

Clinical Trials with QOL/PROs: Making it real with patient advocates

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How do you include patient advocates in....

- Clinical trials
- Scientific meetings
- Medical Science



... you just do.



ABSTRACT

Cancer patients offer a unique perspective on assessing the clinical significance for QOL assessments that differs from that of researchers and clinicians. The authors of the manuscript series supported this hypothesis and indicated that patients had raised significant issues that were not previously considered in the state of the science. They further encouraged the patient advocates to set out their ideas formally in a manuscript so that other researchers and clinicians could benefit from this unique perspective. To the authors' knowledge, no group of cancer patients has been involved in participating in the development of a research project. The present article represents the summary of our findings in reviewing and participating in the scientific process.

INTRODUCTION

The authors reviewed the six papers, not for scientific merit but for sensitivity to the primacy of the patient, while understanding there are other parameters that researchers must consider as well. Clearly, QOL studies play multiple roles in the healthcare and public policy realms. Patients and patient advocates must understand that the data accrued with QOL instruments have implications beyond the individual patient. Conversely, it is the responsibility of researchers to ensure that the instruments accurately reflect patients' perspectives.

It is a privilege to offer the following commentary on each of the six papers in the series. While the reviewers are passionate about the rights of the patient, we wish to be fair and to offer constructive criticism. We understand that researchers and clinicians are on our side. We also know that patients and clinicians have their own agendas. This paper is an attempt to unify the agendas, always in the best interest of the patient.

REVIEW OF MANUSCRIPTS

In "Methods to explain the clinical significance of quality of life measures,"¹ the authors maintain a theme of patient involvement in the decision-making process that sets an important tone for the rest of the papers in the series. They

Participating in a clinical trial is a personal choice and an individual experience. We would like to get your feedback on how well we did in meeting your needs.

Y N U

Y N U

Y N U

Y N U

Y N U

 AMERICAN CHEMICAL SOCIETY

**Cynthia Chauhan
Wayland Eppard
Marlene Frost
Michele Halyard
Albert Wu
Jeff Sloan**

Outline

- Introduction and Background (5 minutes)
- Perspectives (12 minutes, 3 minutes each)
 - Researcher
 - Clinician Observer
 - Analyst
 - Other Patient / Support Person
- Patient Assessment (15 minutes)
 - Clinician Assessor
- Patient Response (5 minutes)
- Questions / Discussion (8 minutes)



FDA Guidance on Patient Reported Outcomes: *Discussion, Dissemination, and Operationalization*



February 23-25, 2006
Chantilly, Virginia

Co-Sponsored by Mayo Clinic, College of Medicine and the
FDA's Center for Drug Evaluation and Research (CDER)



For questions regarding participation
reference 2006R4379, contact:
Mayo School of Continuing Medical Education
Telephone: 800-323-2688 or 507-284-2509
Web: www.mayo.edu
FAX: 507-284-0532
E-mail: cmes@mayo.edu

DENOUEMENT: A PATIENT-REPORTED OBSERVATION

Cynthia Chauhan

- **EDITOR'S NOTE:** The following is intended to tie together the material in this body of work to remind all of us that at the heart of all that we do in assessing PRO's is a human being. In short, it's all about the patient.
- **CYNTHIA'S COMMENTARY**
- It has been my privilege to work with the Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group, observing and learning from how you as professionals view, interpret, relate to my reality. You are all obviously bright, well-intentioned, altruistic people who are concerned about patient wellbeing, and I thank you from the bottom of my heart not just for myself but for all patients. I have watched you struggle with concepts and fight for opportunity and recognition. I want to respond to and perhaps invite you to reframe some of the issues I have watched you address and shy away from....(Value in Health 2007).



Form Approved Through 38FR22007		UNH No. 0826-0001	
Department of Health and Human Services Public Health Services		LEAVE BLANK--FOR PHS USE ONLY.	
Grant Application		Type	Activity
Do not exceed character length restrictions indicated.		Review Group	Family
		Council/Board (Month, Year)	Date Received
1. TITLE OF PROJECT (Do not exceed 61 characters, including spaces and punctuation.) NOCTG Patient Advocate Committee Community Education Initiative An R25E Grant			
2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES (If "Yes," state number and title)			
Number: Title:			
3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR		New Investigator <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	
3a. NAME (Last, first, middle) Sloan, Jeff A.	3b. DEGREE(S) PhD	3c. eRA Commons User Name	
3d. POSITION/TITLE Professor of Oncology Professor of Biostatistics		3e. MAILING ADDRESS (Street, city, state, zip code) Cancer Center Statistics Kahler 1A 700 First Street SW Rochester, MN 55905	
3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Health Sciences Research			
3g. MAJOR DIVISION			





Our Team
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D.V. Satele
A.C. Dueck
G.S. Soori
D.B. Johnson
S.J. Mandrekar
J.C. Buckner

**Patients might think differently
about trial participation than researchers..**



Our Results in One Sentence

**Patients value participation in clinical
trials regardless of personal outcome.**

Background

- Patient trial experience may give insight into quality of life factors affecting accrual, retention and outcome.
- While patients are vital to clinical trial success, we know little about their post-trial opinions.
- This trial examined patient opinion of their trial and treatment decision making.

The response to our idea was animated



Everyone knew our findings before we mounted the study

- During concept development, we were told repeatedly that the results would be obvious:
 - Patients who had a treatment success would be satisfied and thought it was worth it
 - Patients who did not have a treatment success would not think it was worth it

Methods

- Patients enrolled on designated North Central Cancer Treatment Group (NCCTG) phase II or III treatment trials
- Assessments:
 - Control Preferences Scale at baseline
 - Was It Worth It (WIWI) satisfaction
 - at the ends of cycle 1 and active protocol treatment.
- The primary endpoint was the proportion of patients reporting worthwhile participation.
- Fisher Exact tests compared patient opinion across subgroups.

Was It Worth It (WIWI) Questionnaire

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Overall, did your quality of life change by participating in this research study (circle one response)?

It improved

It stayed the same

It got worse

Overall how was your experience of participating in this research study (circle one response)?

Better than I expected

The same as I expected

Worse than I expected

If there was **one thing** that could have been done to improve your experience in this research study, what would it be?

Would you like to talk to someone about your concerns (circle one response)? Yes No

The control preferences scale

2. Circle the letter next to the phrase below that best describes the role you would **have preferred**.

The Control Preferences Scale

Active Role

A. I prefer to make the decision about which treatment I will receive.

B. I prefer to make the final decision about my treatment after seriously considering my doctor's opinion.



Collaborative Role

C. I prefer that my doctor and I share responsibility for deciding which treatment is best for me.

Passive Role

E. I prefer to leave all decisions regarding my treatment to my doctor.

D. I prefer that my doctor makes the final decision about which treatment will be used, but seriously consider my options.

Results

- 264 patients were enrolled on 25 protocols and treated at 79 sites.
- 86% of patients were in phase II studies
- 89% had stage IV disease.

Patient Demographics

Age (median, range)	64 (29-86)
Race (white, black, other)	96%, 2%, 2%
Gender (female, male)	50%, 50%
Study Phase (II, III)	97%, 3%
Performance Status (0, 1, other)	55%, 43%, 1%
Clinical Stage (I, II, III, IV, other)	2%, 1%, 6%, 89%, 2%
Tumor Type (adenocarcinoma, breast, lung, melanoma, pancreatic, other)	6%, 21%, 23%, 15%, 25%, 12%

Primary findings

- At the end of cycle 1, patients felt
 - the trial was worthwhile (74%)
 - would do it again (85%)
 - would recommend it to others (82%).
- 85% of patients reported undiminished QOL.
- 7% rated the trial worse than expected.
- End of treatment responses were similar.

Primary findings

- Satisfaction rates varied by tumor site ($p=0.04$).
- Pancreatic and breast cancer patients were less likely than patients with other tumor types to choose to do the study again.
- 11% of patients having tumor response rated the trial as not worthwhile
- 66% of patients with progressive disease rated it worthwhile.

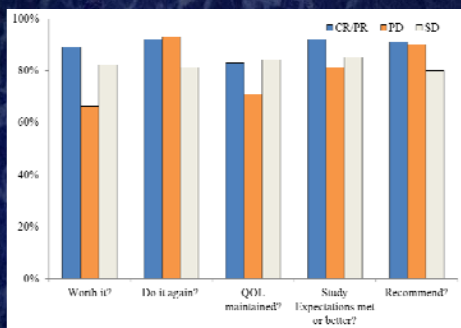
Answered yes to...	Response by End of Tx WiWi scores			
	CR/PR	PD	SD	p-value
Worth it?	89%	66%	82%	0.01
Do again?	92%	93%	81%	0.07
QOL maintained?	83%	71%	84%	0.01
Study expectations met or better?	92%	81%	85%	<0.01
Recommend?	91%	90%	80%	0.15

Role preference and satisfaction

- Patients with concordant preferred and actual treatment decision making roles rated participation higher than patients with discordant treatment decision making roles.
- Patients with concordant preferred and actual treatment decision making roles were more likely to do the study again ($p=0.01$) and recommend participation to others ($p=0.04$).

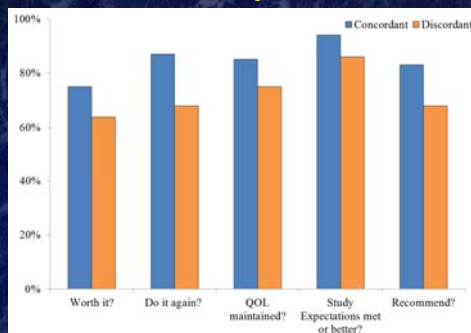
CPS by 1 month WIWI scores			
Answered yes to...	Concordant (N=230)	Discordant (N=28)	p-value
Worth it?	75%	64%	0.13
Do again?	87%	68%	0.01
QOL maintained?	95%	75%	0.38
Study expectations met or better?	94%	86%	0.11
Recommend?	83%	68%	0.04

Distribution of WIWI by Response



Treatment outcome does not have overwhelming impact on patient satisfaction.

Distribution of WIWI by CPS Discordance



Other factors, such as CPS Discordance, display a significant effect on patient satisfaction.

Conclusions

- Most patients endorsed their clinical trial experience. Yet contrary to popular beliefs, treatment outcome did not have an overwhelming impact on patient satisfaction.
- Many factors, including role preference discordance, should be considered when determining factors contributing to patient satisfaction in cancer treatment trials.
- Assessing patient satisfaction will inform future study design that can potentially improve patient accrual and retention.

- When advocates and researchers work together, amazing things can happen for all involved.





Quality of Life (QOL) is one of a myriad of Patient-reported outcomes (PROs),
And an umbrella term for things other than survival and tumor response

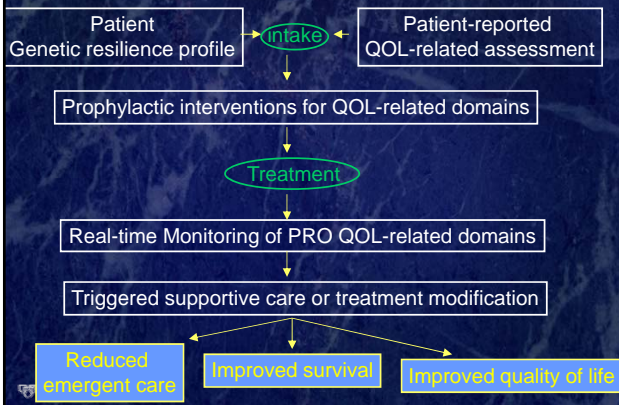
QUEST PHARMACEUTICALS

What is a PRO?

- **Measurement of any aspect of a patient's health status that comes directly from the patient**
- **Examples:**
 - **Function**
 - **Symptoms (intensity, frequency)**
 - **Satisfaction (with medication)**
 - **Well-being**
 - **Quality of life (QOL).**



The Vision: QOL PROs as an integrated vital sign



Research: the slaying of a beautiful idea by an ugly reality



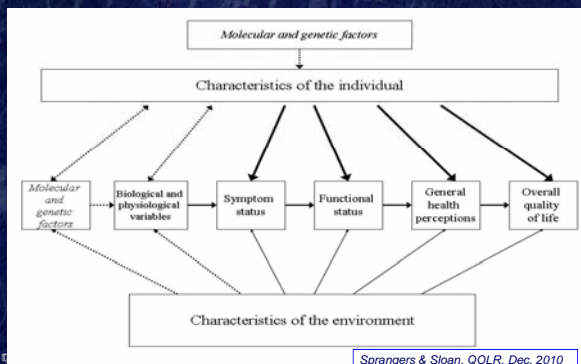
Fifteen Years Ago (September, 1995)

- Plethora of assessment tools for quality of life (QOL) and patient-reported outcomes (PROs)
- Disappointing recent clinical trial results in terms of missing data, clinical significance, reliability issues
- "...so you're suggesting we should all do with QOL what a dog does to a fire hydrant..."

Today

- Guidelines for virtually all outstanding issues
 - **missing data** (Fairclough, *Design and Analysis of Quality of Life Studies in Clinical Trials*, Chapman-Hall, 2010)
 - **clinical significance** (Sloan et al, MCP, 2002)
 - **psychometrics** (Sloan et al, *Current Problems in Cancer*, 2005/2006)
 - **regulatory issues** (Sloan et al, *Value in Health*, 2008)
 - **Item response theory** (Reeve et al, QOLR, 2007)
 - **Inclusion in clinical practice** (Guyatt et al, MCP/VIH, 2008)
 - **Genetics** (Sloan et al, December 2010, QOLR)

A Theoretical Model for Quality of Life

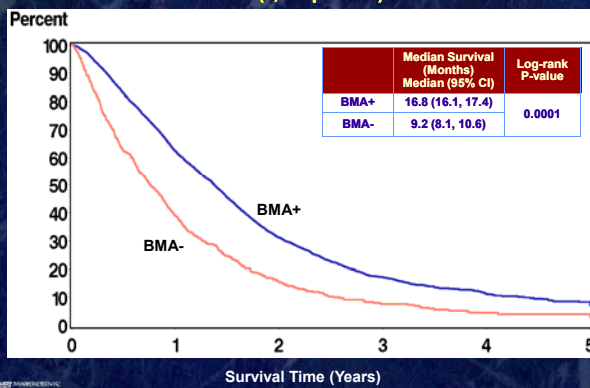


Hold that thought...

I have data relating to a new biomarker
A prognostic factor
for cancer patient survival

It is called BMA

Biomarker Assay (BMA) Positive versus Negative 23 trials (3,704 patients)



Median survival (months) across sites

Site	BMA-	BMA+	P-value
GI	9.1	16.7	<0.0001
GU	15.5	52.4*	0.0032
Lung	7.0	10.8	0.0003
Breast	16.6	26.2	0.0002

* Not reached (projected)

Multivariate Cox Model for Survival

Variable	P-Value	Hazard Ratio (95% CI)
BMA-	<.001	1.56 (1.40, 1.75)
Performance Score (1-2 versus 0)	<.001	1.77 (1.62, 1.93)
Age	0.075	1.00 (1.00, 1.01)
Minority	0.219	0.91 (0.79, 1.06)
GI	<.001	1.37 (1.14, 1.65)
Lung	<.001	2.02 (1.65, 2.47)
Breast	0.006	0.64 (0.47, 0.88)
GU	0.078	1.46 (0.96, 2.21)

Replication of results

- A recent meta-analysis (n=13,874) indicated that 36 of 39 studies indicated that analogues of BMA+ were significantly associated with overall survival (*Gotay, JCO, 26: 1355 -1363, March 2008*)
- Another meta-analysis involving over 10,000 patients indicated that BMA+ analogue was prognostic for survival (*Efficace, ASCO 2008*)
- A literature review of over 100 studies from 1982 to 2008 indicated that BMA+ measures were significant independent predictors of survival duration (*Montazeri, HQLQ, 7:102, 2009*)

Is this convincing evidence that BMA+ is a promising prognostic factor for cancer patient survival?

- What is BMA+?

BMA- = a score of 5 or less in patient-reported QOL on a 0-10 scale

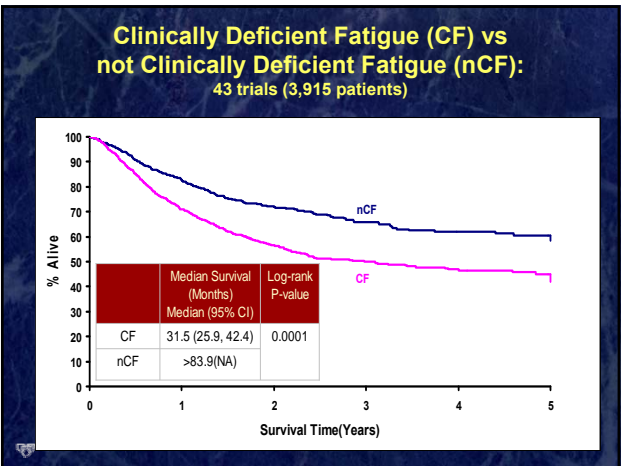
Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. your overall Quality of Life?

0 1 2 3 4 5 6 7 8 9 10
As bad as As good as
it can be it can be

**This is a reliable and valid measure
for cancer patient populations**
(Sloan, MCP, 2002 & JCO, 2012; Huschka, Cancer, 2005; Locke, JPSM, 2007)
cut-off validation:
Butt, JPSM, 2008; Sloan, Value in Health, 2007; Temel, J Thorac Oncol, 2006



How are you Doing? An empirically-based model of prognostic factors for survival

Fatigue

5-15%

Overall QOL

10-20%

Performance Status

10-25%

Routinely collected in all phase III clinical trials NCCTG/Alliance

So how do we use this clinical trial science to make it real in the clinic?

- We know that a deficit in patient-reported overall QOL is associated with a doubling of the risk of death across a broad spectrum of cancer patients.
- We know the cutoff is similar across many PRO domains.
- We also know that a change of two points on a 0-10 scale is non-ignorable.



We know incorporating PROs into Oncology Practice improves communication (Detmar, JAMA, 2002; Velikova, JCO, 2012)

- Incorporating standardized QOL assessments in daily clinical oncology practice facilitates the discussion of QOL issues and can heighten physicians' awareness of their patients' QOL.
- But what do we do with PRO information?



Putting PROs into Practice Realtime

HFIR Statistical Systems SAS Data Management System

Real Time QOL Initiative

Linear Analogue Self Assessment (LASA)

Please check the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. Your overall quality of life? (0=As bad as it can be, 10=As good as it can be)

N/A 0 1 2 3 4 5 6 7 8 9 10

2. Your overall mental (intellectual) well being? (0=As bad as it can be, 10=As good as it can be)

N/A 0 1 2 3 4 5 6 7 8 9 10

3. Your overall physical well being? (0=As bad as it can be, 10=As good as it can be)

N/A 0 1 2 3 4 5 6 7 8 9 10

4. Your overall emotional well being? (0=As bad as it can be, 10=As good as it can be)

N/A 0 1 2 3 4 5 6 7 8 9 10

5. Your level of social activity? (0=As bad as it can be, 10=As good as it can be)

N/A 0 1 2 3 4 5 6 7 8 9 10

6. Your overall spiritual well being? (0=As bad as it can be, 10=As good as it can be)

Realtime Output: Intervention Triggers

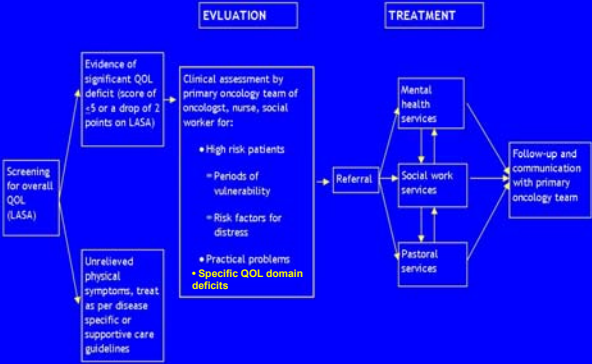
Pt Z2111111: LASA Scores by Week Since Treatment Started

Please click on the QOL domain links for Disease Management Pathways.

Items in **MAROON** represent complaints that are worse than average (5 points or below) and may warrant attention.
Items in **RED** represent a drop of 2 points or more
Items in **GREEN** represent a 2 points or more improvement on the measure since the last visit.

Factor Measured (0=worst QOL and 10=best QOL)	Baseline	Week 1	Week 3	Week 5	Last Week of Rx	Last Week of Rx Minus Week 5
Quality of Life	9	7	10	7	8	1
Mental (intellectual) WB	8	10	7	6	9	3
Physical WB	7	6	7	9	3	-6
Emotional WB	9	8	6	8	7	-1
Social Activity Level	7	4		10	10	0
Spiritual WB	6	10	6	7	9	2
Pain Frequency	2	2		4	2	-2
Pain Severity	3	5		0	3	3
Fatigue Level	2	6	1	1	1	0
Level of Support	9	8	5	10	8	-2
Financial Concerns	7	7	9	9	10	1
Legal Concerns	10	8	9	8	7	-1

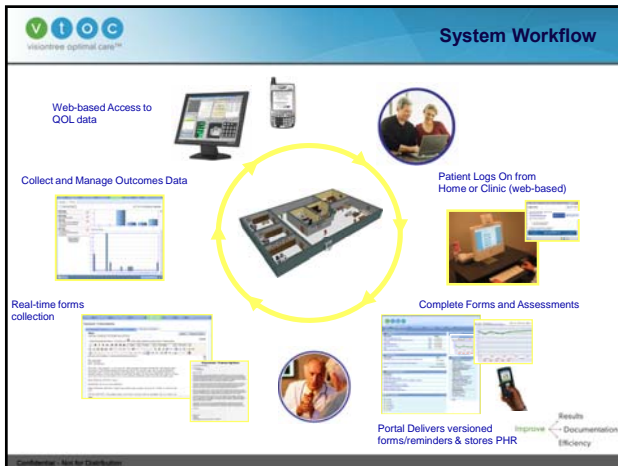
Clinical Pathway for Overall QOL Deficit Management



We now have the technology to make PRO collection easier

Electronic Web-Based Technology
Significantly Improves Quality of Life (QOL)
Data Collection:
Analysis of RTOG 0828
(In press, *Practical Radiation Oncology*, 2013)

Benjamin Movsas, M.D.
Herndon Chair for Oncology Research
Henry Ford Health System



Results

- This prospective study demonstrated a dramatic increase in the 6 month QOL compliance rates from ~50% to ~90% ($p < 0.001$) by switching from paper forms to a web-based technology.
- The web-based approach almost eliminated institutional error as a cause of missing data by using real-time email reminders.
- The system saved the RA's an average of 10 minutes per QOL form

A couple of new ideas for QOL/PRO Research that we are testing

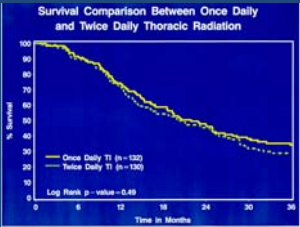


Combining PRO/QOL data with survival:
a peak into the near future



NCCTG Trial TDTRT vs ODTTR

Twice-Daily Thoracic Radiotherapy (TDTRT) for the treatment of lung cancer versus Once-Daily Thoracic Radiotherapy (ODTTRT)

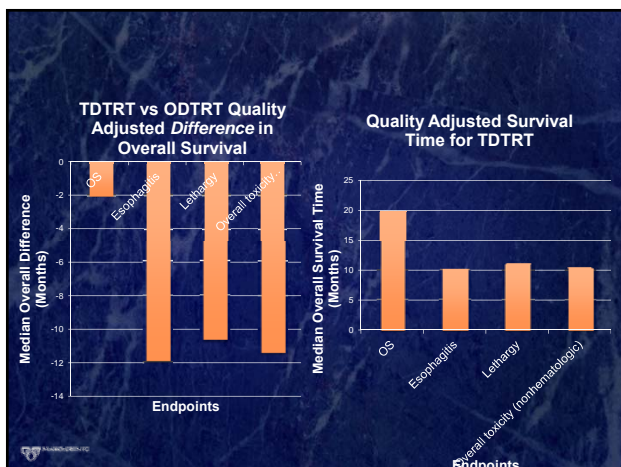


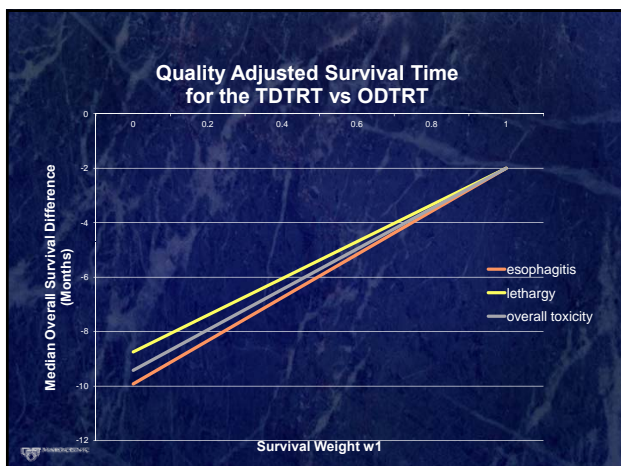
Median Overall Survival:

TDTRT 20 months
ODTTRT 22 months
log-rank p=0.49

Toxicities	TDTRT	ODTTRT(control)	Difference
Esophagitis	12.3%	5.3%	7%
Lethargy	7.7%	3%	4.7%
Overall Toxicity (nonhematologic)	53.9%	39.4%	14.5%

Bonner JA et al. JCO 1999;17:2681-2691







Genetics and PROs: Is there a QOL gene?



The far? Future: discovering the genetics of PROs

- It has been estimated that up to 33% of self-reported health is due to genetics (Sprangers, Twin Research and Human Genetics, 2009)
- Inflammatory pathway biomarkers are related to patient reported overall QOL and fatigue (Sloan, JCO, 2012)
- International consortium exploring the genetic underpinnings of pain, mood, fatigue, physical well-being, overall QOL (Sprangers, QOLR, 2010)
- Much more detail at www.geneqol.org



List of candidate genes drawn from the literature and GENEQOL consortium work to be explored relating to specific PRO-based symptom and QOL variables

PRO-based Symptom/QOL	Candidate Genes/polymorphisms
Fatigue, Insomnia	cytokine gene polymorphisms IL1B—511 (C/T) and IL6—174 (G/C), IL6—251 (T/A), IL2—330 (T/G), TNFα—308 (G/A), mu opioid receptor gene OPRM1, folate genes DPYD, MTHFR and TYMS, the -118A > C polymorphism in gene HSP70-1, heat shock protein HSP70 genes (HSPA1A, HSPA1B and HSPA1L)
Pain	catechol-O-methyltransferase (COMT), monoamine oxidase A (MAO-A), serotonin transporter gene (SLC6A4/ 5-HTT), transient receptor potential family A subtype 1 (TRPA1), opioid receptor subtype 1 (OPRD1), fatty acid hydrolase (FAAH), interleukin-1-receptor (IL-1RN), cytochrome P450 enzymes (CYP)
Nausea, Anorexia	5-hydroxytryptamine type 3B (5-HT3B) receptors, interleukin-1-receptor (IL-1RN), cytochrome P450 enzyme 2D6 (CYP2D6), monoamine oxidase A (MAOA)
Depressed Mood, Outlook	epsilon4 allele of the apolipoprotein E (APOE) gene, guanine nucleotide-binding protein (GNB3), methylenetetrahydrofolate reductase (MTHFR), dopamine transporters (SLC6A3, SLC6A4), catechol-O-methyltransferase (COMT), monoamine oxidase A (MAO-A), serotonin transporter gene (SLC6A4/ 5-HTT)
Total Symptom Severity, Overall QOL	All of the above



Sprangers MA, Sloan JA et al. Twin Res Hum Genet 2009 12(3):301-11.



It will take bravery and creativity to make this vision a reality



- PRO ideas, like other things, can be made real through creative collaborations.

