Genetic Variations and Patient-Reported Quality of Life Among Patients With Lung Cancer

Jeff A. Sloan, Mariza de Andrade, Paul Decker, Jason Wampfler, Curtis Oswald, Matthew Clark, and Ping Yang

All authors: Mayo Clinic, Rochester, MN.

Submitted December 29, 2010; accepted December 20, 2011; published online ahead of print at www.jco.org on March 26, 2012.

Supported by National Institutes of Health Research Grants No. CA77118, CA80127, and CA84354 (P.Y.).

J.A.S. and M.d.A. contributed equally to this work.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Jeff A. Sloan, PhD, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: jsloan@mayo.edu.

© 2012 by American Society of Clinical Oncology

0732-183X/12/3014-1699/\$20.00

DOI: 10.1200/JCO.2010.34.5629

ABSTRACT

Purpose

Recent evidence has suggested a relationship between the baseline quality of life (QOL) self-reported by patients with cancer and genetic disposition. We report an analysis exploring relationships among baseline QOL assessments and candidate genetic variations in a large cohort of patients with lung cancer.

Patients and Methods

QOL data were provided by 1,299 patients with non-small-cell lung cancer observed at the Mayo Clinic between 1997 and 2007. Overall QOL and subdomains were assessed by either Lung Cancer Symptom Scale or Linear Analog Self Assessment measures; scores were transformed to a scale of 0 to 10, with higher scores representing better status. Baseline QOL scores assessed within 1 year of diagnosis were dichotomized as clinically deficient (CD) or not. A total of 470 single nucleotide polymorphisms (SNPs) in 56 genes of three biologic pathways were assessed for association with QOL measures. Logistic regression with training/validation samples was used to test the association of SNPs with CD QOL.

Results

Six SNPs on four genes were replicated using our split schemes. Three SNPs in the *MGMT* gene (adjusted analysis, rs3858300; unadjusted analysis, rs10741191 and rs3852507) from DNA repair pathway were associated with overall QOL. Two SNPs (rs2287396 [*GSTZ1*] and rs9524885 [*ABCC4*]) from glutathione metabolic pathway were associated with fatigue in unadjusted analysis. In adjusted analysis, two SNPs (rs2756109 [*ABCC2*] and rs9524885 [*ABCC4*]) from glutathione metabolic pathway were associated with pain.

Conclusion

We identified three SNPs in three glutathione metabolic pathway genes and three SNPs in two DNA repair pathway genes associated with QOL measures in patients with non-small-cell lung cancer.

J Clin Oncol 30:1699-1704. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Human genetic variation can modulate the risk of developing cancer, the risk of developing symptoms related to treatment, and the outcome of cancer disease processes and treatments.¹ There is emerging evidence for a genetic basis of patient-reported quality-of-life (QOL) outcomes.² Combining two disparate fields of endeavor like genetics and QOL assessment compounds the challenges each encounters, requiring careful attention to the capabilities, complexities, and limitations of both. The successes and challenges of QOL data have been well documented, including issues such as missing data, reliability, validity, and responsiveness to change.³ Similarly, genetic investigations have inherent validity and reliability challenges.^{4,5} For example, results of a report published in *Science* that purported to have identified 150 genetic variants of longevity

came into question, because different genotyping platforms had been used to scan the genome.⁶ The point here is that combining two fields of scientific enquiry requires careful attention to the capabilities, complexities, and limitations of both.

Fortunately, there are guidelines and established procedures for undertaking sound research in both fields. In QOL, multiple international efforts have produced techniques to resolve issues surrounding missing data and psychometrics so that patient-reported outcome (PRO) measures are actually more scientifically sound than clinician ratings.⁷⁻¹⁰ In genetic research, multiple guidelines exist^{11,12} to ensure high-quality scientific procedures are followed.

The concept of exploring the genetic basis of QOL was first put forward by Sloan et al¹³ in a 2004 American Society of Clinical Oncology plenary presentation¹⁴ as an ancillary investigation

of a practice-changing colorectal cancer clinical trial¹⁵ and subsequently published in *Current Problems in Cancer*.¹⁶ In this study, results indicated that among the limited number of genetic and QOL variables available, there was an unusually large number of relationships among these two influences. In particular, overall QOL and fatigue were found to have strong relationships with genetic polymorphisms of the dihydropyrimidine dehydrogenase and thymidylate synthetase variants. Subsequently, an international consortium (ie, GENEQOL; <http://www.geneqol.org>) was formed and began a concerted effort to review the state of the science and explore ways to move forward in a methodologic manner. The first publication of this group summarized the work to date in this area and provided the scientific background for the general field.¹⁷ Subsequently, a special issue of *Quality of Life Research* contained a series of articles summarizing the genetic background of common symptoms such as pain,¹⁸ fatigue,¹⁹ mood,^{2,20} and overall well-being.²¹ In addition, Sprangers et al²¹ presented an updated theoretic version of the classic Wilson and Cleary model that incorporated genetic variables into the structure of QOL assessment, interpretation, and manifestation.

At the same time, genetic studies in lung cancer have seen similar advances.²² Findings have included an understanding of the relationship between cytokines and lung cancer QOL²³ as well as the impact of smoking and health promotion behaviors on QOL of patients with lung cancer.²⁴ This combination of scientific advances and available resources allowed for the present investigation to explore the relationship between pathway-based genetic variations and multidomain QOL in a large cohort of patients with lung cancer.

PATIENTS AND METHODS

Starting in 1997, all patients with a pathologic diagnosis of primary lung cancer evaluated and treated at Mayo Clinic (Rochester, MN) were prospectively enrolled and observed for outcome research, using protocols approved by the Mayo Clinic Institutional Review Board; all participants provided written informed consent.^{25,26} Procedures for identifying and observing patients with lung cancer enrolled onto this program have been previously described.^{25,26} The follow-up process started within 6 months after diagnosis and continued annually until death. More than 90% of eligible patients with lung cancer participated. On enrollment, all patients completed baseline health-related surveys and were then mailed similar surveys on an annual basis. Information on demographics, previous or concurrent illnesses, tobacco usage and exposure, tumor staging, and cancer therapy were abstracted by study personnel from medical records and entered into a database. Participants self-identified their race on questionnaires. Baseline QOL assessment was defined as data derived from the first completed QOL questionnaire, and as such, there were no missing data issues for the questionnaires.

QOL Assessments

QOL was assessed using both the Lung Cancer Symptom Scale^{27,28} and a series of numeric linear analog self-assessment measures²⁹ to capture overall QOL and relevant domains of physical, mental, emotional, and social QOL as well as symptom measures of pain, fatigue, coughing, and dyspnea. Each QOL domain was scored on a scale of 0 to 10. A cutoff of score 5 or higher indicated a clinically meaningful deficit in that particular domain.³⁰ These assessments have been demonstrated to be valid and reliable for assessing the QOL of patients with cancer in numerous oncology clinical trials and observational studies.³¹ In fact, the linear analog self-assessment measures are the most often used measures for assessing QOL in cancer control trials supported by the National Cancer Institute Division of Cancer Prevention.³² Furthermore, these particular measures of overall QOL and domains were used in the pilot exploration of a relationship between QOL and genetic variables.¹⁶

Sample Preparation and Genotyping

The 175 SNPs in 56 genes included in the study were carefully selected in a two-step process using existing genotype data from the same parent cohort of patients.³³⁻³⁵ All patients who consented to blood DNA samples were genotyped using two custom-designed GoldenGate panels (Illumina, San Diego, CA): one with the 470-SNP panel and the other with the 1,025-SNP panel. One hundred seventy-five SNPs were included in both panels; these formed the basis for the current analyses (Appendix Table A1, online only). Between the two panels, 70 genes were selected from multiple pathways involved in chemotherapies (platinum, taxane, gemcitabine, and epidermal growth factor receptor inhibitor) after a review of the literature. Tag SNPs were identified via SNPApp, a tag SNP selection program developed by the Bioinformatics Core at the Mayo Clinic. SNPApp queries multiple public SNP data repositories (Hapmap, SeattleSNPs, and National Institute for Environmental Health Science SNPs) that contain information on known SNPs, using ldSelect (<http://droog.gs.washington.edu/ldSelect.html>) to identify tag SNPs for the genes or regions of interest. SNPs within 5 kb of each gene with a minor allele frequency (MAF) ≥ 0.05 for European populations were used as candidate SNPs, and tag SNPs were identified with a pairwise linkage disequilibrium threshold of $r^2 \geq 0.8$. For a given gene, the SNP selection procedure used the SNP data repository with the greatest number of SNPs with a MAF ≥ 0.05 and the greatest number of linkage disequilibrium bins that met GoldenGate assay (Illumina) quality score thresholds. Nonsynonymous SNPs were preferentially selected as tags when they were identified, provided that their metrics were equivalent to those of alternative tag SNPs.

Genotyping and quality control were performed in the Mayo Clinic Genomics Shared Resource. Concordance among the three genomic control DNA samples (parents, child, trio) in duplicates and within-plate replicates was 100%. All samples were successfully genotyped, with an average call rate of 99.1%; 111 SNPs failed genotyping. Of the SNPs with genotyping data, the call rate was $> 95\%$, and the MAF was > 0.001 for all. SNPs with a Hardy-Weinberg equilibrium (HWE) test $P < .001$ ($n = 16$) and/or monomorphic ($n = 17$) were excluded. In developing this article, the authors reviewed the REMARK criteria for genetics studies to ensure that all the relevant criteria were met.

Statistical Methods

Patient cases were defined as those with lung cancer with QOL score > 5 , and controls were patients with lung cancer with QOL ≤ 5 . This cutoff has been validated and confirmed by our group and others.^{30,31} Patient case/control analysis was performed across the following QOL domains: overall, pain, fatigue, coughing, and dyspnea.

Before any analysis, we assessed whether the SNP distribution varied between patient cases and controls; the allele frequencies were well matched, with a correlation coefficient of > 0.98 for each patient case/control group. We also assessed the frequency distribution at each SNP locus for HWE under the allele Mendelian biallelic expectation using the χ^2 test. To investigate the association of SNPs with poor (score ≤ 5) versus good QOL (score > 5), a logistic regression that included each SNP as an independent variable was used. We considered three genetic models: additive, dominant, and recessive. The additive genetic model assumed each SNP as a continuous measure (0, 1, 2), where 0, 1, or 2 was the number of copies of the minor allele. The dominant genetic model assumed each SNP as a discrete measure (0, 1), where 0 was the zero copy of the minor allele, and 1 was at least one copy of the minor allele. The recessive model was similar to the dominant model, except that 0 represented zero and one copy of the minor allele, and 1 represented two copies of the minor allele. We considered two scenarios to study the power of the study. The first scenario used one SNP with common allele frequency (Table 1; overall unadjusted model, rs3852507). The second scenario used one SNP with a smaller allele frequency (Table 1; fatigue unadjusted model, rs9524885). In the first case, the power was 57%, and in the second, 71%, considering a type I error of 0.05.

For this analysis, we randomly split our sample into test (approximately one third of the patients) and replication samples (approximately two thirds of the patients). SNPs with P values less than .05 in the test sample were assessed for validation in the replication sample. Pooled analyses of the test and replication samples were performed on SNPs that replicated ($P < .05$ in each

Table 1. Association Results: Significant Findings for Relationships Between SNPs and QOL Variables

Split	Chromosome	Pathway	Gene	SNP	Position	No. of Patients			MAF		OR	95% CI	P
						Total	Patient Cases	Controls	Patient Cases	Controls			
Overall random unadjusted*													
One third	10	DNA	MGMT	rs10741191	131197266	407	293	114	0.45	0.36	1.38	1.01 to 1.88	.0407
Two thirds	10	DNA	MGMT	rs10741191	131197266	892	664	228	0.45	0.38	1.34	1.08 to 1.67	.0086
Overall	10	DNA	MGMT	rs10741191	131197266	1299	957	342	0.45	0.37	1.36	1.13 to 1.622	< .001
One third	10	DNA	MGMT	rs3852507	131289606	407	293	114	0.55	0.46	1.38	1.03 to 1.87	.03385
Two thirds	10	DNA	MGMT	rs3852507	131289606	892	664	228	0.51	0.45	1.27	1.03 to 1.58	.02746
Overall	10	DNA	MGMT	rs3852507	131289606	1299	957	342	0.52	0.45	1.30	1.10 to 1.55	.00282
Overall random adjusted													
One third	10	DNA	MGMT	rs3858300	131232119	405	293	114	0.40	0.34	1.48	1.04 to 2.11	.03029
Two thirds	10	DNA	MGMT	rs3858300	131232119	892	664	228	0.41	0.36	1.29	1.01 to 1.64	.04227
Overall	10	DNA	MGMT	rs3858300	131232119	1297	957	342	0.41	0.36	1.34	1.10 to 1.64	.00377
Fatigue random unadjusted													
One third	14	GSH	GSTZ1	rs2287396	76863945	404	210	194	0.15	0.10	1.53	1.02 to 2.30	.03887
Two thirds	14	GSH	GSTZ1	rs2287396	76863945	877	441	436	0.15	0.11	1.45	1.09 to 1.92	.01
Overall	14	GSH	GSTZ1	rs2287396	76863945	1281	651	630	0.15	0.11	1.48	1.17 to 1.86	< .001
One third	13	GSH	ABCC4	rs9524885	94733590	404	210	194	0.11	0.16	0.66	0.45 to 0.98	.03785
Two thirds	13	GSH	ABCC4	rs9524885	94733590	877	441	436	0.11	0.16	0.68	0.52 to 0.89	.00487
Overall	13	GSH	ABCC4	rs9524885	94733590	1281	651	630	0.11	0.16	0.67	0.54 to 0.84	< .001
Pain random adjusted													
One third	10	GSH	ABCC2	rs2756109	101548736	400	344	58	0.39	0.5	0.62	0.42 to 0.94	.02259
Two thirds	10	GSH	ABCC2	rs2756109	101548736	885	759	126	0.44	0.49	0.74	0.55 to 0.98	.0373
Overall	10	GSH	ABCC2	rs2756109	101548736	1285	1103	184	0.42	0.49	0.70	0.55 to 0.88	.00275
One third	13	GSH	ABCC4	rs9524885	94733590	400	344	58	0.13	0.20	0.58	0.35 to 0.98	.0406
Two thirds	13	GSH	ABCC4	rs9524885	94733590	885	759	126	0.13	0.19	0.70	0.49 to 0.99	.04502
Overall	13	GSH	ABCC4	rs9524885	94733590	1285	1103	184	0.13	0.20	0.66	0.49 to 0.88	.00503

Abbreviations: GSH, glutathione; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism.

*Random means individuals were randomly assigned to testing and validating sets.

sample). Both univariable and multivariable analyses were performed. The multivariable analyses included age, sex, smoking status (never, former, current), surgery (yes or no), radiation therapy (yes or no), chemotherapy (yes or no), and performance score as covariates. Disease stage was not included in the multivariable analysis because of preliminary collinearity checks, which indicated that stage and treatment were highly correlated, and treatment was a stronger predictor than stage for QOL. Hence, only treatment was included in the multivariable analysis.

RESULTS

Patient characteristics are summarized in Table 2. This study included 1,299 patients (47% female; 53% male) who were 65 ± 10 years of age ($\pm$ standard deviation). A majority were former (51%) or current (30%) smokers. Primary histologies included adenocarcinoma (51%) and squamous cell carcinoma (20%). Stage breakdown was as follows: stages I (32%), II (9%), III/limited (32%), and IV/extensive (27%). Eighty-eight percent of patients had a performance score ≤ 1 . QOL domains included overall (74% with score > 5), pain (86%, score > 5), fatigue (51%, score > 5), coughing (79%, score > 5), and dyspnea (62%, score > 5). Descriptions of the QOL data are summarized in Table 3.

From the 470 SNPs used in the analysis, six SNPs on four genes were replicated using our split schemes. Three SNPs in the *MGMT* gene (adjusted analysis, rs3858300; unadjusted analysis, rs10741191 and rs3852507) from DNA repair pathway were associated with overall QOL. Two SNPs (rs2287396 [*GSTZ1*] and rs9524885 [*ABCC4*])

from glutathione metabolic pathway were associated with fatigue in unadjusted analysis. Two SNPs (rs2756109 [*ABCC2*] and rs9524885 [*ABCC4*]) from the glutathione metabolic pathway were associated with pain in adjusted analysis.

Table 1 highlights the six significant SNPs and associated QOL measures by their correspondent odds ratios using an additive genetic model. Similar results were obtained using recessive and dominant genetic models (results not shown). Three SNPs (rs3858300, rs10741191, and rs10741191) on the *MGMT* gene were associated with 34%, 36%, and 30% higher risk of reporting a deficit in overall QOL, respectively. SNP rs2287396 on the *GSTZ1* gene was associated with a 47% higher risk of reporting a deficit in fatigue. SNP rs9524885 on the *ABCC4* gene was associated with a 33% lower risk of reporting clinically significant deficits in fatigue. SNPs associated with pain were rs2756109 and rs9524885 on the *ABCC4* gene, with a 30% and 34% lower risk of pain, respectively.

DISCUSSION

We identified three SNPs in four glutathione metabolic pathway genes and three in two DNA repair pathway genes associated with QOL measures in patients with non-small-cell lung cancer. Our findings represent a step forward in advancing our knowledge regarding the relationship between genetic processes and PROs. In our study, overall QOL was related to SNPs on the DNA repair gene *MGMT*. This gene has previously been reported to be related to biologic function in

Table 2. Patient Demographics and Clinical Characteristics

Characteristic	No.	%
Age at diagnosis, years		
No. of patients	1,299	
Mean	64.8	
SD	10.35	
Range	18.0-93.0	
Sex		
Female	605	46.6
Male	694	53.4
Cigarette smoking status		
Never	248	19.1
Former	664	51.1
Current	387	29.8
Cell type		
Missing	0	
Adenocarcinoma/BAC	659	50.7
Squamous cell	264	20.3
Small cell	135	10.4
Other NSCLC	179	13.8
Carcinoid/salivary	62	4.8
Stage		
Missing	6	
I	409	31.6
II	120	9.3
III/limited	415	32.1
IV/extensive	349	27
First performance status		
No. of patients	1,297	
Mean	0.72	
SD	0.72	
Median	1	
Range	0.0-4.0	
Surgery		
No	565	43.5
Yes	734	56.5
Chemotherapy		
No	400	30.8
Yes	899	69.2
Radiation		
No	774	59.6
Yes	525	40.4

Abbreviations: BAC, bronchioloalveolar carcinoma; NSCLC, non-small-cell lung cancer; SD, standard deviation.

Table 3. QOL Results for 1,299 Patients Reported Within 1 Year of Diagnosis

QOL	No.	%
Overall > 5		
Missing	0	
No	342	26.3
Yes	957	73.7
Pain > 5		
Missing	12	
No	184	14.3
Yes	1,103	85.7
Fatigue > 5		
Missing	18	
No	630	49.2
Yes	651	50.8
Coughing > 5		
Missing	12	
No	277	21.5
Yes	1,010	78.5
Dyspnea > 5		
Missing	14	
No	494	38.4
Yes	791	61.6

Abbreviation: QOL, quality of life.

patients with lung cancer.³⁶ The proteins coded for by the *MGMT* gene protect cells against the somatic point mutations frequently observed in various human neoplasms. Inactivation of the *MGMT* gene by promoter hypermethylation is associated with increased frequency of G:C → A:T transitions in the *KRAS* and *TP53* genes in lung cancers.³⁶ The concept that these biologic functions translate into an impact on overall QOL is hence plausible and consistent with our previous research.

The *ABCC2* and *ABCC4* genes have been linked to chemotherapy resistance.³⁷ These genes were also found to be related to fatigue in our previous work in patients with colorectal cancer.¹⁶ *ABCC* proteins transport various molecules across extra- and intracellular membranes and might be a means of identifying which patients with cancer are likely to experience debilitating toxicity from anticancer agents such as cisplatin. These genes transport organic anions, including

protease inhibitors, and have a role in pain associated with statin therapy.³⁸ Similarly, the *GSTZ1* gene is involved in processing anticancer agents that result in fatigue. *GSTZ1* is a member of the glutathione S-transferase super family, which encodes multifunctional enzymes important in the detoxification of electrophilic molecules, including carcinogens, mutagens, and several therapeutic drugs, by conjugation with glutathione.³⁹ This enzyme also plays a role in the catabolism of phenylalanine and tyrosine. The relationship seen with fatigue in our study furthers the hypothesis that interactions at the cellular level can result in impaired signal processing, which translates at the macro level into overall fatigue.⁴⁰

Several *a priori* hypotheses were born out by empirical study. Specifically, genetic components for patient-reported fatigue and overall QOL were identified, similar to those found in the previous work of our team and others. We previously found 21 SNPs in cytokine genes associated with symptom burden and QOL outcomes.^{13,14,16} Our investigation involving patients with colorectal cancer demonstrated relationships among patient-reported QOL domains and polymorphisms associated with the metabolism of anticancer chemotherapy agents.¹⁶

There are two obvious next steps. First, replication studies are needed to refine our specific genetic markers related to patient-reported QOL-related domains. Recent advances in the science of PRO assessment have shown that self-reported symptoms (phenotype) can be measured with high reliability. The GENEQOL consortium has generated from the literature a list of most likely candidate genes to pursue and has had preliminary success in validation of pain, fatigue, and overall QOL outcomes.² This group has also presented a theoretic framework and identified biologic pathways to explain how QOL variables can have a genetic underpinning.^{17,21}

The second step is to explore whether the newly identified genetic biomarkers can be used in a clinical setting to indicate that an individual is susceptible to experiencing deficits in QOL domains in response

to cancer diagnosis, disease process, treatment, and recovery. This is similar to using other biomarkers such as *CA125* or *BRCA1* to identify patients at risk for cancer recurrence or identify which agent is more likely to be successful.⁴¹ There are numerous supportive care interventions available on identification of a QOL deficit risk. For example, if a patient is identified as being genetically predisposed to deficits in fatigue during cancer treatment, prophylactic monitoring can be initiated for hemoglobin levels, and patient-reported fatigue can be assessed. Interventions might include pharmacologies (eg, erythropoietin stimulating agents, ginseng), physical therapy (eg, exercise), and psychosocial initiatives (eg, stress management). One might consider less toxic regimens for such patients or have a priori protective dose modification plans to prevent or alleviate the expected fatigue. Identifying patients at high risk for QOL-related deficits can actually improve the course of treatment by maintaining patient QOL throughout the disease process. Earlier, we demonstrated that a psychosocial intervention could improve patient QOL.⁴² Recent work has indicated that deficits in QOL are related to increased mortality among a broad spectrum of patients with cancer.^{43,44}

There are notable limitations of this study. The lung cancer survivors were drawn from a single Midwest institution with a population homogeneous for race, socioeconomic status, and treatment modalities. Although the sample used did represent a mixture of lung cancer histologic types, there was no evidence that QOL was histologic type specific, despite the fact that there was significant difference in survival, particularly among patients with carcinoids (typical or atypical).

The key aspect of this body of work is that the assessments have been well studied and established to be as reliable, valid, and reproducible as any other laboratory biomarker.⁴⁵ Hence, given that we now

know these valid PRO assessments can identify vulnerable subpopulations reliably, and we are beginning to uncover the biologic processes that lead to deficits in PRO QOL domains, we can think of these measures as just another surrogate end point biomarker (SEB). The source of the SEB may be a patient's cognitive report rather than a laboratory specimen, but psychometric research has demonstrated equal if not superior prognostic characteristics and less measurement error among PROs compared with laboratory-based alternatives. As with any SEB, PROs are not perfect, but they do not have to be perfect; they need to be useful and practical for improving cancer care. The evidence produced by this and other recent work for integrating PRO assessments into routine practice and other clinical and basic research as just another vital sign is mounting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jeff A. Sloan, Mariza de Andrade, Paul Decker, Matthew Clark, Ping Yang

Financial support: Ping Yang

Administrative support: Ping Yang

Provision of study materials or patients: Ping Yang

Collection and assembly of data: Paul Decker, Jason Wampfler, Curtis Oswald, Ping Yang

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Sherbt GV, Lakshmi MS: The Genetics of Cancer: Genes Associated with Cancer Invasion, Metastasis and Cell Proliferation. Waltham, MA, Academic Press, 1997
2. Sprangers MA, Bartels M, Veenhoven R, et al: Which patient will feel down, which will be happy? The need to study the genetic disposition of emotional states. *Qual Life Res* 19:1429-1437, 2010
3. Sloan JA, Dueck AC, Erickson PA, et al: Analysis and interpretation of results based on patient-reported outcomes. *Value Health* 10:S106-S115, 2007 (suppl 2)
4. Hübner C, Petermann I, Browning BL, et al: Triallelic single nucleotide polymorphisms and genotyping error in genetic epidemiology studies: MDR1 (ABCB1) G2677/T/A as an example. *Cancer Epidemiol Biomarkers Prev* 16:1185-1192, 2007
5. Pluzhnikov A, Below JE, Konkashbaev A, et al: Spoiling the whole bunch: Quality control aimed at preserving the integrity of high-throughput genotyping. *Am J Hum Genet* 87:123-128, 2010
6. Sebastiani P, Solovieff N, Puca A, et al: Genetic signatures of exceptional longevity in humans. *Science* [epub ahead of print on July 1, 2010]
7. Fayers PM, Hopwood P, Harvey A, et al: Quality of life assessment in clinical trials: Guidelines and a checklist for protocol writers—The UK Medical Research Council experience: MRC Cancer Trials Office. *Eur J Cancer* 33:20-28, 1997
8. De Haes J, Curran D, Young T, et al: Quality of life evaluation in oncological clinical trials: The EORTC model. *Eur J Cancer* 36:821-825, 2000
9. Bottomley A, Jones D, Claassens L: Patient-reported outcomes: Assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. *Eur J Cancer* 45:347-353, 2009
10. Efficace F, Bottomley A, Osoba D, et al: Beyond the development of health-related quality of life (HRQOL) measures: A checklist for evaluating HRQOL outcomes in cancer clinical trials—Does HRQOL evaluation in prostate cancer research inform clinical decision making? *J Clin Oncol* 21:3502-3511, 2003
11. Bogardus ST Jr, Concato J, Feinstein AR: Clinical epidemiological quality in molecular genetic research: The need for methodological standards. *JAMA* 281:1919-1926, 1999
12. Pelias MZ: Federal regulations and the future of research in human and medical genetics. *J Contin Educ Health Prof* 21:238-246, 2001
13. Sloan JA, McLeod H, Sargent D, et al: Preliminary evidence of relationship between genetic markers and oncology patient quality of life (QOL). *J Clin Oncol* 22, 2004 (suppl; abstr 5)
14. Hampton T: Patients' genes may influence quality of life before cancer chemotherapy. *JAMA* 292:673-674, 2004
15. Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22:23-30, 2004
16. Sloan JA, Zhao CX: Genetics and quality of life. *Curr Probl Cancer* 30:255-260, 2006
17. Sprangers MA, Sloan JA, Veenhoven R, et al: The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Res Hum Genet* 12:301-311, 2009
18. Shi Q, Cleeland CS, Klepstad P, et al: Biological pathways and genetic variables involved in pain. *Qual Life Res* 19:1407-1417, 2010
19. Barsevick A, Frost M, Zwiderman A, et al: I'm so tired: Biological and genetic mechanisms of cancer-related fatigue. *Qual Life Res* 19:1419-1427, 2010
20. Chauhan C: Optimists doing something different: A patient's view of geneQOL research. *Qual Life Res* 19:1405-1406, 2010
21. Sprangers MA, Sloan JA, Barsevick A, et al: Scientific imperatives, clinical implications, and theoretical underpinnings for the investigation of the relationship between genetic variables and patient-reported quality-of-life outcomes. *Qual Life Res* 19:1395-1403, 2010
22. Sugimura H, Yang P: Long-term survivorship in lung cancer: A review. *Chest* 129:1088-1097, 2006
23. Rausch SM, Clark MM, Patten C, et al: Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. *Cancer* 116:4103-4113, 2010

24. Clark MM, Novotny PJ, Patten CA, et al: Motivational readiness for physical activity and quality of life in long-term lung cancer survivors. *Lung Cancer* 61:117-122, 2008
25. Yang P, Allen MS, Aubry MC: Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest* 128:452-462, 2005
26. Svobodnik A, Yang P, Novotny PJ, et al: Quality of life in 650 lung cancer survivors 6 months to 4 years after diagnosis. *Mayo Clin Proc* 79:1024-1030, 2004
27. Hollen PJ, Gralla RJ, Kris MG, et al: Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer* 29A:S51-S58, 1993 (suppl 1)
28. Hollen PJ, Gralla RJ, Kris MG, et al: Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). *Support Care Cancer* 7:140-148, 1999
29. Locke DE, Decker PA, Sloan JA, et al: Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manage* 34:628-638, 2007
30. Butt Z, Wagner LI, Beaumont JL, et al: Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. *J Pain Symptom Manage* 35:20-30, 2008
31. Sloan JA, Berk L, Roscoe J, et al: Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials network. *J Clin Oncol* 25:5070-5077, 2007
32. Buchanan DR, O'Mara A, Kelaghan JW, et al: Challenges and recommendations for advancing the state-of-the-science of quality-of-life assessment in symptom management trials. *Cancer* 110:1621-1628, 2007
33. Sun Z, Chen J, Aakre J, et al: Genetic variation in glutathione metabolism and DNA repair genes predicts survival of small-cell lung cancer patients. *Ann Oncol* 21:2011-2016, 2010
34. Pankratz VS, Sun Z, Aakre J, et al: Systematic evaluation of genetic variants in three biological pathways on patient survival in low-stage non-small cell lung cancer. *J Thorac Oncol* 6:1488-1495, 2011
35. Li Y, Sun Z, Cunningham JM, et al: Genetic variations in multiple drug action pathways and survival in advanced-stage non-small cell lung cancer treated with chemotherapy. *Clin Cancer Res* 17:3830-3840, 2011
36. Krześniak M, Butkiewicz D, Samojedny A, et al: Polymorphisms in TDG and MGMT genes: Epidemiological and functional study in lung cancer patients from Poland. *Ann Hum Genet* 68:300-312, 2004
37. Colombo S, Soranzo N, Rotger M, et al: Influence of ABCB1, ABCC1, ABCC2, and ABCG2 haplotypes on the cellular exposure of nelfinavir in vivo. *Pharmacogenet Genomics* 15:599-608, 2005
38. Niemi M: Transporter pharmacogenetics and statin toxicity. *Clin Pharmacol Ther* 87:130-133, 2010
39. Blackburn AC, Woollatt E, Sutherland GR, et al: Characterization and chromosome location of the gene GSTZ1 encoding the human zeta class glutathione transferase and maleylacetoacetate isomerase. *Cytogenet Cell Genet* 83:109-114, 1998
40. Fang YY, Kashkarov U, Anders MW, et al: Polymorphisms in the human glutathione transferase zeta promoter. *Pharmacogenet Genomics* 16:307-313, 2006
41. Recht A, Edge SB, Solin LJ, et al: Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19:1539-1569, 2001
42. Rummans TA, Clark MM, Sloan JA, et al: Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: A randomized controlled trial. *J Clin Oncol* 24:635-642, 2006
43. Gotay CC, Kawamoto CT, Bottomley A, et al: The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol* 26:1355-1363, 2008
44. Montezari A: Quality of life data as prognostic indicators of survival in cancer patients: An overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* 7:102, 2009
45. Hahn EA, Cella D, Chassany O, et al: Precision of health-related quality-of-life data compared with other clinical measures. *Mayo Clin Proc* 82:1244-1254, 2007