Studying the Biological Underpinnings of Quality of Life: Update on the GeneQol Consortium Activities

Mirjam A.G. Sprangers, Melissa Thong and Jeff Sloan

ISOQOL, Miami, October 2013
Co-Authors

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Eddy Wierenga  University of Amsterdam, The Netherlands
Jasvinder Singh  University of Alabama, USA
Objectives

• To provide an update of the GeneQol Consortium activities
• To provide an updated overview of the biological pathways, candidate genes and molecular markers involved in QOL domains
Objectives

• To provide an update of the GeneQol Consortium activities

• To provide an updated overview of the biological pathways, candidate genes and molecular markers involved in QOL domains
Brief History

2009-date
Overall objective
To establish strong collaborative and interdisciplinary relationships to translate and conduct clinically relevant research to identify and investigate potential genes and genetic variants involved in QOL
Translational Objective

Results of this work will enable providers to identify which patients are likely to experience symptoms and QOL deficits from disease and its treatments in order to:

– intervene prophylactically,
– monitor patient well-being,
– improve treatment decision-making, and
– improve outcomes
The Future?

As you can see from your genetic printout you only think you're depressed whereas you are in fact a jolly, happy full of the joys of spring type person!
“Doctors will eventually use genetic patterns for several tasks -- to tell whether a cancer will spread, to predict how various therapies such as specific drugs or radiation will work, and perhaps even to see how someone's QOL will be affected.”

(Sloan and Zhao, 2006)
<table>
<thead>
<tr>
<th>cellular biology</th>
<th>molecular biology</th>
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<tr>
<td>behavioral genetics</td>
<td>pharmacogenetics</td>
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<td>clinical psychology</td>
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GENEQOL Consortium
The Mayo Clinic/University of Amsterdam International Consortium for Genetics and Quality of Life Research
Mayo School of Continuing Medical Education

Genetic Disposition and Patient-Reported Quality of Life Outcomes

February 26, 2009
Leighton Auditorium
Siebens Building
Mayo Clinic
Rochester, MN

Program Directors
Jeff A. Neumaier, Ph.D.
Mirjam Spranger, Ph.D.
Meeting Objectives

• Develop a list of potential biological pathways, genes and genetic variants involved in QOL domains, by reviewing the state of the art regarding current genetic knowledge

• Design a research agenda to investigate and validate those genes and genetic variants of QOL
Five Outcomes Under Study

- Negative emotional states (i.e. depression, anxiety)
- Positive emotional states (i.e. happiness, subjective wellbeing, life satisfaction)
- Perceived or self-rated physical health or functioning
- Pain
- Fatigue
The Establishment of the GENEQOL Consortium to Investigate the Genetic Disposition of Patient-Reported Quality-of-Life Outcomes

Mjara A. G. Sprangers\(^{1}\), Jeff A. Sloan\(^{2}\), Ruut Veenhoven\(^{1}\), Charles S. Cleeland\(^{3}\), Michelle Y. Halyard\(^{4}\), Amy P. Abersuch\(^{5}\), Frank Banz\(^{6}\), Andrea M. Barritt\(^{7}\), Mark Barseghian\(^{8}\), Dorothy H. Bots\(^{9}\), Cynthia Clauw\(^{10}\), Aneesha C. Dadu\(^{11}\), Marcelo H. Frosti\(^{12}\), Per Hall\(^{13}\), Pål Kleppstad\(^{14}\), Richard G. Martin\(^{15}\), Christina Maszkowski\(^{16}\), Marnia Moss\(^{17}\), Benjamin Moss\(^{18}\), Croswell J. F. Van Noorden\(^{19}\), Donald L. Partridge\(^{20}\), Nancy L. Pederson\(^{21}\), Mary E. Popla\(^{22}\), Quiling Shi\(^{23}\), Genni Shimozaki\(^{24}\), Javvinder A. Singh\(^{25}\), Ping Yang\(^{26}\), and Alice H. Zwiers\(^{27}\)

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\(^{2}\) Department of Health Sciences Research, Mayo Clinic, Rochester, MN, United States of America
\(^{3}\) University of California, Irvine, CA, United States of America
\(^{4}\) Department of Social Science, Erasmus University Rotterdam, Rotterdam, The Netherlands
\(^{5}\) Department of Integrative Research, The University of Texas, M. D. Anderson Cancer Center, Houston, TX, United States of America
\(^{6}\) Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, United States of America
\(^{7}\) Duke Cancer Genes Research Program, Duke University Medical Center, Durham, NC, United States of America
\(^{8}\) Laboratory of Neurogenetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
\(^{9}\) Nursing Research and Education, Fox Chase Cancer Center, Philadelphia, PA, United States of America
\(^{10}\) Department of Biological Psychology, RD University, Amsterdam, the Netherlands

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 the primary patient-reported quality-of-life outcomes as initial target: 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 these 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 new quality-of-life domains. Intriguing questions arising from this endeavor are discussed.
Scientific imperatives, clinical implications, and theoretical underpinnings for the investigation of the relationship between genetic variables and patient-reported quality-of-life outcomes

Mirjam A. G. Spruyt &, Joff A. Shua &, Andreus Baracevich &,
Cynthia Chauhan &, Alphonse C. Burch &, Hyo Rast &,
Quilling Shi &, Cornelis J. F. Van Noorden &: The GENEQOL Consortium

Biological pathways and genetic variables involved in pain

Quilling Shi & Charles C. Cleland & Pål Klepsjå &
Christine Młoski & Nancy L. Pederson

Which patient will feel down, which will be happy? The need to study the genetic disposition of emotional states

Mirjam A. G. Spruyt &, Melpa Bergetis &, Reni Veenhoven &, Frank Bass &,
Nicholas G. Martin &, Miriam Meulig &, Benjamin Mavas &, Mary E. Brough &,
Gen SHMIS &, Dick Snuk &: The GENEQOL Consortium

Optimists doing something different: a patient’s view of geneQOL research

Cynthia Chauhan

I’m so tired: biological and genetic mechanisms of cancer-related fatigue

Andrea Baracevich &, Marlene Frost &,
Alfie Zwienerman &, Pål Hall &,
Michele Hautard &: GENEQOL Consortium

The Generation R study: a candidate gene study and genome-wide association study (GWAS) on health-related quality of life (HRQOL) of mothers and young children

Helm Rast &, Liese van Bass &, Vincent V. Wall &,
Joanne M. Landgraaf &, David Feeny &, Henriette A. Moll &,
Albert Hofman &, Johan P. Mackenbach
Patient-reported quality of life refers to the physical, functional, and psychosocial consequences of disease and treatment as experienced by patients themselves. There is emerging evidence for a genetic basis of patient-reported quality of life.

The overall objective of the GeneQoL Consortium is to establish strong collaborative and interdisciplinary relationships to conduct clinically relevant research to identify and investigate biological mechanisms, potential genes and genetic variants involved in quality of life.

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. The Consortium targets data of patients as well as general populations.

Our vision for the future is that emerging insight into the genetic basis 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 tailor preventive strategies and/or specific support and treatment.

Members

The GeneQoL Consortium currently involves 40 members representing a wide range of disciplines, including cellular biology, molecular biology, behavioral genetics, pharmacogenetics, biological psychology, genetic epidemiology, statistical genetics, sociology, psychiatry, medical psychology, clinical psychology, nursing, and oncology.

New Contributing Members are Welcome

The members live in 10 different countries.

http://geneqol-consortium.org/
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Portfolio: Planned Papers

Table I: Brief communications/reviews to put the genetic disposition of patient reported outcomes on the agenda

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<th>Objective</th>
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<td>To provide evidence that quality-of-life research is stringent and generates meaningful results, to summarize emerging evidence for a genetic basis of quality-of-life outcomes, to provide the rationale for pursuing this line of research and the establishment of the GENEQOL consortium, to outline a range of research objectives that evolve from this work.</td>
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### Table II: Reviews relevant for the genetic disposition of patient-reported outcomes

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<td>1. Statistical challenges in the analysis of quality-of-life and genetic variables: Substantial but surmountable</td>
<td>To highlight the statistical challenges associated with genetic studies that incorporate quality-of-life data, to present available statistical strategies, and to show that analytical challenges of quality-of-life and genetic variables can be overcome with available methods.</td>
<td>Quality of Life Researchers / Qual Life Res</td>
<td>Dueck, Schwartz / Spargers</td>
<td>Zwinderman, Yang, Bottomley, Coens, Reeve, Sloan</td>
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## Table III: Data-driven Papers

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<tr>
<td>1. Gene expression and quality of life in patients with Marfan disease</td>
<td>To examine the association between level of gene expression and the SF-36 in a group of 67 Marfan patients (congenital heart disease)</td>
<td>PLoS One</td>
<td>Thong / Sprangers</td>
<td>Schoomans, Radonic, Mulder, Zwinderman</td>
<td>Planned</td>
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• To provide an updated overview of the biological pathways, candidate genes and molecular markers involved in QOL domains
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• To provide an updated overview of the biological pathways, candidate genes and molecular markers involved in QOL domains: fatigue, pain, emotional functioning (depressed mood, well-being/happiness), social functioning, overall QOL
Disclaimer

• The abundance of data in the literature is overwhelming
• This presentation is far from exhaustive
Disclaimer

• The abundance of data in the literature is overwhelming
• This presentation is far from exhaustive
• We present a selection of the most interesting findings
• Full paper is under review
Literature Search

• Literature search in PubMed (2007-2012)
• For pain and depressed mood: 2011-2012
• Articles or book chapters found through reference checking or personal communication (until June, 2013)
Literature Search

- For pain and depressed mood: 2011-2012
- Articles or book chapters found through reference checking or personal communication (until June, 2013)
- A gene or molecular marker is included if there is at least one publication (either empirical, meta-analysis or review) reporting its significant association with a QOL domain
<table>
<thead>
<tr>
<th>Quality of Life Domains</th>
<th>Biological Pathways*</th>
<th>Candidate genes</th>
<th>Biomolecular markers</th>
<th>Literature</th>
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<tbody>
<tr>
<td>Pain</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Disease-related pain/pain perception</td>
<td>• Dorsal pain</td>
<td>• COMT, CRHBP</td>
<td>-NR-</td>
<td>(41-50)</td>
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<tr>
<td></td>
<td>• Synaptic synapse</td>
<td></td>
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<tr>
<td></td>
<td>• Serotoninergic synapse</td>
<td>• 5-HT (SLC6A4), 5-HT2A, HTR1A, TPH1</td>
<td>-NR-</td>
<td>(2, 46, 51-56)</td>
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<td></td>
<td>• Cytokine-cytokine receptor interaction</td>
<td>• CX3CR1</td>
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<td>(57)</td>
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<td></td>
<td>• Neuropeptide ligand-receptor interaction</td>
<td>• OPRM1, HTR1A</td>
<td>-NR-</td>
<td>(50, 56, 58)</td>
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<td></td>
<td>• Phagosome</td>
<td>• HLA-DRB1</td>
<td>-NR-</td>
<td>(55)</td>
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<td>• Endocrine and other factor-regulated calcium reabsorption</td>
<td>• ER-α</td>
<td>• Estrogen</td>
<td>(46)</td>
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<td>(46, 49)</td>
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<tr>
<td></td>
<td>• Glucocorticoid/Mineralocorticoid receptor</td>
<td>• SERPINA6</td>
<td>-NR-</td>
<td>(49)</td>
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<td></td>
<td>• Adipocytokine signaling pathway</td>
<td>• POMC</td>
<td>-NR-</td>
<td>(49)</td>
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<td></td>
<td>• Sodium channel transporter</td>
<td>• SCN9A</td>
<td>-NR-</td>
<td>(59, 60)</td>
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Candidate Gene Approach
Hypothesis driven genetic marker selection, e.g. based on expected biological pathway
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Hypothesis driven genetic marker selection, e.g. based on expected biological pathway

Advantage: Knowledge-based
Disadvantage: May miss important genes
Genome Wide Association Studies: GWAS
Agnostic approach to examine genetic variants across the whole genome
Genome Wide Association Studies: GWAS

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Genome Wide Association Studies: GWAS
Agnostic approach to examine genetic variants across the whole genome

Advantage:
Unexpected finding

Disadvantage:
Huge sample sizes
Pain
Candidate Gene Approach For Pain

Dopaminergic synapse

COMT
Candidate Gene Approach For Pain

Dopaminergic synapse

COMT

Serotonergic synapse

5HTT
Candidate Gene Approach For Pain

Dopaminergic synapse

COMT

Serotonergic synapse

5HTT

Neuroactive ligand-receptor interaction

OPRM1
Candidate Gene Approach For Pain

- Dopaminergic synapse
- Serotonergic synapse
- Neuroactive ligand-receptor interaction
- Sodium chemical transporter

- COMT
- 5HTT
- OPRM1
- SCN9A
Candidate Gene Approach For Pain: Conclusions

- Major pathways involved are related to: neurotransmission, inflammation, and response to analgesics
- COMT is associated with multiple sorts of pain
GWAS For Pain

- FAM119A
- rs13361160
- CREB
- TCL1A
- L1A
GWAS For Pain

Chromosome 5p15.2

FAM119A  TCL1A  CREB

rs13361160
GWAS For Pain: Conclusions

- Studies limited to single cohorts in specialized settings
- Identified gene candidates not intuitively biological plausible
- Inflammation and neuronal transmission are promising targets
Depressed Mood
GWAS for Depression
GWAS for Depression: Conclusions

• A number of GWAS studies did not report any significant finding
• Results are inconclusive due to small effect sizes
Candidate Gene Approach for Depression

- Numerous susceptible genes have been suggested without conclusive results.
- One study reviewed and integrated 5,055 candidate genes, and ranked these based on magnitude of evidence (Kao et al, 2011).
Candidate Gene Approach for Depression

Serotonergic pathway

DBH

SLC6A4
Candidate Gene Approach for Depression

- 
- Serotonergic pathway
  - DBH
  - SLC6A4
- Neurotrophin signalling pathway
  - BDNF
  - GSK3B
  - NGFR
Candidate Gene Approach for Depression: Conclusions

• Neurotransmitter and neuroplasticity theories have the strongest evidence for their relationship with depressed mood.
• Further experiments and replication efforts are needed
Wellbeing/Happiness
Candidate Gene Approach For Well-Being/Happiness

5-HTT

MAOA

Serotonergic synapse
GWAS For Well-Being/Happiness
Well-being/Happiness: Conclusions

- Evidence that 5-10% of the variance in responses to questionnaires is accounted for by additive effects of SNPs (Rietveld et al., 2013)
- Large-scale genome-wide meta-analysis on > 100,000 genotyped individuals is underway
Social Functioning
Candidate Gene Approach For Social Functioning

Neuroactive ligand receptor interaction

OXTR
Candidate Gene Approach For Social Functioning

- Neuroactive ligand receptor interaction
  - OXTR
- Serotonergic synapse
  - HTR2A
Candidate Gene Approach For Social Functioning

- **Neuroactive ligand receptor interaction**
  - OXTR

- **Serotonergic synapse**
  - HTR2A

- **Dopaminergic synapse**
  - DRD4
  - MAO-A
GWAS For Social Functioning
Social Functioning: Conclusions

• Most evidence for involvement of oxytocin-related genes
• Serotonergic and dopaminergic pathways are also important
Summary

• There is promising evidence of genetic involvement in multiple QOL phenotypes through a variety of biological pathways
• This review provides a platform of the inclusion of pathways and genes/molecular markers in the design of future studies
Discussion: Limitations

• Inclusion of any gene/molecular marker found significant at least once
Discussion: Limitations

• Inclusion of any gene/molecular marker found significant at least once
  Ultimately, some genetic variables will fail to demonstrate a relationship with QOL
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• The number of genetic studies published to date varied widely across the different QOL domains
Discussion: Limitations

• Inclusion of any gene/molecular marker found significant at least once
  Ultimately, some genetic variables will fail to demonstrate a relationship with QOL

• The number of genetic studies published to date varied widely across the different QOL domains
  There is a varied level of evidence for individual biomarker relationships
Clinical Implications

• Ultimately, the goal of this research is to identify and use biological markers in clinical practice.
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• Screening for predispositions to deficits in QOL holds the same clinical implications as screening for predispositions to disease and treatment outcomes.
Clinical Implications

• Ultimately, the goal of this research is to identify and use biological markers in clinical practice.

• Screening for predispositions to deficits in QOL holds the same clinical implications as screening for predispositions to disease and treatment outcomes.

• For example, perhaps it is time to begin screening patients for cytokine markers to provide prophylactic interventions to prevent QOL deterioration, such as fatigue?
Do you have questions?

m.a.sprangers@amc.uva.nl