The Establishment of the GENEQOL Consortium to Investigate the Genetic Disposition of Patient-Reported Quality-of-Life Outcomes

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Abstract

To our knowledge, no comprehensive, interdisciplinary initiatives have been taken to examine the role of genetic variants on patient-reported quality-of-life outcomes. The overall objective of this paper is to describe the establishment of an international and interdisciplinary consortium, the GENEQOL Consortium, which intends to investigate the genetic disposition of patient-reported quality-of-life outcomes. We have identified five primary patient-reported quality-of-life outcomes

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as initial targets: negative psychological affect, positive psychological affect, self-rated physical health, pain, and fatigue. The first tangible objective of the GENEQOL Consortium is to develop a list of potential biological pathways, genes and genetic variants involved in these quality-of-life outcomes, by reviewing current genetic knowledge. The second objective is to design a research agenda to investigate and validate those genes and genetic variants of patient-reported quality-of-life outcomes, by creating large datasets. During its first meeting, the Consortium has discussed draft summary documents addressing these questions for each patient-reported quality-of-life outcome. A summary of the primary pathways and robust findings of the genetic variants involved is presented here. The research agenda outlines possible research objectives and approaches to examine these and new quality-of-life domains. Intriguing questions arising from this endeavor are discussed. Insight into the genetic versus environmental components of patient-reported quality-of-life outcomes will ultimately allow us to explore new pathways for improving patient care. If we can identify patients who are susceptible to poor quality of life, we will be able to better target specific clinical interventions to enhance their quality of life and treatment outcomes.

Patient-Reported Quality-of-Life Outcomes

The objective of disease-based quality-of-life research is to gain insight into the impact of disease and treatment on patient-reported outcomes and, thus, to enhance patients' well-being. Patient-reported quality of life refers to the physical, functional, and psychosocial consequences of disease and treatment as experienced by patients themselves. Thus, by definition, it is the subjective experience reflecting the patients' point of view. Much progress has been made in recent years in terms of finding ways to incorporate the patients' subjective experience into medical research. Indeed, validated patient-reported quality-of-life instruments are now available and empirical evidence about disease and treatment outcomes has been collected for most disease sites and treatment modalities. Perhaps the most provocative finding in this area of research is that patient-reported quality of life is often superior to more objective clinical assessments for predicting patients' survival (Gotay et al., 2008).

Patient-reported quality of life is not only affected by disease and treatment. Recent data provided preliminary evidence that the genetic disposition of patients may impact their quality of life. Research on twins has provided ample empirical evidence of a genetic predisposition for negative emotional states, such as depression, anxiety, and psychosocial distress. To provide an example of the latter state, Rijsdijk and colleagues (2003) found that the overall heritability of psychosocial distress as assessed with the General Health Questionnaire ranged from 20% to 44%. Additionally, an increasing number of studies showed substantial heritability of positive emotional states, such as subjective well-being and life satisfaction. Heritability estimates ranged between 40% and 50%, whereas the remaining variance was accounted for by environmental influences unique to an individual. No effects of environmental influences shared by members of the same family were found (Bergeman et al., 1991; Harris et al., 1992b; Lykken & Tellegen, 1996; Newman et al., 1998; Røysamb et al., 2002, 2003; Stubbe et al., 2005; Tellegen et al., 1988; Nes et al., 2006).

Genetic influences have also been reported for self-rated health (Christensen et al., 1999; Harris et al., 1992a; Kendler et al., 2000; Leinonen et al., 2005; Romeis et al., 2000; Røysamb et al., 2003; Silventoinen et al., 2007; Svärdh et al., 1998; Svedberg et al., 2001, 2005, 2006). Typically, in these studies, health is assessed with the use of either a short scale or a single item, such as the question: "How would you rate your health in general?" (Christensen et al., 1999). To our knowledge, only one study examined the heritability of patient-reported quality of life as assessed with the SF-36, the most widely used generic health status questionnaire, in a non-clinical, community sample of middle-aged males. This study also indicated genetic effects, albeit of a moderate magnitude (Romeis et al., 2005). To date, the precise amount of the variance in self-rated health that is accounted for by genetic factors is unknown.

Sloan & Zhao (2006) were the first to examine the direct link between polymorphisms and cancer patients' quality of life, using a large randomized North Central Cancer Treatment Group clinical trial. A clinically meaningful effect size was pre-specified that would have to be observed to indicate a potential relationship. More than triple the number of relationships between genetic variables and patient-reported quality-of-life outcomes were observed than would be expected by chance alone. They found evidence for relationships between overall quality of life, symptom distress, and fatigue with variant genotypes of three enzymes involved in folate metabolisms, dihydropyrimidine dehydrogenase (DPYD), methylenetetrahydrofolate reductase (MTHFR), and thymidylate synthetase (TYMS). Recently, Yang et al. (2009) evaluated the role of glutathione-related genotypes on quality of life in advanced non-small cell lung cancer patients who participated in a clinical trial. Patients carrying the glutathione peroxidase 1 (GPX1-CC) genotype had a clinically significant decline in overall quality of life, physical, functional, and emotional well-being. The authors suggested that GPX1 might be an inherited factor in predicting patients' quality of life.

The findings from the few studies performed so far are sufficiently compelling to justify further exploration of the relationships between genetic variants and patient-reported quality-of-life endpoints. The overall objective of this paper is to describe the establishment of a Consortium, which purports to translate and plan clinically relevant research to identify and investigate potential biological pathways, genes and genetic variants involved in patient-reported quality of life. Insight into the genetic versus environmental components will ultimately allow us to explore new pathways for improving patient care. If we can identify patients who are susceptible to poor quality of life, we will be able to better target specific support, such as psychological and/or pharmacological treatment.

The GENEQOL Consortium

Overall Objective

To our knowledge, no comprehensive, interdisciplinary initiatives have been taken to examine the role of genetic variants on patient-reported quality-of-life outcomes and their relevance to disease. We therefore established the Mayo Clinic/University of Amsterdam International Consortium for Genetics and Quality of Life Research, the GENEQOL Consortium in short. The overall objective of this Consortium is to establish strong collaborative and interdisciplinary relationships to translate and plan clinically relevant research to identify and investigate potential genes and genetic variants involved in quality of life. Given the potentially large number of genetic and quality-of-life variables that could be explored, there is a danger for unfocused and individualistic research efforts. Hence, we purport to adopt a coordinated, focused and efficient approach to determine the optimal path of exploration to uncover relationships between genetic variants and quality-of-life variables. The specific objectives are: (1) to develop a list of potential biological pathways, genes and genetic variants involved in quality of life, by reviewing current genetic knowledge; and (2) to design a research agenda to investigate and validate those genes and genetic variants involved in quality of life of individual patients, by creating large data sets on pooled sources.

Selecting an Initial Set of Patient-Reported Quality-of-Life Outcomes

Patient-reported quality of life is a multidimensional construct incorporating at least three broad domains, i.e., physical, psychological, and social. These broad domains can be further subdivided. For example, physical functioning can refer to the ability to perform a range of activities of daily living, as well as physical symptoms resulting either from the disease itself or from treatment. Psychological functioning may range from severe psychological distress to a positive sense of well-being, but may also encompass cognitive functioning. Social functioning may refer to quantitative and qualitative aspects of social relationships and

interactions, and may also refer to societal integration. Beyond this core set of quality-of-life domains, additional issues may be relevant for specific groups of patients, depending on the functional domains affected by the disease or treatment, such as sexual functioning and body image in patients undergoing mutilating surgery. Additionally, there is consensus that patient-reported quality-of-life assessments also entail an overall judgment of health and/or quality of life (Cella & Tulsky, 1990; Siegrist & Junge, 1989).

Given this large number of domains, we selected five important quality-of-life outcomes, i.e., negative and positive psychological affects, overall health, and the two most prevalent symptoms across general and disease populations. The first Consortium activities were therefore focused on the genetic disposition of: (1) negative psychological affect (i.e., depression, anxiety, symptom distress), (2) positive psychological affect (i.e., happiness, life satisfaction, subjective well-being, overall quality of life), (3) perceived or self-rated physical health, or functioning, (4) pain, and (5) fatigue.

Gathering the Initial Consortium Members

We invited researchers with a strong background and experience in at least one of the relevant disciplines, including cellular and molecular biology, behavioral genetics, pharmacogenetics, oncology, statistical genetics, genetic epidemiology, nursing, medical psychology, biological psychology, clinical psychology, psychiatry, and sociology. Additionally, researchers had expertise in at least one of the identified five quality-of-life domains. Collectively, this group has an extensive track record of peer-reviewed articles in highly-ranked journals and successful grant applications obtained from a wide range of prestigious granting agencies. The number of participants was limited to 28 to keep the size of the group manageable and to facilitate the opportunity for meaningful and directed discussions.

Procedure

The Consortium participants were combined to form five interdisciplinary teams related to the five identified quality-of-life outcomes. Each team had a designated leader and five to six assigned contributors. Each team was asked the following questions: (1) which potential biological pathways have been considered and/or shown to describe a possible genetic disposition for the indicated quality-of-life outcome? (2) Which genes and genetic variants have been considered and/or shown to have a potential association with the indicated quality-of-life outcome? (3) What datasets are available to explore the association of genes and the indicated quality-of-life outcome? (4) How would you design a new prospective study to explore the association of genes and the indicated quality-of-life outcome? Teams were asked to base their answers on current knowledge (i.e., scientific literature, ongoing research). The team leaders, in consultation with their team members, were asked to produce a 2–3 page draft response to the questions.

The first Consortium meeting took place at the Mayo Clinic, Rochester, MN on February 26–28, 2009. It started with an open registration pre-meeting given by a number of Consortium members summarizing research in their respective areas of expertise. Given the multitude of disciplines involved, this workshop provided a forum for Consortium members to learn of the advances in other research areas and thus provided an introduction to the closed meeting. The open registration meeting purported also to serve as a networking opportunity for others outside of the Consortium.

The open meeting was followed by a closed two-day meeting, which focused on the genetic disposition of the five quality-of-life outcomes. The teams presented a 30-minute discussion of their responses to the posed questions and a 60-minute open discussion of the issues. At the end of each day, a one-and-half hour slot was devoted to synthesizing the discussions, providing

conclusions regarding the candidate biological pathways, genetic variants and the research agenda for the presented quality-of-life components. The timing of the conference schedule thus resulted in each topic, including the overall discussion, receiving 120 minutes of the group's collective attention. The final slot at the end of the second day was devoted to wrapping up the discussions, planning the next steps for the Consortium and assigning tasks and homework to the participants.

Summary of Findings

As a caveat, we would like to note that the description of the following areas is not intended to be comprehensive and that we cannot and do not claim to pay credit to the depth and richness of these research fields in the context of this paper. Our aim is to stimulate the investigation of the genetic disposition of these quality-of-life domains by highlighting the primary results in the respective fields.

Biological Pathways and Genetic Variables

Negative Psychological Affect—A substantial amount of research related to negative psychological affect has been conducted in psychiatric patients, e.g., those with major depressive or anxiety disorder. The focus here is on "normal", non-pathological, negative feelings, for example distress in response to a negative life event, such as the diagnosis of a disease. Since there is evidence that negative affect behaves as a continuous trait, we expect a similar biological substrate for non-pathological as for pathological negative affect.

The hypothalamo-pituitary-adrenal (HPA) axis is considered to be the 'final common pathway' for most depressive symptoms (Bao et al., 2008) and thus may be important for patient-reported distress. The following hypothesis for the pathogenesis of depression was formulated by Bao et al. (2008). "In depressed patients, stress acting on the HPA system results in a disproportionately high activity of the HPA system because of a deficient cortisol feedback effect due to the presence of glucocorticoid resistance." (p. 541). Other candidate genes and pathways that may be involved in depression may result from an impaired dopamine system (Dunlop & Nemeroff, 2007). Decreased levels of serotonin are thought to be of importance in anxiety disorders (Lesch et al., 2003). Furthermore, *changes* in sex hormone levels may play an important role in the vulnerability to mood disorders. Finally, the suprachiasmatic nucleus is supposed to be related to circadian and circannual fluctuations in mood and to sleeping disturbances in depression (Bao et al., 2008).

The following five genes were significantly associated to major depression disorder in meta-analysis of polymorphisms that had been investigated in at least three studies (López-León et al., 2008): apolipoprotein E (APOE), guanine nucleotide-binding protein (GNB3), methylenetetrahydrofolate reductase (MTHFR), dopamine transporter (SLC6A3), and serotonin transporter (SLC6A4). There are many other potentially important genes related to the HPA-axis (e.g., arginine vasopressin, AVP; oxytocin, OXTR), the dopamine pathway (e.g., dopamine transporter, DAT; catechol-o-methyltransferase, COMT; and the D_4-receptor, DRD4), and the serotonin pathway (5-HTT; and monoamide oxidase, MAO-A). The first genome wide association (GWA) study of depression (Sullivan et al., 2009) suggested evidence for the involvement of the pre-synaptic protein piccolo (PCLO) on chromosome 7.

Of all the identified quality-of-life outcomes, negative psychological affect is the one most widely studied. Since depression and anxiety disorders are the foci of other consortia, we decided not to pursue this domain in the context of the GENEQOL Consortium, other than for comparison with related quality-of-life domains.

Positive Psychological Affect—The prefrontal cortex is the candidate brain area for happiness and positive emotional states that may be related to taste (Kringelbach et al., 2003), smell (Rolls et al, 2003a) or other input via the somaotosensory system (Rolls et al., 2003b). Some electro-encephalographic (EEG) studies suggest that positive affect states are associated with increased left cortical power in the alpha frequency compared to the right hemisphere (Davidson, 2004; Tomarken et al., 1992). There is evidence that dopamine modulates positive affect states (Burgdorf & Panksepp; 2006). At the subneocortical level, a number of peptide systems have been implicated in positive affective states, e.g., neurotensin and cocaine- and amphetamine-regulated transcript (CART) (both closely associated with dopamine), neuropeptide Y, and oxytocin (Burgdorf & Panksep, 2006). Finally, reduced activity of the neuroendocrine (Steptoe et al. 2005a, 2005b, 2008) and cardiovascular systems (Burgdorf & Panksep, 2006), as well as increased activity of the immune system (Burgdorf & Panksep, 2006) may all be involved in positive affect states. However, genes or genomic regions of interest for positive affect have not yet been published.

Physical Health—Separating the biological pathways involved in self-perceived health from those of other health domains is particularly challenging, since its genetic influence is related to the genetic liability of a wide variety of related physical as well as psychological variables. For example, related physical phenotypes include metabolic efficiency (Gottfredson, 2004), disease severity, maximal walking speed and exercise behavior (de Moor, 2007). Related psychological attributes were found to encompass, for example, adaptation to stressful environments (Gottfredson, 2004), resilience to stressful situations (Curtis et al., 2003), perceived sense of control (Johnson, 2005a; 2005b), intelligence (Gottfredson, 2004), affective disorders (Vinberg et al., 2007), and depressive symptoms (Leinonen et al., 2005).

As a result, the list of potential genetic variables for perceived or self-rated physical health is particularly long. Since one might assume that physical performance and health-related fitness are also associated with self-perceived physical health, the list can easily be expanded. For example, the in 2005 updated list for physical performance and health-related fitness included 156 autosomal gene entries, five others on the X chromosome, and 17 mitochondrial genes (Rankinen et al., 2006).

The epsilon4 allele of the APOE gene has been investigated for association with health-related outcomes in the elderly (Blazer et al., 2003; Goldman, et al., 2004). Whereas Blazer and colleagues (2003) did not find a significant association of APOE4 allele in cross-sectional or longitudinal analyses of older adults, Goldman et al. (2004) found that the APOE4 allele was predictive of self-rated health in Taiwanese respondents aged 54 years and older.

Stress and strain in both work and home environments are also related with self-rated health (Orpana et al., 2007; Staland-Nyman et al., 2008; Holmgren et al., 2009). The battery of stress response genes, especially the heat shock protein HSP70 genes -- HSPA1A, HSPA1B and HSPA1L -- present in the MHC-III region on the short arm of chromosome 6 have been related to stress response in studies among Danish twins (Singh et al., 2004). One of the heat shock protein genes HSP70-1 was found to be related to poor self-related health (Singh et al., 2007). To our knowledge, there are no published GWA studies of genetic determinants of self-reported physical health.

Pain—There are several pathways with a possible genetic disposition for pain. The first pathway plays a role in the central nervous system (CNS). One of its best characterized genes codes for catechol-O-methyltransferase (COMT). COMT mediates the inactivation of catecholamine neurotransmitters, including dopamine, adrenaline, and noradrenaline. Reduced COMT activity appears to result in increased sensitivity for pain and temporal summation of pain (Zubieta et al., 2003).

Studies targeted at the second, peripheral pain pathway, focus on genes that are involved in neurotransmission. Genes evidenced to be associated with pain perception and responses to analgesics, include, monoamino-oxidase A (MAO-A) (Shih, 2004), dopamine receptor (DRD2, DRD3, and DRD4) (Li et al., 2000), dopamine transporter (DAT) (Cevoli et al., 2006), adrenergic receptor (ADRB2) (Diatchenko et al., 2006), serotonin transporter (SLC6A4) (Herken et al., 2001), transient receptor potential subfamily A member 1 (TRPA1) (Kim et al., 2004), and TRP subfamily V member 1 (TRPV1) (Kim et al., 2006) genes.

The third inflammatory, pathway includes cytokines that are thought to be mediators between the CNS and the immune system and brain cytokines that mediate sickness response (Cleeland et al., 2003). Candidate genes include ligands for interleukin (IL) 1-receptor (IL-1RN): IL-1α, IL-1β (Solovieva et al., 2004), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) (Reyes-Gibby et al., 2007, 2008).

The final pathway is involved in the response to analgesics and includes absorption, metabolism, distribution, and interaction with targets of analgesics. A range of genetic variations has been identified that alter the effectiveness of analgesic drugs (Rollason et al., 2008). Compelling evidence has been found for genetic variation in the cytochrome P450 (CYP) isoenzyme CYP2D6 for codeine analgesic efficacy (Sindrup et al., 1995). Genetic variation in the COMT (Rakvåg et al., 2005) and mu opioid receptor (OPRM1) genes (Klepstad et al., 2004) is related to morphine analgesic efficacy. Evidence for other genes is inconclusive, but melanocortin-1 receptor (MC1R) (Mogil et al., 2005) and ABC family member B1 (ABCB1) (Campa et al., 2007) may be involved. It should be noted that there is a lack of studies investigating analgesic efficacy for opioids other than codeine and morphine. A GWA study among 110 patients with acute post-surgical pain reported a candidate SNP (rs2562456) associated with analgesic onset (Kim et al., 2009). Large-scale GWA studies related to pain have not been published yet.

Fatigue—Cancer-related fatigue can be defined as a "persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning" (Mock et al., 2000). Whereas the pathophysiological mechanisms involved in cancer-related fatigue are not completely understood (Gutstein, 2001), dysregulation of several systems, both biochemical and physiological, are likely involved (Ryan et al., 2007). Proposed mechanisms of cancer-related fatigue include cytokine dysregulation, brain serotonin (5-HT) neurotransmitter dysregulation, alterations in adenosine triphosphate (ATP), muscle metabolism, and vagal afferent activation, and disruption in circadian rhythm (Ryan et al., 2007).

Alterations in any part of the circadian system can result in disruption of arousal and sleep patterns. Specific suprachiasmatic nuclei (SCN) peptides that have the ability to regulate activity and sleep patterns, include epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), neuregulin-1 (NRG-1), prokineticine-2 (PK2), and cardiotrophin-like cytokine (CLc). All five peptides have been shown to reversibly inhibit activity and deregulate 24-hour sleep patterns. Circadian rhythm may also be affected through SCN downstream signal disruption that occurs in the dorsal or ventral nuclei or by signals from input from the brain's visceral, limbic, and cortical systems.

Several lines of evidence suggest that increased inflammatory marker levels are related to increased fatigue (Rich, 2007; Reyes-Gibby et al., 2008; Collado-Hidalgo et al., 2008; Ahlberg et al., 2004; Meyers et al., 2005). Gene polymorphisms have been identified in the regulator (promoter) regions of genes that encode proinflammatory cytokines. These polymorphisms could differentially influence susceptibility to cancer-related fatigue. Because cancer-related symptoms are complex, they are likely to be influenced by the cumulative effect of several gene polymorphisms (Reyes-Gibby et al., 2008). Several cytokine genes and their

polymorphisms have been proposed as candidate markers for the study of cancer-related fatigue (Reyes-Gibby et al., 2008). These include IL-1B (Reyes-Gibby et al., 2008; Collado-Hidalgo et al., 2008); IL-6 (Rich, 2007; Reyes-Gibby et al., 2008; Collado-Hidalgo et al., 2008; Ahlberg et al., 2004; Meyers et al., 2005); TNFα (Bower et al., 2002; Shafqat et al., 2005); IL-8 (Reyes-Gibby et al., 2007; Reyes-Gibby, 2008); and IL-2 (Reyes-Gibby, 2008). To date, there are no published GWA studies of cancer-related fatigue yet.

Setting Out the Research Agenda

Objectives—We will start studying the genetic underpinning of positive psychological affect, general physical functioning/health, pain, and fatigue. We will gradually add new quality-of-life domains to our research portfolio, e.g., social functioning and other symptoms. Possible objectives include: (a) to study the biological pathways that impact the variability in quality-of-life data; (b) to analyze and compare the association between genetic and quality-of-life variables extracted from population-based and patient-based cross-sectional and longitudinal data sets; (c) to test the genetic differences in subjects with extreme phenotypes for a single symptom or symptom clusters; (d) to test differences in quality of life between subjects grouped according to a particular genetic makeup (e.g., on the basis of the number of possible alleles of a particular gene); (e) to examine the extent to which different quality-of-life domains share similar genes; (f) to examine the extent to which different operationalizations of same quality-of-life domains share similar genes; (g) to examine the effect of interventions (e.g., cancer therapy, psychosocial interventions to increase happiness) on the association between genes/gene expressions on the one hand and quality-of-life domains (e.g., symptoms, positive affect) on the other; and (h) to test personalized interventions using our knowledge of the biological pathways for and genetic variants involved in quality of life to improve patient care.

Identifying Available Data Sets—We need large-scale data sets of general populations that include both genetic and quality-of-life variables. To date, such data sets are scarce or at least untapped. Exceptions are the Twin Registries of, for example, Australia, The Netherlands, and Sweden, which include both genetic and quality-of-life data. Open access data bases (e.g., via dbGAP Web portal) rarely include quality-of-life data. We expect this to change rapidly. Large-scale, longitudinal, population-based studies focusing on different phenotypes, including quality-of-life related variables, are increasingly collecting biomarkers, and/or DNA for targeted or genome wide sequencing. Examples include household panels, such as the British Household Panel Survey and the German Socio-Economic Panel.

We also need large-scale data sets of disease populations. To date, many clinical trials include both genetic markers and quality-of-life data, such as those conducted by the North Central Cancer Treatment Group and the European Organization for Research and Treatment of Cancer. However, sample sizes are relatively small and DNA analysis is usually restricted to a limited number of genes that are primarily involved in cancer. Ongoing, large-scale patient-based studies collecting clinical and biological data may be of interest as they may purport the addition of quality-of-life data. For example, a Dutch cohort of congenital heart disease patients and Swedish cohorts on breast and prostate cancer patients will start collecting quality-of-life data.

Since the availability of such data sets is key to furthering this field, the Consortium aims to stimulate international and interdisciplinary collaboration to enable the combined collection of genetic and quality-of-life data and the pooling of such data sets in general and disease populations.

Delineating the Analytical Approach—The following three approaches will be conducted, separately and/or in combination, wherever possible and appropriate. First,

advances in molecular and genetic technology now enable the use of whole genome scanning. Such GWA studies are conducted without a specific hypothesis on the genes and pathways involved because thousands of single nucleotide polymorphisms (SNPs) can be examined simultaneously. However, the costs involved and the need for enormously large samples may render this approach not very feasible.

Second, another type of association study is hypothesis-driven focused on candidate genes examined in specific pathways. SNPs with frequency of at least 5% are sufficiently prevalent to be candidates for genetic association studies. Sequencing a selection of the aforementioned candidate genes is a viable option and can identify both common and rare variants.

Third, in addition to simple sequence variations, we can analyze changes in copy number of a small part of the genome, so called copy number variants (CNVs). For CNV analysis one can analyze existing GWA data, but many CNVs will be missed. However, in case an association is found with a quality-of-life dimension/phenotype one can perform a detailed analysis of these regions. This can be either direct copy number analysis or a sequence-based approach.

Discussion

The field of patient-reported quality of life has never focused on that which is innate to the patient. Thus, there is a compelling need to reveal the genetic variables that play a role in patient-reported quality of life. Clearly, this path is complex, considering the potential number of genes, the interaction between these genes, the interaction between genes and environmental (e.g., life style) factors, and the number of quality-of-life variables that may be involved. To date, genetic research has burgeoned thanks to technical advancements, such as high-throughput genotyping. However, in pursuing the delineation of the relationship between genes and quality of life, both genetic and quality-of-life research is hindered by a mono-disciplinary approach. Few genetic researchers are working with patient-reported quality-of-life endpoints, and similarly few quality-of-life researchers are engaged in genetic research. It is of paramount importance to join forces among the disparate disciplines. Therefore, we have established the international and interdisciplinary GENEQOL Consortium to provide the requisite foundation and research culture to stimulate the development of this field. We were able to broach the language barriers of the disciplines involved. Interestingly, we found more commonality of the diverse experiences and were closer to outlining the biological pathways and genetic variables involved in the target quality-of-life outcomes and in setting a research agenda than we had anticipated. We hereby purport to adopt a sound scientific procedure integrating and building on the extant knowledge gained in the relevant disciplines. This is particularly important since genetic research is faced with many challenges, such as weak gene-disease associations (Khoury et al., 2007) and inconsistency of results (Ioannidis, 2007). Finding the optimal path to uncover the relationships between genetic variants and patient-reported quality-of-life variables will be a challenge in itself.

One of the advantages of studying the genetic disposition of quality of life, which encompasses multiple domains, is that it allows the investigation of overarching questions that are not likely to be addressed by consortia focusing on only one domain, e.g., depression or fatigue. The current knowledge regarding the biological pathways, and genetic variables involved in the five identified quality-of-life domains points to a number of such intriguing questions.

First, to what extent are negative and positive affect opposite ends of the same continuum? For example, the dopamine system is involved in negative as well as positive affect. The question arises whether the genetic influences overlap entirely or only in part. Genetic analyses are needed to disentangle the biological and genetic substrates of negative and positive affect, using data sets that include information on both phenotypes.

Second, given the high degree of biological and genetic overlap among these and other qualityof- life components, the question arises what part of the biological substrate is shared and what is unique to each component? For example, the genes that influence well-being and depressive symptoms are to a large degree the same genes that influence self-rated health and personality. Furthermore, genes in the cytokine pathway do not only control depression but also pain and fatigue (Reyes-Gibby et al., 2007, 2008; Irwin et al., 2007) and thus also self-rated health. Given the biological and genetic overlap of quality-of-life domains one may wonder whether we should expand our focus even further to include the wider fitness of the organism. For example, the combined use of a variety of measures may be most informative, including measures of: (1) brain functioning (EEG, MRI); (2) mental health (depression, anxiety, happiness); (3) personality (extraversion, internalization, neuroticism); (4) physiological functioning (HPA axis, immune system, autonomic nervous system); and (5) cognitive/neuropsychological functioning.

Third, genetic research requires very large sample sizes, which may be achieved primarily by pooling different data sets. The question then arises whether different operationalizations of the same construct affect the findings. In other words, can we pool data sets that include different quality-of-life measures? Studies are needed that examine the extent to which different measures assessing similar quality-of-life domains are based on one or more underlying biological substrates.

Fourth, the studies to date were conducted in both healthy volunteers and ill patients. The question arises to what extent the findings in healthy individuals are applicable to somatically or psychiatrically ill patients, and vice versa. For example, the extent to which negative affect behaves as a continuous trait where the same biological and genetic mechanisms are at stake in clinical depression as in non-pathological somberness remains to be empirically tested. Another example is pain. Studies are needed that increase our insight into the relevant biological mechanisms underlying pain experience. Pre-clinical studies may be performed where pain is experimentally induced in healthy volunteers, who are opioid naïve, and do not take other medication. The question about the extent to which the findings of such studies are applicable to patients needs to be examined in clinical studies in, for example, cancer patients, who have comorbidities and multiple medications to treat these conditions, including long-term opioids. Clearly, the applicability of the findings in other respondent groups needs to be continuously empirically examined.

The fifth but far from trivial question is how to move forward practically. Analyses of biological pathways will be a challenge because of the type of tissue required, which likely needs to be obtained from the CNS. Therefore, a first practical approach of the consortium will be the use of blood samples to establish genetic background (e.g., genetic variants) and gene expression profiles (e.g., cytokine levels) in relation to patient-reported quality of life.

With the establishment of the GENEQOL Consortium, it is our hope that the intriguing questions surrounding the genetic disposition of quality of life will be set on the research agenda and be studied widely. The GENEQOL Consortium aims to facilitate such investigations by supporting communication among members and with others outside the Consortium, and thus enabling networking and access to knowledge, skills, and ideas. The overall aim is to compile and pool existing and new data to carry out genetic analyses. As a means of communication within the Consortium and with others outside the Consortium, a website was built -- www.geneqol.org -- with open access and restricted access for Consortium members only. We actively welcome new, contributing members who are willing to identify relevant studies, obtain access to existing data sets, volunteer for tasks, or forward new and useful ideas and suggestions. Such combined efforts are needed to further research into the relatively novel question about the genetic disposition of quality of life.

Acknowledgments

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