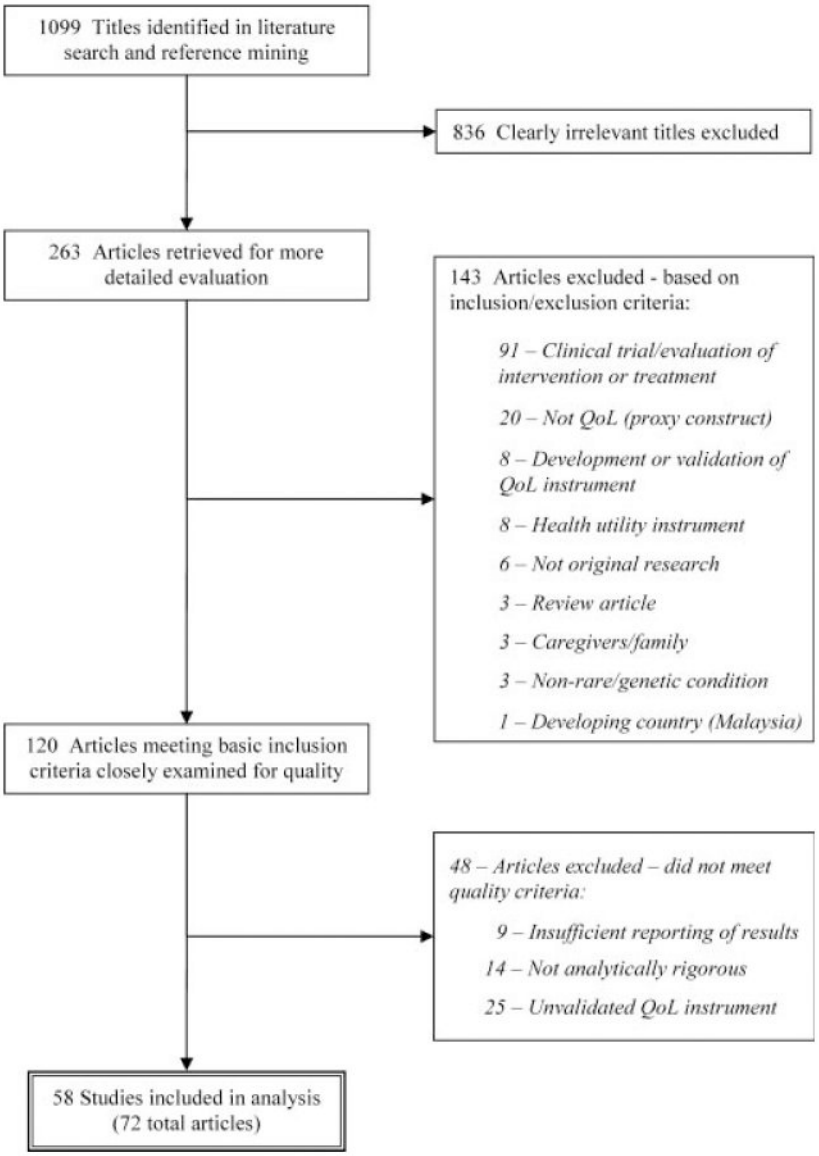

FIG. 1. Flow diagram of study selection process

TABLE I

Basic Inclusion Criteria

Inclusion criteria	Studies excluded
Target population: affected with rare genetic condition	Non-rare, non-genetic, and/or multifactorial conditions
	Familial cancer syndromes
	Unaffected family members or caregivers
	Located in developing country
Article type: original research	Non-research publications, such as: commentaries, essays, consensus statements, reviews, case reports, economic analyses, and articles dealing with ethical or legal issues
	Articles not available in English
Study purpose: at least one primary aim was to describe QoL and/or predictors	Clinical trials or studies evaluating the effectiveness of a drug, surgery, or medical intervention on a clinical outcome
	Studies about the development/validation of a QoL instrument
	Do not measure QoL, use a proxy variable instead

TABLE II

Quality Criteria

Adequate
Conceptualization of QoL
Comprehensive strategy for recruiting participants
Use of validated, multidimensional QoL instrument
Analytically rigorous, including attainment of sufficient sample size and use of appropriate control/comparison group
Reported
Specific objectives and hypotheses
Clear description of study design, recruitment source, inclusion and exclusion criteria
Sample characteristics and demographics
Clearly defined key variables and measures
Comprehensive presentation of QoL data on all domains of instrument
Detailed description of analyses performed and statistical significance of results

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TABLE III

Summary of QoL Studies and Selected Findings[1]

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
Achondroplasia	Gollust et al. 2003a,b (*USA*)	189 adults from support org.	XS	QLI	Individuals with achondroplasia had globally poorer QoL than their unaffected first-degree relatives In multivariate regression, affected status was only modestly signif. for total QoL (P= 0.039) and physical QoL (P= 0.024), and NS for the other three QoL domains When controlling for demographics and affected status, greater perceived seriousness and lower self-esteem were strongly associated with poorer QoL in all domains
Charcot-Marie-Tooth disease	Padua et al. 2008a,b (*Italy*)	98 adults/teens (14 y+) with CMT1A, clinic patients	L(2 y)	SF-36	Globally poorer QoL compared to pop. norm QoL scores at baseline and 2 y follow-up were NS different Clinical/neurophysiological features (e.g., ability to toe-walk, nerve conduction) associated with QoL scores in some physical health domains, few correlations with psychosocial QoL
	Redmond et al. 2008 (*Australia*)	295 adults with CMT1A and CMT2, from support org.	XS	SF-36	Globally poorer QoL compared to pop. norm, NS differences in QoL between CMT types Physical symptoms (e.g., leg weakness, cramps) associated with lower QoL in some domains
	Vinci et al. 2005 (*Italy*)	121 adults/teens (15 y+), clinic patients	XS	SF-36	Globally poorer QoL compared to norm Disease duration negatively associated with physical QoL (PCS) but not psychosocial QoL (MCS)
	Teunissen et al. 2003 (*The Netherlands*)	43 adults/teens with CMT2, clinic patients	L (5 y)	SF-36	Signif. poorer QoL in most domains compared to pop. norm In the longitudinal cohort (n = 27), NS change in any QoL domains over the 5-year period, although clinical status/disability had worsened
Congenital adrenal hyperplasia	Jaaskelainen and Voutilainen 2000 (*Finland*)	32 adult clinic patients	XS	SF-36	Greater QoL in physical and psychosocial domains compared to population norms
Cystic fibrosis (CF)	Gee et al. 2003, 2005, Abbott et al. 2007, 2008 (*UK*)	223 adult clinic patients	XS	CFQoL	Lung function signif. associated with QoL in most domains Coping styles: higher optimism signif. associated with higher QoL, higher distraction

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					signif. associated with lower QoL, hopefulness and avoidance NS associated with QoL
	Britto et al. 2002, 2004, Arrington-Sanders et al. 2006 (*USA*)	162 adults and children (5 y +), clinic patients	XS	SF-36 CHQ	Adults (n=48) had signif. poorer physical QoL compared to pop. norm, but NS differences in psychosocial QoL domains Among children/adolescents (n = 114), parent-rated QoL was signif. poorer in all physical domains compared to norms, but only signif. difference in psychosocial domains was for self-esteem Lung function NS correlated with QoL, but frequency of pulmonary exacerbations was signif. associated with poorer physical QoL Parent-rated QoL was signif. poorer than child/adolescent self-rated QoL in physical domains, but NS different for psychosocial domains
	Havermans et al. 2008 (*Belgium*)	57 adult clinic patients	XS	CFQ	Lung function signif. negatively associated with QoL in some physical health domains After controlling for lung function, anxiety and depression signif. associated with 6/12 psychosocial and 3/12 physical QoL domains
	Palermo et al. 2006 (*USA*)	46 children/adolescents (8–17 y), clinic patients	XS	CFQ	Pain signif. associated with QoL in physical health domains, NS for emotional or social domains
	Riekert et al. 2007 (*USA*)	76 adult clinic patients	XS	CFQ	Depression signif. associated with poorer QoL in all domains
	Szyndler et al. 2005 (*Australia*)	52 adolescents (12–18 y), clinic patients	XS	CFQ	Higher levels of psychopathology and lower optimism for the future signif. associated with poorer QoL in most domains Family functioning characteristics signif. associated with QoL in some domains
	Thomas et al. 2006 (*Australia*)	162 children/adolescents (2–19 y), clinic patients	XS	PedsQL CFQ	Globally poorer QoL compared to norm Lung function signif. negatively associated with some CFQ domains, NS with any PedsQL
Darier's and Hailey–Hailey diseases	Harris et al. 1996 (*UK*)	201 adults/teens (13 y+), clinic patients	XS	DLQI	QoL was most negatively affected in the symptoms/feelings domain (highest score of all the domains); however, mean DLQI scores were within “small” to “moderate” effect range, indicating that the disease did not have a major negative impact on patients' QoL NS correlation between clinical severity and QoL; NS difference in QoL between disease

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					groups (DD vs. HHD), despite differences in symptoms
Ehlers–Danlos syndrome	Berglund and Nordstrom 2001, Berglund et al. 2003 (*Sweden*)	77 adults from support org.	XS	SIP	Globally poorer QoL compared to pop. norm Greater acceptance of disability and sense of coherence signif. associated with better QoL
Fabry disease	Miners et al. 2002 (*UK*)	38 male adult clinic patients	XS	SF-36	Globally poorer QoL compared to male pop. norm Compared to patients with severe hemophilia [Miners et al., 1999], Fabry patients had signif. poorer psychosocial QoL (MCS), but physical QoL (PCS) NS different
	Ries et al. 2005 (*USA*)	25 male children and adolescents (6–18 y), clinic patients	XS	CHQ	Among children (n = 9), parent-rated QoL was poorer than norms in all domains, but differences were statistically signif. for two domains Teens (n = 15, self-report) had signif. more pain (lower QoL) and better QoL in behavior, social, and emotional domains than norm
	Street et al. 2006 (*USA*)	202 adult female heterozygotes, from support org. and clinic	XS	SF-36	Globally poorer QoL compared to female pop. norm
Familial dysautonomia	Sands et al. 2006 (*USA*)	145 adults and children (4 y +), clinic patients	XS	SF-36 CHQ	Among adults (n = 74), NS differences in QoL than pop. norm Among children (n = 71), parent-rated QoL was signif. poorer in all physical domains and 2/4 psychosocial domains compared to norm; physical and psychosocial summary scores were also significantly poorer than children with various other chronic medical conditions
Friedrich Ataxia	Epstein et al. 2008 (*USA*)	130 adult clinic patients	XS	SF-36	Compared to age/sex-matched control group and to pop. norm, patients had signif. poorer QoL in all domains except RE and MCS (NS differences) Disease duration and clinical severity (neurological impairment) signif. associated only with PF domain; disability signif. associated with PF and GH domains
	Wilson et al. 2007 (*Australia*)	63 adult clinic patients	XS	SF-36	Globally poorer QoL compared to pop. norm, physical worse than psychosocial QoL Clinical severity (neurological impairment) signif. associated with only PF domain After controlling for severity and disease duration, age of onset was signif. associated with QoL in some domains, with adult-onset

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					patients having lower QoL than patients whose disease began <18 y
					In multivariate regression, age of onset and severity were strongest predictors of PCS, whereas disease duration was the only factor signif. associated with MCS
Galactosemia	Bosch et al. 2004 (*The Netherlands*)	63 adults and children (1 y +), from support org.	XS	TAPQoL TACQoL TAAQoL	For all age groups, trend towards poorer QoL in most domains compared to healthy norms, but differences were statistically significant only in some domains (small sample sizes: n = 17 adults, n = 25 children/adolescents, n = 22 young children)
Gaucher disease	Damiano et al. 1998 (*USA*)	212 adults/teens (14 y+) on enzyme replacement therapy, clinic patients	XS	SF-36	Signif. poorer QoL in physical domains compared to norm, NS differences for psychosocial domains
					Ageing and clinical status (e.g., joint replacement, splenectomy) signif. associated with poorer QoL in some domains
Glycogen storage disease type 1	Storch et al. 2008 (*USA*)	29 children/adolescents (6–18 y), clinic patients	XS	PedsQL	Compared to healthy control group, patients had signif. lower QoL in physical and social domains, NS differences in emotional and school domains
					Compared to sample of children with various chronic medical conditions, NS differences in QoL
Hemophilia and coagulation disorders	Miners et al. 1999 (*UK*)	164 male adult clinic patients	XS	SF-36	Hemophilia patients had signif. worse QoL than pop. norm in physical domains, but NS differences in psychosocial domains
					Compared to patients with mild/moderate disease, patients with severe hemophilia had signif. poorer physical QoL, NS differences in psychosocial domains
	Tusell et al. 2002 (*Spain*)	70 male adults with severe hemophilia, clinic patients	XS	SF-36	Signif. poorer QoL than pop. norm in all domains except mental health and emotional role-functioning
	Walsh et al. 2008 (*Canada*)	47 male adults with mild hemophilia A from same kindred, identified through population survey	XS	SF-36	Compared to control cohort of unaffected age-matched male relatives, affected males had significantly poorer QoL in GH and RE domains, trend towards poorer QoL in all other domains
					In multivariate regression analysis, clinical status/symptoms (heart disease and joint damage) were signif. predictors of PCS, but affected status was NS (suggests that the difference in physical QoL between hemophilia

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					and control is largely explained by heart disease and joint damage, rather than hemophilia itself)
	Solovieva 2001, Solovieva et al. 2004 (*Finland*)	164 adults with hemophilia, von Willebrand disease, and Factor XIII deficiency, clinic patients	L(3 y)	SF-36	Signif. poorer physical QoL and greater mental QoL than healthy control group NS change in QoL in most domains between baseline and 3-year follow-up In multivariate regression analysis, patients with severe disease and/or whose disease severity increased were more likely to have reduction in QoL over time
Hereditary hemorrhagic telangiectasia	Geisthoff et al. 2007 (*Germany*)	77 adults/teens (13 y+), clinic patients	XS	SF-36	Signif. poorer QoL in all domains except pain compared to pop. norm Clinical symptoms (e.g., epistaxis) signif. correlated with some QoL domains Greater perceived consequences (strain on profession, private life, and psyche) and worries about HHT signif. associated with lower QoL in all domains ($P < 0.05$)
	Pasculli et al. 2004 (*Italy*)	50 adult clinic patients	XS	SF-36	Poorer QoL in all domains except pain than pop. norm Clinical symptoms (e.g., epistaxis) signif. associated with PCS but not MCS
Huntington disease	Helder et al. 2001, 2002 (*The Netherlands*)	77 adults recruited from clinic and support org.	XS	SF-36 SIP	As assessed by the SIP: QoL was globally poorer than pop. norm Psychosocial aspects impacted to a greater extent than physical aspects Cognitive/motor functioning and disease duration predicted a signif. amount of variance in physical SIP but not psychosocial SIP As assessed by the SF-36, QoL was signif. poorer in most physical health domains, but NS differences for psychosocial domains; After controlling for demographics and illness-related variables, coping and illness perceptions predicted signif. amount of variance in QoL Coping: “acceptance” positively associated with mental health QoL domain; venting of emotions, behavioral and mental disengagement were negatively associated with QoL Illness identity and “cure” perceptions associated with some QoL domains
Hyperimmunoglobulinemia type D	van der Hilst et al. 2008 (*International*)	28 adult clinic patients	XS	SF-36	Poorer QoL in some domains than pop. norm Symptoms (frequency of attacks) signif.

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					associated with physical QoL, NS psychosocial QoL
Marfan syndrome	Peters et al. 2002 (*USA*)	174 adults recruited from clinic and support org.	XS	QLI	Individuals with Marfan syndrome had signif. poorer QoL in psychological/spiritual domain than patients with cardiovascular disease, NS difference in physical health/functioning domain
Muscular dystrophies	Ahlstrom et al. 1994, Ahlstrom and Gunnarsson 1996, Ahlstrom and Sjoden Ahlstrom and Sjoden, 1996a, Natterlund et al. 2000, Bostrom et al. 2005 (*Sweden*)	57 adults with various MD types, identified through general population survey	L (10 y)	SIP	Globally poorer QoL compared to pop. norm, greater impact (worst QoL) in physical dimension
					NS difference in QoL between types of MD, despite differences in physical disability
					Disability signif. negatively associated with physical QoL and, to a lesser extent, psychosocial QoL
					Coping strategies signif. associated with psychosocial and overall QoL, NS for physical QoL
					Psychosocial well-being NS correlated with QoL
					QoL signif. deteriorated over the 10-year period, physical QoL to a greater extent than psychosocial QoL
					Disability signif. increased over time, whereas NS change in psychosocial well-being
	Piccininni et al. 2004 (*Italy*)	45 adults with various MD types, clinic patients	XS	SIP	Globally poor QoL (SIP scores in “clinically-significant impairment” range), QoL in physical dimension worse than psychosocial dimension
					Disability signif. negatively associated with QoL
					Higher psychological well-being signif. associated with better QoL
					Anxiety and depression signif. negatively correlated with QoL
	Grootenhuis et al. 2007 (*The Netherlands*)	107 adults and children (8 y +) with various MD types, clinic patients	XS	TAAQoL TACQoL	Children (n = 18) and adolescents (n = 22) with MD had signif. poorer QoL on some domains, but signif. better QoL in the physical functioning domains compared to healthy norms for the same age group
					Adults with MD (n = 67) had signif. poorer QoL on 8/12 domains compared to healthy norms

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					Clinical severity signif. negatively associated with fine motor functioning and social functioning domains of QoL among adults
	Antonini et al. 2006 (*Italy*)	20 adults with myotonic dystrophy, clinic patients	XS	SF-36	Globally poorer QoL compared to healthy matched controls and pop. norm
					Clinical severity signif. associated with poorer QoL in physical domains, NS for psychosocial QoL
					Anxiety and depressive symptoms signif. associated with poorer QoL in RP and MH domains
	Ford et al. 2006 (*New Zealand*)	36 adults with various MD types, clinic patients	XS	SF-36	QoL signif. poorer in physical health domains as compared to pop. norm, NS for psychosocial QoL
					NS differences between patients with myotonic dystrophy versus other MD types
Neurofibromatosis type 1	Graf et al. 2006 (*Switzerland*)	46 children and adolescents (7–16 y), clinic patients	XS	TACQoL	Self-reported and proxy-reported QoL were signif. poorer than norm in the majority of domains
					Clinical severity and visibility signif. associated with poorer QoL in emotional domains
					Family functioning: greater cohesion and lower conflict signif. associated with better QoL when rated by parents, NS relationships with child self-reported QoL
					Family history: parents with NF1 rated their children's emotional QoL lower than did parents without NF1; family history was NS associated with children's self-reported QoL
	Kodra et al. 2009 (*Italy*)	129 adults clinic patients	XS	SF-36 Skindex	Significantly poorer QoL in all SF-36 domains than pop. norm
					Impact of NF1 on QoL was greater for psychosocial aspects than physical health aspects
					Visibility signif. associated with poorer skin-specific QoL (Skindex) on all domains, but NS associated with SF-36 scores
	Krab et al. 2009 (*The Netherlands*)	58 children and adolescents (7–17 y), clinic patients	XS	CHQ	Parent-rated QoL was signif. poorer than pop. norm in 6/8 domains
					Adolescents (n = 43 self-report) had signif. better QoL in behavior domain than norm

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					Severity signif. associated with some QoL domains; visibility NS associated with QoL
	Oostenbrink et al. 2007 (*The Netherlands*)	34 young children (1–6 y), clinic patients	XS	ITQoL	Signif. poorer QoL in some domains compared to healthy reference sample
					Visibility signif. negatively associated with health perceptions domain of QoL
	Page et al. 2006 (*USA*)	166 adults recruited from clinic and support organization	XS	SF-36 SkinDex	Signif. poorer QoL in all SF-36 domains than population norms;
					Impact of NF1 on QoL was greater for psychosocial aspects than physical health aspects
					Visibility signif. associated with poorer skin-specific QoL (Skindex) on all domains, but NS associated with SF-36 scores
					Clinical severity signif. associated with poorer QoL in all SF-36 domains and 2/3 Skindex domains (functioning and physical symptoms, NS emotional symptoms)
	Wolkenstein et al. 2001 (*France*)	128 adult clinic patients	XS	SF-36 SkinDex	Signif. poorer QoL in all SF-36 domains than population norms
					Impact of NF1 on QoL was greater for psychosocial aspects than physical health aspects
					Visibility signif. associated with poorer QoL on all Skindex domains and most SF-36 domains
					Clinical severity signif. associated with poorer QoL in some SF-36 domains, but NS associated with Skindex scores
	Wolkenstein et al. 2009 (*France*)	79 children and adolescents (8–16 y), clinic patients	XS	DISABKIDS CDLQI	Using DISABKIDS, impact on total QoL was greater (i.e., worse QoL) for NF1 than for asthma
					Using the CDLQI, impact on QoL was lower for NF1 (i.e., better QoL) than for other skin diseases (psoriasis, eczema, acne)
					Disease complications/symptoms signif. associated with greater impact (lower QoL)
Osteogenesis imperfecta	Widmann et al. 2002 (*USA*)	30 adult clinic patients	XS	SF-36	QoL signif. poorer in most physical health domains than norm, NS differences in psychosocial QoL
Phenylketonuria	Landolt et al. 2002 (*Switzerland*)	37 children/adolescents (3–18 y) on treatment, clinic patients	XS	TACQoL	As rated by parents, children/adolescents with PKU had signif. poorer QoL than norms in one psychosocial domain (positive emotional

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
					functioning), but NS differences in any other QoL domains
	Simon et al. 2008 (*Germany*)	67 adult clinic patients on treatment	XS	PLC	No signif. differences in any QoL domains compared to pop. norm
Pompe disease	Hagemans et al. 2004 (*International*)	210 adults from support org.	L (1 y)	SF-36	Disability signif. associated with lower QoL in PF, SF, and RE domains
					Longer disease duration signif. associated with lower PF scores, but higher RP and MH scores
					Mean QoL scores for the Dutch subgroup (n = 51) were signif. lower than population norms for 3/4 physical health and 2/4 mental health domains; NS differences for BP, RE, and MH
					In the Dutch cohort who were followed longitudinally (n = 38), no signif. change in QoL over the 1 y follow-up period, even among those who reported physical deterioration
Porphyria	Holme et al. 2006 (*UK*)	220 adults and children (5 y +) with erythropoietic protoporphyria, clinic patients	XS	DLQI CDLQI	For both adults and children, QoL was markedly impaired (mean DLQI/CDLQI scores were within the “very large effect” range)
					Clinical severity signif. associated with QoL
	Millward et al. 2001 (*UK*)	81 adults with acute porphyrias, clinic patients	XS	MOS	Globally poorer QoL compared to pop. norm
					Patients manifesting symptoms had signif. lower QoL than patients without symptoms (latent)
					Patients with acute intermittent porphyria had more pain and poorer social functioning than patients with other types (variegate porphyria and hereditary coproporphyria)
Prader–Willi syndrome	Caliandro et al. 2007 (*Italy*)	29 adults and children (5 y +), clinic patients	XS	SF-36 CHQ	Compared to pop. norm, adults and children had signif. poorer QoL in most domains
Sickle cell disease	McClish et al. 2005 (*USA*)	308 adult clinic patients	XS	SF-36	Patients with sickle cell had signif. poorer QoL in all domains except mental health, as compared to population norms and patients with cystic fibrosis
					Pain signif. negatively associated with QoL in all domains except mental health
	Palermo et al. 2002 (*USA*)	58 children/adolescents (5–18 y), clinic patients	XS	CHQ	Globally poorer QoL than healthy controls
					Disease complications negatively
					associated with physical QoL, but NS with psychosocial QoL

Genetic condition	References	Study population (N, age, recruit source)	Study Design	QoL Scale[2]	Selected Findings
	Panepinto et al. 2005 (*USA*)	99 children and adolescents (5–18 y), clinic patients	XS	CHQ	Parent-rated QoL was signif. poorer than norm in physical and psychosocial domains Adolescents (n = 53) self-rated their QoL as signif. poorer than norms in physical domains, but NS different in psychosocial domains QoL as rated by parents tended to be lower than adolescents' self-reported QoL Disease complications (number of crises) was signif. negatively correlated with physical QoL
Turner syndrome	Carel et al. 2005 (*France*)	568 adult females treated with growth hormone, clinic patients	XS	SF-36	NS differences in any QoL domains compared to reference sample Psychological distress signif. correlated with lower QoL (women with symptoms of psychological distress had signif. poorer QoL in all domains than those without symptoms) Height and other treatment-related variables NS associated with QoL
X-linked agammaglobulinemia	Howard et al. 2006 (*USA*)	41 male adult clinic patients	XS	SF-12	NS differences in QoL between patients and pop norms, except GH domain Lung disease signif. associated with lower MCS scores, but NS difference in PCS
	Winkelstein et al. 2008 (*USA*)	25 male adult clinic patients	XS	SF-12	Trend towards lower QoL among patients than pop norms, but NS

[1] Abbreviations used in Table III: support org., support organization; signif., significant; NS, not significant; y, years; XS, cross-sectional; L, longitudinal; pop. norm, population norm; PCS, physical component score; MCS, mental component score; PF, physical functioning; RP, role physical; BP, bodily pain; VT, vitality; MH, mental health; GH, general health perceptions; RE, role emotional; SF, social functioning.

[2] See Table V QoL scale abbreviations.

TABLE IV
List of Genetic Conditions by Clinical Category (With Number of Studies)

- **Metabolic disorders**
  - Phenylketonuria (2)
  - Galactosemia (1)
  - Congenital adrenal hyperplasia (1)
  - Porphyrias (2)
  - Glycogen storage disease type 1 (1)
  - Hyperimmunoglobulinemia D (1)
- **Lysosomal storage disorders**
  - Fabry disease (3)
  - Gaucher disease (1)
  - Pompe disease (1)
- **Blood and vascular disorders**
  - Hereditary hemorrhagic telangiectasia (2)
  - Sickle cell disease (3)
  - Coagulopathies
    - Hemophilia (4)
    - Factor XIII deficiency (1)
    - Von Willebrand disease (1)
- **Neuromuscular and neurologic disorders**
  - Muscular dystrophies (5)
  - Charcot-Marie-Tooth disease (4)
  - Friedrich ataxia (2)
  - Familial dysautonomia (1)
  - Huntington disease (1)
- **Dermatologic disorders**
  - Neurofibromatosis type 1 (7)
  - Darier's disease (1)
  - Hailey–Hailey disease (1)
- **Connective tissue disorders**
  - Marfan syndrome (1)
  - Ehlers–Danlos syndrome (1)
- **Skeletal dysplasias**
  - Achondroplasia (1)
  - Osteogenesis imperfecta (1)
- **Chromosomal disorders**
  - Prader–Willi syndrome (1)
  - Turner syndrome (1)
- **Other**
  - Cystic fibrosis (7)
  - X-linked agammaglobulinemia (2)

TABLE V
List of QoL Scales (Alphabetical by Abbreviation, With Number of Studies)

Abbreviations	Scale name	#
CDLQI	Children's Dermatology Life Quality Index	2
CFQ	Cystic Fibrosis Questionnaire	5
CFQoL	Cystic Fibrosis Quality of Life Questionnaire	1
CHQ	Child Health Questionnaire	7
DISABKIDS	DISABKIDS Questionnaire	1
DLQI	Dermatology Life Quality Index	2
ITQoL	Infant/Toddler Quality of Life Questionnaire	1
MOS	Medical Outcomes Study General Health Survey	1
PedsQL	Pediatric Quality of Life Inventory	2
PLC	Profile of Quality of Life in the Chronically Ill	1
QLI	Quality of Life Index	2
SF-12	Medical Outcomes Study Short Form 12	2
SF-36	Medical Outcomes Study Short Form 36	30
SIP	Sickness Impact Profile	4
Skindex	Skin Diseases Quality of Life Index	3
TAAQoL	TNO-AZL Adult Quality of Life	2
TACQoL	TNO-AZL Children's Quality of Life	4
TAPQoL	TNO-AZL Preschool Children Quality of Life	1