Incorporating patient-reported outcomes in clinical research and practice

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• Challenge grant
• PROMIS
• TR01 (antiquated)
Many approaches we could take

- Design studies to understand the biobehavioral pathways that impact variability in PROs
- Design clinical studies to explore which genes may impact PROs with an eye towards improving patient care
- Design studies to test personalized interventions using our knowledge of the biobehavioral pathways for PROs to improve patient care
The Vision: QOL PROs as an integrated vital sign

- Patient Genetic resilience profile
- Intake
- Prophylactic interventions for QOL-related domains
- Treatment
- Real-time Monitoring of PRO QOL-related domains (IVRS)
- Triggered supportive care or treatment modification

- Reduced emergent care
- Improved survival
- Improved quality of life
The GI Intergroup Correlative Sciences Committee has reviewed the above-referenced proposal for a correlative science study using biospecimens obtained on the completed intergroup phase 3 trial in advanced colorectal cancer, N9741 (A randomized phase III trial of combinations of oxaliplatin (OXAL), 5-fluorouracil (5-FU), and irinotecan (CPT-11) as initial treatment of patients with adenocarcinoma of the colon and rectum).
Since 2 correlative science studies comprise this submission: (1) investigating genetic predictors for chemotherapy toxicity, including a candidate gene/SNP analysis and a genome-wide associated study (GWAS), and (2) investigating genetic predictors of quality of life related outcomes, the Committee evaluated each of these studies and their components separately.
The Committee approved the exploratory candidate gene/SNP analysis for investigating genetic predictors for chemotherapy analysis (with clarification on the study regarding the number of pre-specified SNPs to be performed as outlined below); however, the Committee had significant reservations about the GWAS as described and did not feel it could be approved unless the “Comments Requiring a Response” listed below about the GWAS were sufficiently addressed. The Committee also had significant reservations about the investigation of genetic predictors of quality of life and did not feel it could be approved unless additional background information supporting the study could be provided and the other “Comments Requiring Response” related to that study were addressed.
Power calculations are presented for binary endpoints (e.g., toxicity) for both the candidate gene study and the GWAS in Table 3 of section 4.6.1. As indicated by that table, the studies will have power to detect only very large effects. For the candidate gene study, a test based on a log-additive genetic model using significance level 0.001 is reported to have 80% power to detect an allele-specific risk between 2-4 for SNPs with MAF>15% assuming sample sizes 100 to 500. For the GWAS, a significance level of 0.00001 would be used and minimum detectable risks would be in the range 3.5 to >10. For quantitative traits, R2 values of 24%, 9%, and 6% would be detectable with 80% power using a two-sided $\alpha=0.00001$ test with sample sizes 100, 300, and 500, respectively. However, the investigators present power calculations for samples size ranging from 100 to 500. The investigators should state which sample size they believe is most realistic. By GWAS standards, even the largest sample size considered (500) is very small and will only allow for detection of very large effects. The investigators should provide justification that these small sample sizes will be sufficient to identify genome-wide genetic markers than can then be further validated.
COMMENTS REQUIRING A RESPONSE ON THE QOL STUDY:

- Regarding the correlation with the QOL instrument and the underlying hypothesis, the study proposal did not explain how the “Symptom Distress” correlates with mood domains. In particular, the instrument was not presented in detail and no previous background information associated with the scale for similar types of associations was presented from peer-reviewed publications. Also, no information was provided regarding whether the information from the previous abstract presented at ASCO 2004 has been published, and if so, in what journal and with what final analysis/conclusions. In particular, the reviewers were concerned that many of the items listed as “mood domains” are not moods (e.g., anorexia) and so the rationale underlying the hypothesis and conclusions to be drawn from associating the biospecimen data with the QOL information is not clear and needs to be more rigorously defended with convincing background / preliminary data, in addition to providing a clear, in-depth description of the study, the QOL instrument, and the statistical analysis.
There are three outcomes considered (toxicity, efficacy, QOL), but only the toxicity outcomes receive adequate treatment in the statistical considerations. The same general approach will work for a binary efficacy outcome such as tumor response, but the expected proportions of responses may be different and therefore lead to very different power estimates. Time-to-event outcomes such as might be considered for efficacy are not discussed at all. A power estimate is stated for the QOL aims, but there is no way to verify its appropriateness because critical information is not provided such as anticipated SD of QOL score within each genotype group, or the relative sizes of each genotype group (e.g., are the groups of equal size?). Enough information should be provided about the assumptions so that an independent statistician could verify the calculations and verify the approach.
Genetic predictors of patient-reported symptom severity and overall quality of life in cancer patients

- Specific Aim 1: Examine pre-chemotherapy gene-symptom (fatigue, pain, nausea, insomnia, anorexia, depressed mood, outlook, total symptom severity) and gene-QOL associations using candidate gene polymorphisms previously associated with specific cancer-related symptoms or QOL.

- Specific Aim 2: Perform a GWAS study to explore which genes are related to pre-chemotherapy cancer-related symptoms (fatigue, pain, nausea, insomnia, anorexia, depressed mood, outlook, total symptom severity) and overall QOL.

- Specific Aim 3: To determine whether pre-chemotherapy gene-symptom or gene-QOL associations identified in Specific aims 1 and 2 predict deficits in symptom severity and QOL during chemotherapy as well as chemotherapy toxicity, time to progression (TTP) and overall survival (OS).
Specific Aim 4: Test the PROMIS measures for prognostic capability of predicting OS, DFS, and PFS.

Hypothesis: The PROMIS PRO-based measures will demonstrate prognostic capability independent of performance status for OS, DFS, and PFS.

Overview: We will assess the newly developed PROMIS items in a diverse patient population that represents the spectrum of disease burden and symptoms in cancer treatment. We will use the master protocol (see Specific Aim 1: Study Design) involving 1200 cancer patients accrued across the MCPRN network from a variety of tumor types (e.g. colon, lung, breast) and treatment approaches (adjuvant breast cancer; metastatic prostate/bladder cancer; head, neck and gastroesophageal cancer receiving radiotherapy; metastatic lung cancer; metastatic colon cancer; and lymphoma myeloma) to estimate the prognostic ability of the PROMIS measures for OS, DFS, and PFS. Patients enrolled will be followed for these time to event endpoints throughout the grant period, providing a median followup time of 2 years.
• Patients enrolled will be followed for these time to event endpoints throughout the grant period, providing a median followup time of 2 years. This will allow for the identification of subpopulations with particular PRO, as well as providing adequate power to demonstrate that PROs may provide critical prognostic information for routine use in clinical trial research. The demonstration of the PROMIS measures as independent prognostic factors is the first step towards an ultimate goal of identifying symptoms on which clinicians may act to improve patient outcomes. For example, if a patient was identified with a deficit related to fatigue and emotional distress, interventions (pharmaceutical, psychosocial, etc.) could be brought to bear to improve patient well-being. Intervening on identified PRO deficits could improve patient ability to deal with the ardors of cancer and its treatments, which could in turn improve treatment outcome.
• D.4.6. Future Studies

• Dr. Sloan’s most recent consortium-based effort is based on his idea for exploring a genetic basis for PRO outcomes in the same manner that the genetic makeup of common clinical outcomes like treatment response and survival is presently developing. To date, genes that are involved in self-rated health or quality of life are not yet identified. Genetic research, however, has been successful in identifying chromosomal regions and genetic variants for related attributes, such as depression [100], cognition [101], and pain [102]. For example, there is consistent and increasing evidence that DNA sequence variations in the region of chromosome 15q influences susceptibility for unipolar depression [103-105]. To illustrate further, the epsilon4 allele of the APOE gene has been investigated for association with health-related outcomes and has been found to be related to normal cognitive aging [101]. Finally, catechol-O-methyltransferase has been found to be a key regulator of affective mood, cognitive function, and pain perception [102, 106,107]. Other translational research focusing on cancer has explored the genetic basis for physical response to treatment and patient survival. But the degree to which genetic structure impacts psychosocial response to a cancer diagnosis is still unknown.
To date, only Sloan and colleagues [108] have examined the direct link between polymorphisms and cancer patients' quality of life. Using a large randomized North Central Cancer Treatment Group (NCCTG) clinical trial, they found preliminary evidence for relationships between overall quality of life, symptom distress, and fatigue with variant genotypes of two enzymes involved in folate metabolisms. They took a skeptical approach to the analysis and pre-specified a clinically meaningful effect size that would have to be observed to indicate a potential relationship. More than triple the number of relationships between genetic variables and quality-of-life outcomes were observed than would be expected by chance alone.
The few studies that have been performed so far are sufficiently compelling to justify further exploration of the relationships between genetic variants and quality-of-life endpoints among cancer patients. Studies are needed that directly relate gene expressions to quality of life. This path, however, is complex considering the potential number of genes, gene interactions, and 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 quality-of-life endpoints, and similarly few quality-of-life researchers are engaged in genetic research.
• It is therefore of paramount importance to join forces among the disparate disciplines. To avoid a costly and time-consuming shotgun approach based on trial and error, we advocate a sound scientific procedure integrating and building on the extant knowledge gained in the relevant disciplines. The overall objective is to establish strong collaborative and interdisciplinary relationships to translate, plan, and conduct clinically relevant research to identify and investigate potential biological pathways, genes and genetic variants for quality of life. The inaugural meeting of the GENEQOL consortium was held February 26-28, 2009 in Rochester, Minnesota wherein a group of 25 international experts in quality of life, genetics, and related disciplines met, summarized the state of the science on the genetics of PROs related to pain, fatigue, self-perceived health, and psychological attributes, and produced a research agenda to move forward.