# Preventing Versus Reacting: The Changing Paradigm of Symptom Management in Neuro-Oncology


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# Conflict of Interest

GRANT SUPPORT:
MERCK
GENENTECH

# Outline For Discussion

- **Overview of Primary Brain Tumors and Issues Related to Care**
- **Program of Research and Interlocking Ideas**
  - Focus on Improved Symptom Assessment
  - Defining the Impact of Disease & Treatment on Symptoms
  - Evaluate the biologic basis of symptoms
    - Genetic risk
    - Biologic processes

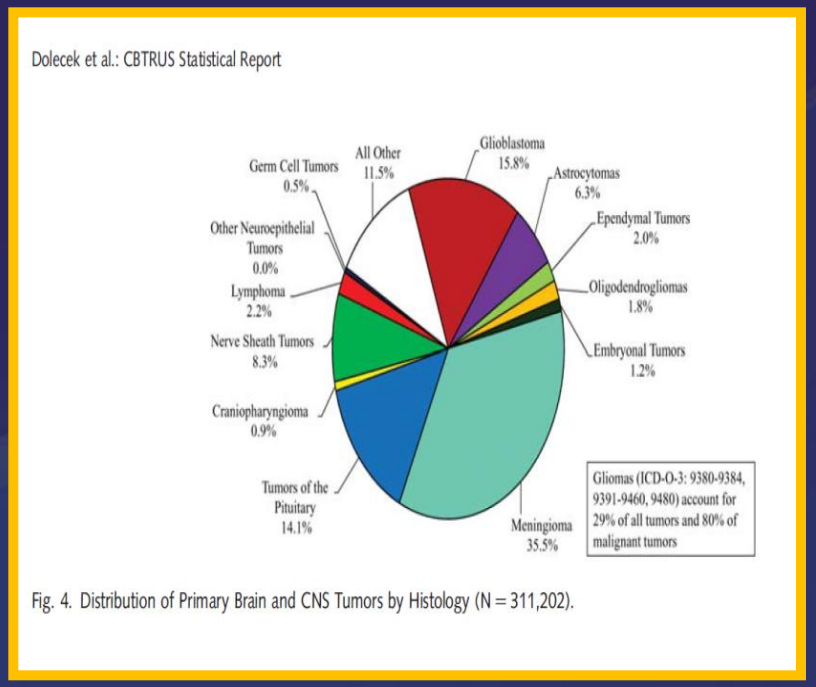
# BACKGROUND

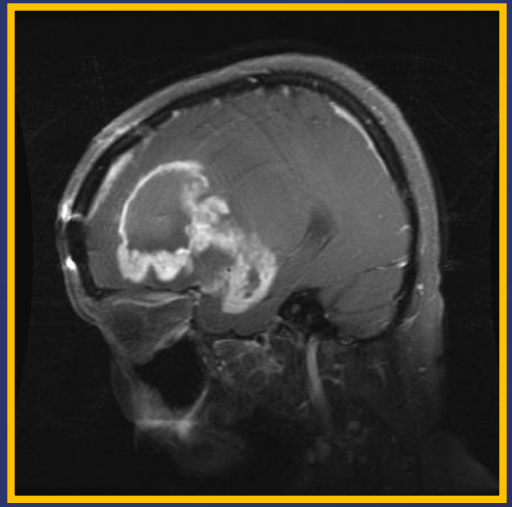
- Primary Brain Tumors arise from the constituent elements of the CNS & primarily stay within the CNS

- An estimated 51,410 new cases of primary nonmalignant *and* malignant brain tumors estimated for 2012 (21,810 malignant)[1]

- Above represents 1.35% of all primary malignant cancers[1]

- An estimated 12,760 deaths will be attributed to primary malignant brain and CNS tumors in the United States in 2005[1]; this represents 2.4% of all cancer deaths[2]

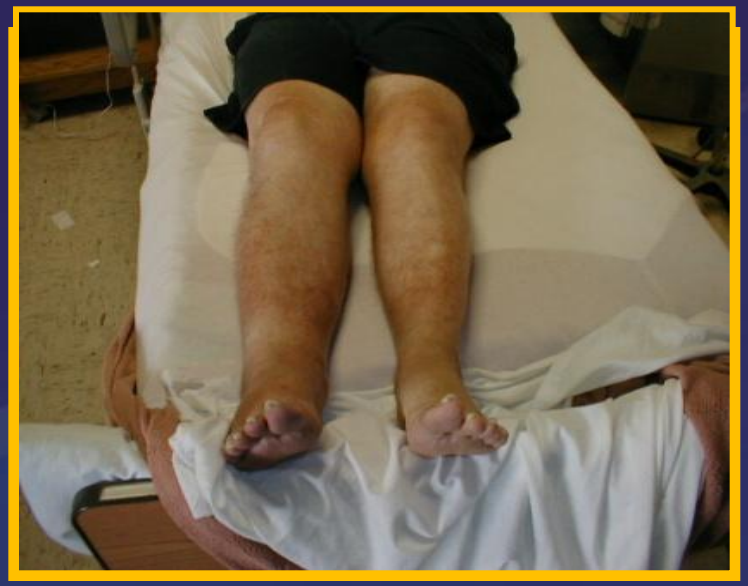


1. CBTRUS: Statistical Report on Primary Brain Tumors in the United States,. www.cbtrus.org/factsheet.htm
2. SEER.cancer.gov/CSR

# COMPLEXITY & Reason

- **Care is complex, involving:**
  - Management of Neurologic Symptoms
  - Management of Medical Complications
  - Management of Toxicity of Therapy
  - End of Life care



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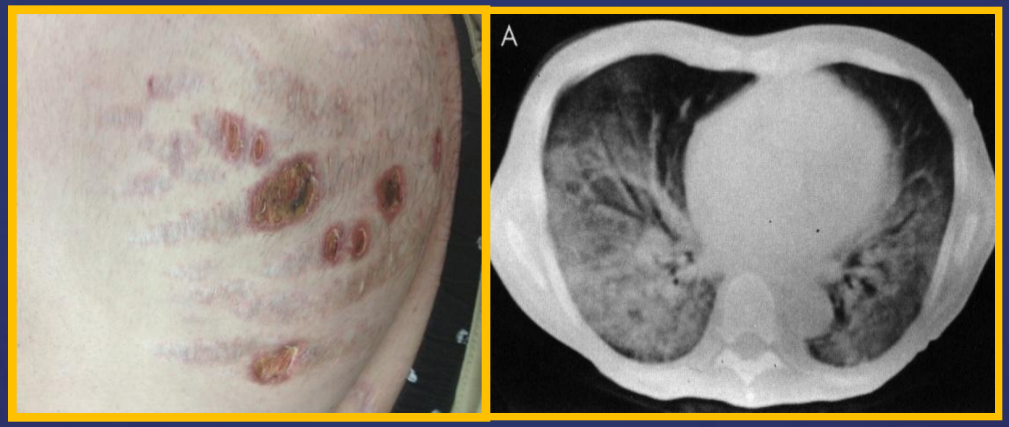


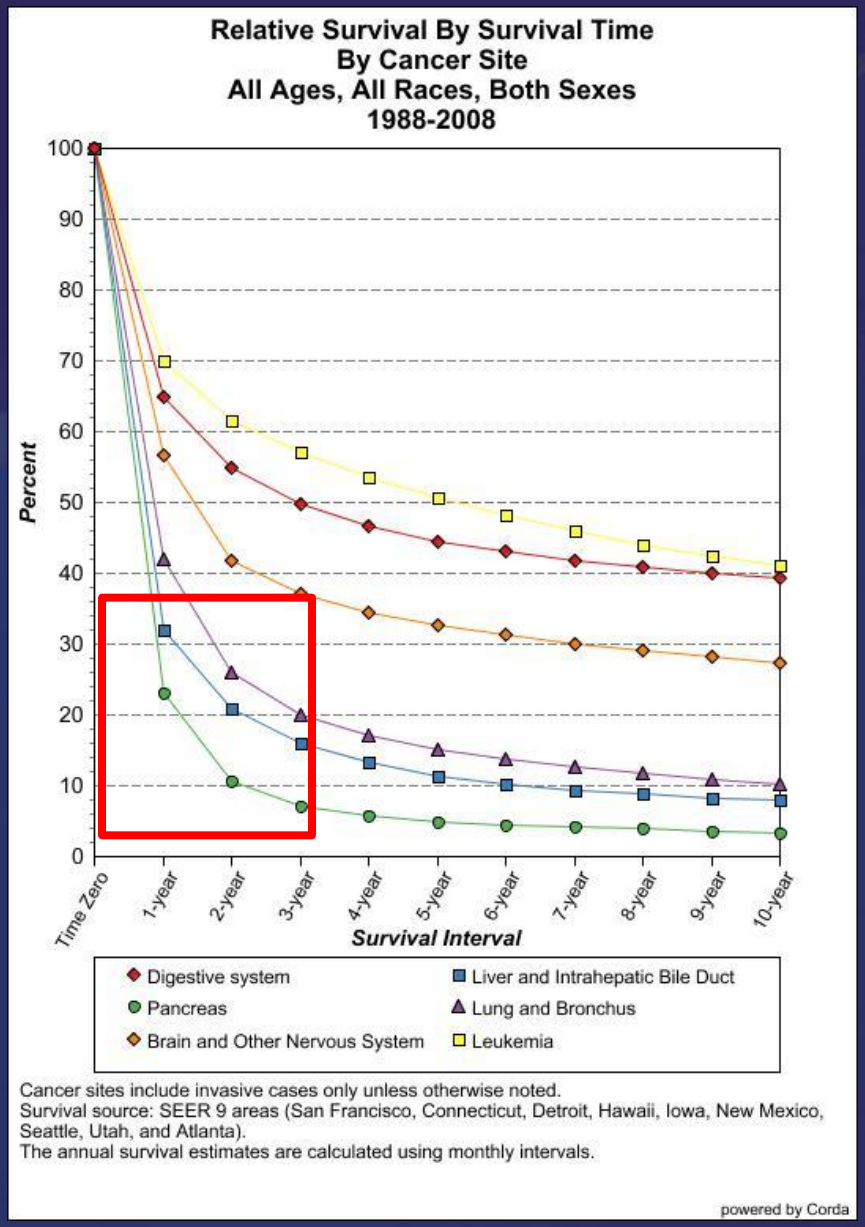

Wen & Kesari, 2008; Stupp et al, 2007

# FUTILITY

- **Primary brain tumors are rare, AND:**
  - In the U.S., primary brain tumors are the second most common cause of cancer death in young males
  - Life expectancy less than one year for the majority with GBM,<20% 5-year survival and average of 7 years for the “benign” astrocytoma
  - Anecdotal experience of a bad outcome can influence the care provided

# PERSPECTIVE

- **Life expectancy is short, but may not be different OR may even be better then other solid tumors**
  - ½ of cancer patients die of their disease[1]
  - ¼ die within 6 months of diagnosis, 63% live only 24 months[2]
  - Those with nonresponsive solid tumors –80% live less than 12 months[2]




http://seer.cancer.gov/faststats/selections.php?#Output


1 Wingo, et al,1995

2 Brescia, 1990, Maltoni, 2002

# IMPACT

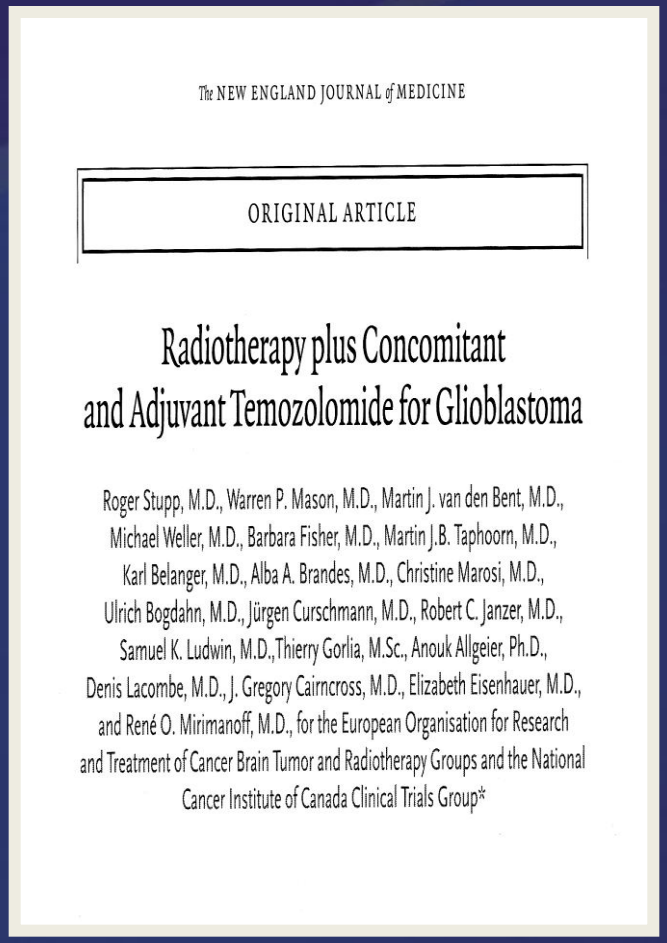
- Studies show inability to work from time of diagnosis:
  - 82% had symptoms which prevented return to work after diagnosis[1]
  - Those with low grade gliomas -nearly 50% were unable to return to work due to deficits[2]
- Qualitative studies indicate patients spend significant portion of their lives feeling ill and unable to perform usual activities [3]
- Recent studies support that there is a significant burden on the caregiver with changes in family roles, impact on financial status, and stress[4]
- Recent studies in the brain & other solid tumor populations show that persons report an average of 11-13 symptoms which occur concurrently[5]
- In patients with systemic cancer, the occurrence of multiple symptoms has been shown to alter quality of life (QOL), function status, disease progression, & survival.[6]

***[1] Fobair, et al, 1990; [2] Armstrong, et al, 2011; [3] Salander, et al, 2000; Strang & Strang, 2001; [4] Sherwood et al, 2006; Janda, 2006: [5] Chang et al, 2000; Armstrong et al, 2010: [6]Ben-Eliyahu et al, 1999; Kiecolt-Glaser et al, 1998***

# Current Issues: Standards of Efficacy

- **Treatments often similar in efficacy with improvement measured in months**
  -(Median survival 12.1 vs 14.6 months)

- **Standard is to evaluate the tumor & not the patient**
  - "Response" Evolved over time
  - Tumor response rate (TRR) - Overall Survival (OS) in the 1980s
  - Time to tumor progression (TTP), disease-free survival, and progression-free-survival (PFS) became accepted in the 1990s.
- **But even today the outcomes are controversial:**
  - Lamborn (2008) ***'6 month PFS strong predictor of survival'***
  - Lassman (2007) '***It remains unclear how to incorporate molecular markers into assessment of response in glioma'***
- ***Both remain unclear in the Wen (2010) RANO paper***



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

# Current Issues in evaluating response to treatment

**Norden (2008) "Avastin alters the recurrence pattern of malignant gliomas"**

- **Tumor may respond and the patient doesn't[1]**
  - Certain toxicities are attributed to treatment, but studies have not been well-designed (ie, lack of baseline measurement prior to radiation therapy or consideration of disease)
- **Current imaging is limited by technique, interpretation, and changing impact of cytostatic agents and 'The Avastin Effect'[2] and pseudoprogression[3]**
- ***Newer therapies designed to be cytostatic-how do you evaluate response?***

1 *Scheibel, et al, 1996; Correa et al, 2007*
*2 Chamberlain et al, 2006; Norden et al, 2008*
*3. Chamberlain, et al, 2007*

# Rationale for Program of Research

- **Patients with CNS tumors often suffer devastating effects as a consequence of the tumor and/or treatment**
  - Often unable to return to work , spend the majority of their lives feeling ill and unable to perform usual activities
  - Differences in toxicity and patient status during survival have become critical variables in making treatment choices

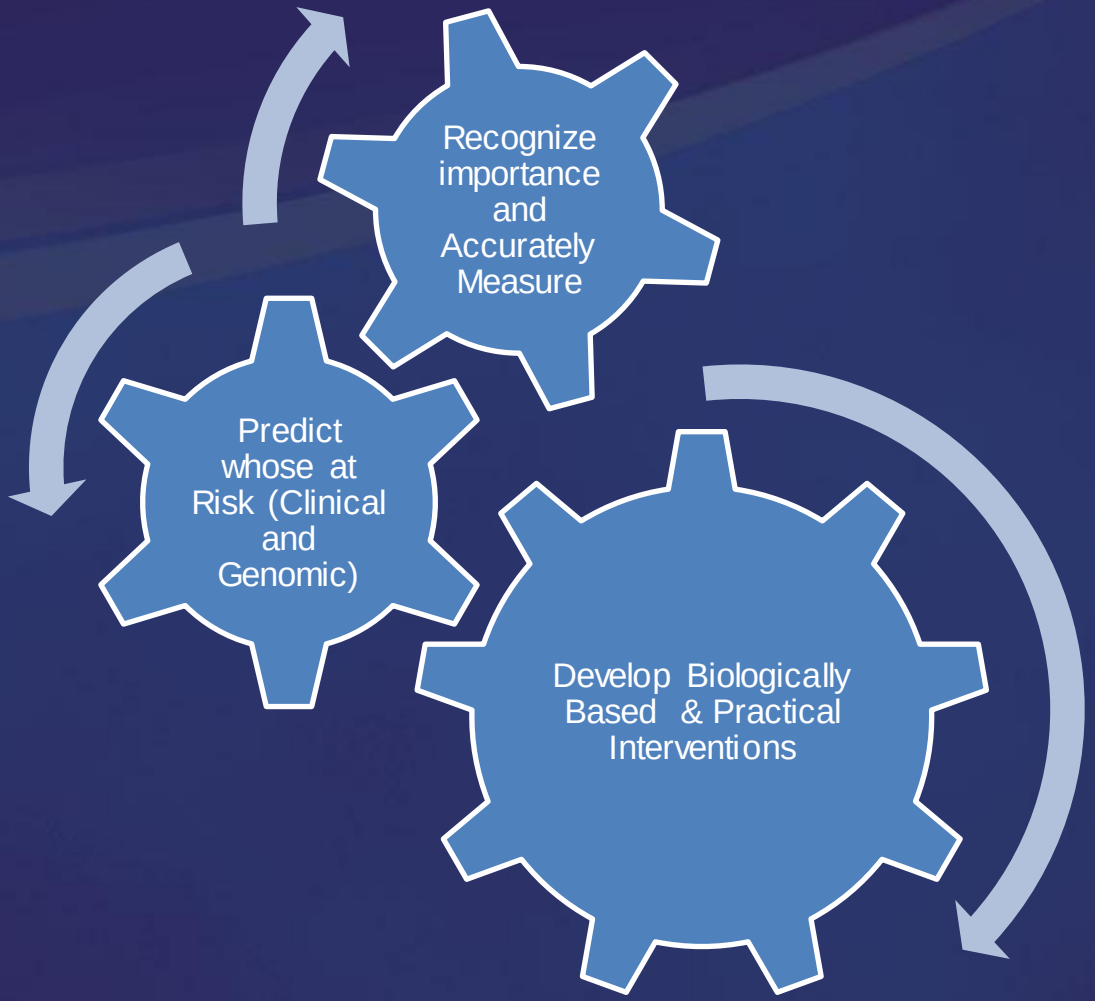
- **Limitations of current outcomes assessment**
  - CNS tumor treatments are often similar in efficacy and survival
  - Current imaging is limited by technique, interpretation, and changing impact of targeted agents
  - Traditional endpoints do not necessarily reflect clinical benefit

- **Tumor related Symptoms and Toxicity associate with therapy has been widely reported, but not collected in a systematic or rigorous way.**

Stage I: Conceptually define the experience of symptoms

# BEGINNING PROGRAM OF RESEARCH

# Stage 2: The Science Behind Symptom Management: INTERLOCKING IDEAS



TOPIC 1

# RECOGNIZE IMPORTANCE AND ACCURATELY ASSESS

# Introduction to Patient-Reported Outcomes (PROs)

- **Symptoms often impossible to 'observe' and studies reveal poor relationship between our assessment & patient evaluation**
- **PRO defined as a measurement of any aspect of a patient's health status that comes directly from the patient (ie without intepretation of the patient's responses by a physician or anyone else)**
- **Increased attention as a result of published guidelines by the FDA on the use of PROs in 2006**
  - Recommended assessment of treatment benefit from the patient perspective

*U.S. Dept. of Health and Human Services FDA Center for Drug Evaluation and Research (2006). Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health and Quality of Life Outcomes, 4(79).*

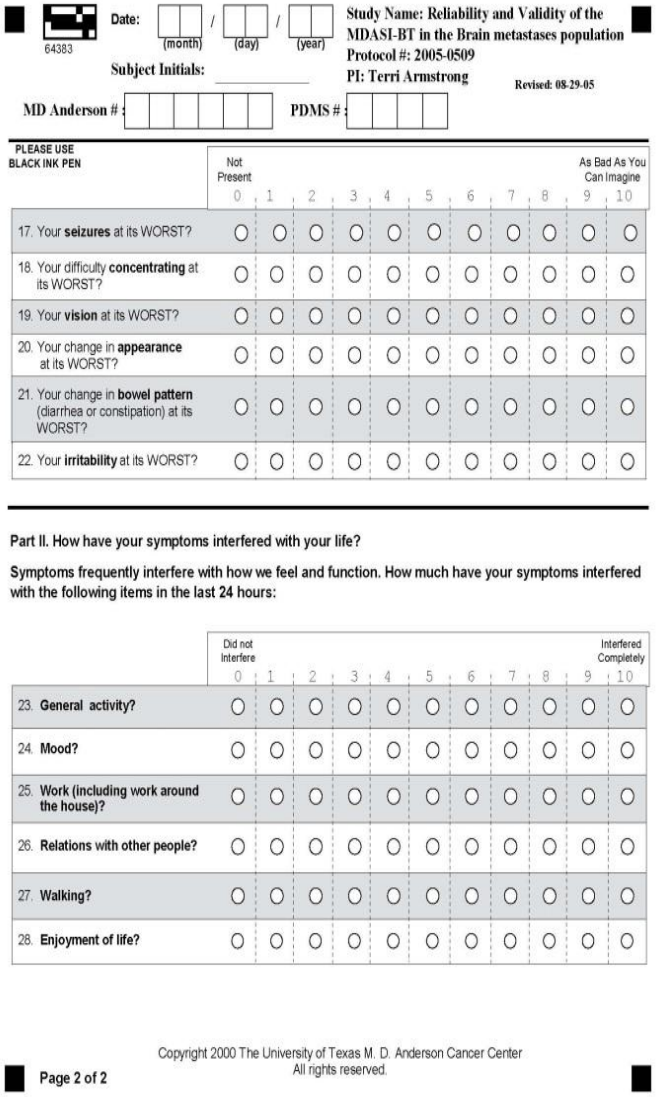
# MDASI – Brain Tumor Module (MDASI-BT)

| Symptom Burden | Symptoms (22) | Interference Items (6) |
|---|---|---|
| MDASI – Brain Tumor Module (MDASI-BT) | 6 factor groupings<br>-General<br>-Gastrointestinal<br>-Constitutional<br>-Neurologic<br>-Cognitive<br>-Affective | -Ability to walk<br>-Ability to work<br>-General activity<br>-Mood<br>-Interactions with others<br>-Enjoyment of life |

- Symptoms associated with primary brain tumors were added to the 13 item MDASI.
- Rated on a scale of 0-10 in terms of severity
- Demonstrated content & discriminant validity & reliability


*Armstrong TS, et al. Oncology Nursing Forum, (2005), 32(3), 669-676, 2005.*

*Armstrong, T. S., et al (2006). J Neurooncol 80(1): 27-35.*

64383

Date: (month) / (day) / (year)

Study Name: Reliability and Validity of the MDASI-BT in the Brain metastases population
Protocol #: 2005-0509
PI: Terri Armstrong
Revised: 08-29-05

Subject Initials:

MD Anderson #:

PDMS #:

PLEASE USE BLACK INK PEN

| | Not Present 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | As Bad As You Can Imagine 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17. Your **seizures** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| 18. Your difficulty **concentrating** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| 19. Your **vision** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| 20. Your change in **appearance** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| 21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST? | O | O | O | O | O | O | O | O | O | O | O |
| 22. Your **irritability** at its WORST? | O | O | O | O | O | O | O | O | O | O | O |

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

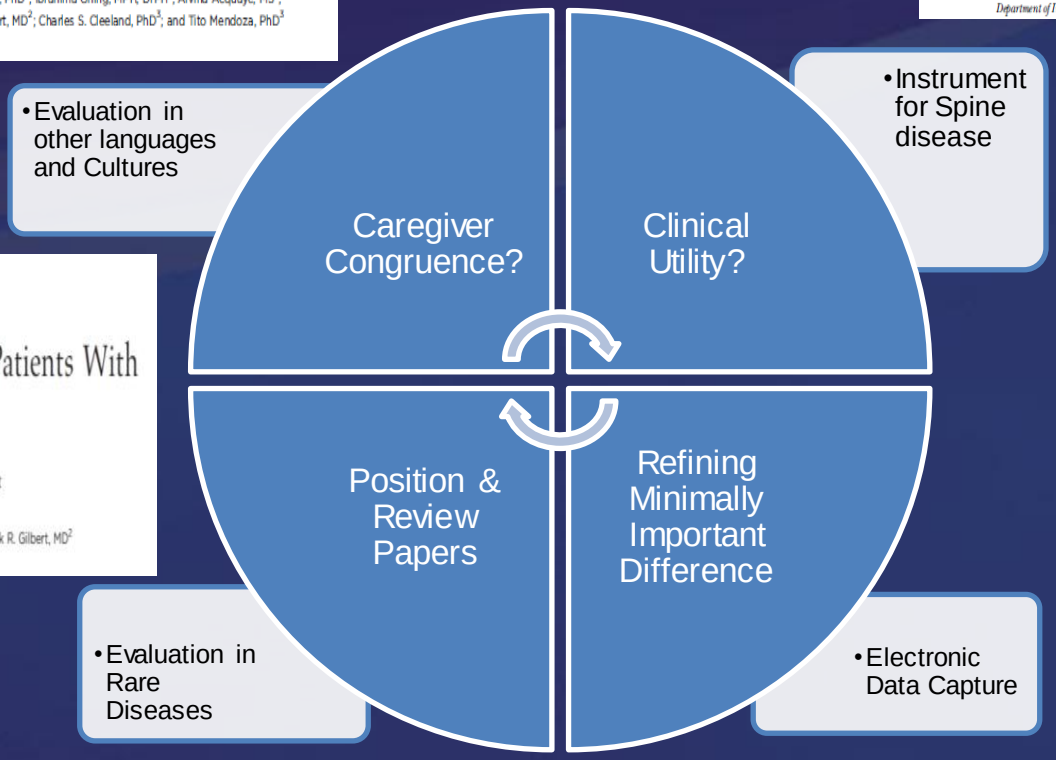
| | Did not Interfere 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Interfered Completely 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 23. **General activity?** | O | O | O | O | O | O | O | O | O | O | O |
| 24. **Mood?** | O | O | O | O | O | O | O | O | O | O | O |
| 25. **Work (including work around the house)?** | O | O | O | O | O | O | O | O | O | O | O |
| 26. **Relations with other people?** | O | O | O | O | O | O | O | O | O | O | O |
| 27. **Walking?** | O | O | O | O | O | O | O | O | O | O | O |
| 28. **Enjoyment of life?** | O | O | O | O | O | O | O | O | O | O | O |

# The Basic Work Continues

Original Article

Congruence of Primary Brain Tumor Patient and Caregiver Symptom Report

Terri S. Armstrong, PhD[1,2]; Jeffrey S. Wefel, PhD[2]; Ibrahima Gning, MPH, DrPH[3]; Alvina Acquaye, MS[2]; Elizabeth Vera-Bolanos, MS[2]; Mark R. Gilbert, MD[2]; Charles S. Cleeland, PhD[3]; and Tito Mendoza, PhD[3]




ARTICLE IN PRESS

Vol. ■ No. ■ ■ 2008 Journal of Pain and Symptom Management 1

*Original Article*

Clinical Utility of the MDASI-BT in Patients with Brain Metastases

Terri S. Armstrong, PhD, Ibrahima Gning, DrPH, Tito R. Mendoza, PhD, Jeffrey S. Weinberg, MD, Mark R. Gilbert, MD, Melissa L. Tortorice, BS, and Charles S. Cleeland, PhD

*Department of Integrative Nursing Care (T.S.A.), The University of Texas Health Science Center School*

J Neurosurg Spine 12:421–430, 2010

Reliability and validity of the M. D. Anderson Symptom Inventory–Spine Tumor Module

Clinical article

Terri S. Armstrong, Ph.D., A.N.P.-B.C.,[1,2] Ibrahima Gning, D.D.S., Dr.P.H.,[3] Tito R. Mendoza, Ph.D.,[3] Elizabeth Vera-Bolanos, M.S.,[2] Mark R. Gilbert, M.D.,[2] Laurence D. Rhines, M.D.,[4] Jeffrey S. Weinberg, M.D.,[4] Gisela Sanchez-Williams, R.N., M.S.N., A.N.P.-B.C.,[4] Victor Levin, M.D.,[2] Allen W. Burton, M.D.,[5] and Charles Cleeland, Ph.D.[3]

Original Article

Clinical Course of Adult Patients With Ependymoma

Results of the Adult Ependymoma Outcomes Project

Terri S. Armstrong, PhD[1,2]; Elizabeth Vera-Bolanos, MS[2]; and Mark R. Gilbert, MD[2]

Original Article

The Impact of Symptom Interference Using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) on Prediction of Recurrence in Primary Brain Tumor Patients

Terri S. Armstrong, PhD, ANP-BC[1,2]; Elizabeth Vera-Bolanos, MS[2]; Ibrahima Gning, DDS, DrPH[3]; Alvina Acquaye, MS[2]; Mark R. Gilbert, MD[2]; Charles Cleeland, PhD[3]; and Tito Mendoza, PhD[3]

Curr Oncol Rep
DOI 10.1007/s11912-012-0276-2

NEURO-ONCOLOGY (MR GILBERT, SECTION EDITOR)

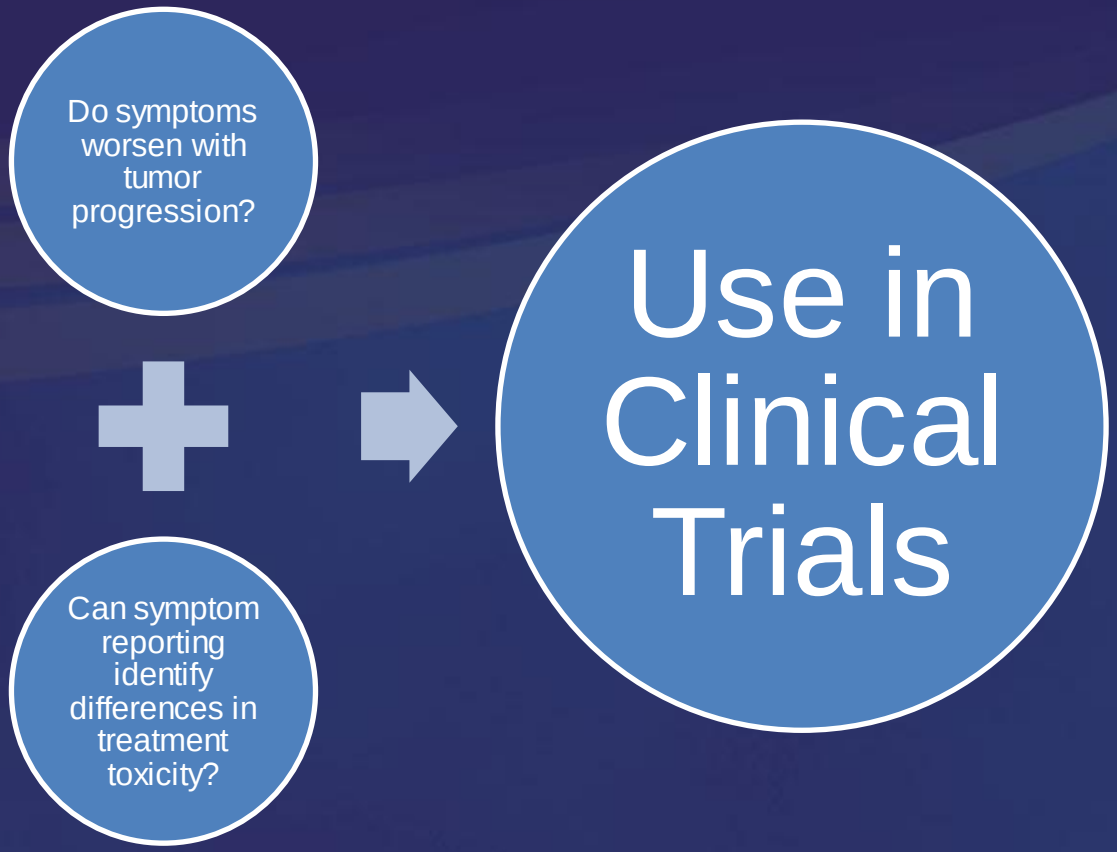
**Measuring Clinical Benefit: Use of Patient-Reported Outcomes (PRO) in Primary Brain Tumor Clinical Trials**

**Terri S. Armstrong**

Net Clinical Benefit: Functional Endpoints in Brain Tumor Clinical Trials

*Terri S. Armstrong, DSN, APRN, BC, and Mark R. Gilbert, MD*

# MDASI-BT, Treatment, and Tumor Status




## Why?

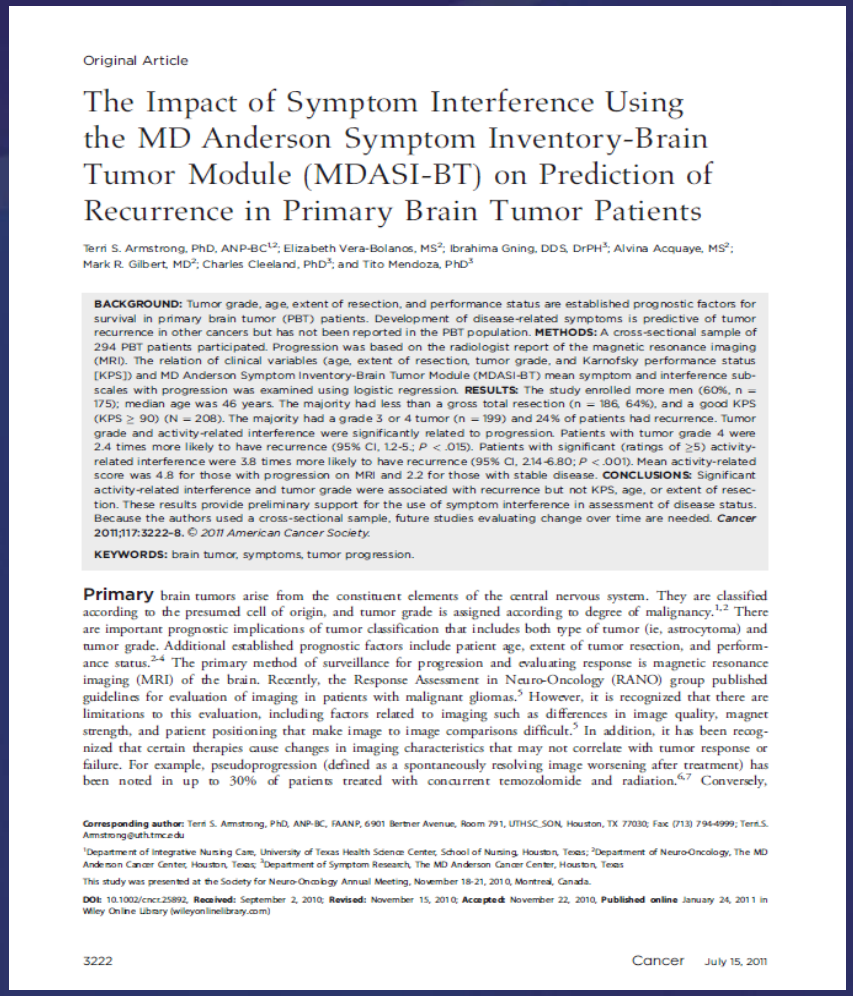
-Recognized in practice that we need a way to assess the impact of treatment

-Rare disease-so clinical trials provide access to patients

# Do patient's symptom report reflect disease status? MDASI-BT Prediction of Recurrence at time of MRI Imaging

(Armstrong et al, 2006, J. Neuro-Oncology & Armstrong et al, 2010, *Cancer*)

| Mean Score Type | Mean Score | Significance |
|---|---|---|
| **Mean Symptom Severity** | | |
| Stable Disease | 1.47 | 0.01 |
| Recurrent Disease | 2.39 | |
| **Mean Core Symptom Score** | | |
| Stable Disease | 1.70 | 0.01 |
| Recurrent Disease | 2.62 | |
| **Mean BT Symptom Score** | | |
| Stable Disease | 1.29 | 0.01 |
| Recurrent Disease | 2.23 | |
| **Mean Interference Score** | | |
| Stable Disease | 2.02 | 0.01 |
| Recurrent Disease | 4.24 | |



Original Article

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Terri S. Armstrong, PhD, ANP-BC[1,2]; Elizabeth Vera-Bolanos, MS[2]; Ibrahima Gning, DDS, DrPH[3]; Alvina Acquaye, MS[2]; Mark R. Gilbert, MD[2]; Charles Cleeland, PhD[3]; and Tito Mendoza, PhD[3]

**BACKGROUND:** Tumor grade, age, extent of resection, and performance status are established prognostic factors for survival in primary brain tumor (PBT) patients. Development of disease-related symptoms is predictive of tumor recurrence in other cancers but has not been reported in the PBT population. **METHODS:** A cross-sectional sample of 294 PBT patients participated. Progression was based on the radiologist report of the magnetic resonance imaging (MRI). The relation of clinical variables (age, extent of resection, tumor grade, and Karnofsky performance status [KPS]) and MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) mean symptom and interference subscales with progression was examined using logistic regression. **RESULTS:** The study enrolled more men (60%, n = 175); median age was 46 years. The majority had less than a gross total resection (n = 186, 64%), and a good KPS (KPS ≥ 90) (N = 208). The majority had a grade 3 or 4 tumor (n = 199) and 24% of patients had recurrence. Tumor grade and activity-related interference were significantly related to progression. Patients with tumor grade 4 were 2.4 times more likely to have recurrence (95% CI, 1.2-5.; $P < .015$). Patients with significant (ratings of ≥5) activity-related interference were 3.8 times more likely to have recurrence (95% CI, 2.14-6.80; $P < .001$). Mean activity-related score was 4.8 for those with progression on MRI and 2.2 for those with stable disease. **CONCLUSIONS:** Significant activity-related interference and tumor grade were associated with recurrence but not KPS, age, or extent of resection. These results provide preliminary support for the use of symptom interference in assessment of disease status. Because the authors used a cross-sectional sample, future studies evaluating change over time are needed. *Cancer* 2011;117:3222–8. © *2011 American Cancer Society.*

**KEYWORDS:** brain tumor, symptoms, tumor progression.

**Primary** brain tumors arise from the constituent elements of the central nervous system. They are classified according to the presumed cell of origin, and tumor grade is assigned according to degree of malignancy.[1,2] There are important prognostic implications of tumor classification that includes both type of tumor (ie, astrocytoma) and tumor grade. Additional established prognostic factors include patient age, extent of tumor resection, and performance status.[2-4] The primary method of surveillance for progression and evaluating response is magnetic resonance imaging (MRI) of the brain. Recently, the Response Assessment in Neuro-Oncology (RANO) group published guidelines for evaluation of imaging in patients with malignant gliomas.[5] However, it is recognized that there are limitations to this evaluation, including factors related to imaging such as differences in image quality, magnet strength, and patient positioning that make image to image comparisons difficult.[5] In addition, it has been recognized that certain therapies cause changes in imaging characteristics that may not correlate with tumor response or failure. For example, pseudoprogression (defined as a spontaneously resolving image worsening after treatment) has been noted in up to 30% of patients treated with concurrent temozolomide and radiation.[6,7] Conversely,

**Corresponding author:** Terri S. Armstrong, PhD, ANP-BC, FAANP, 6901 Bertner Avenue, Room 791, UTHSC_SON, Houston, TX 77030; Fax (713) 794-4999; Terri.S.Armstrong@uth.tmc.edu

[1]Department of Integrative Nursing Care, University of Texas Health Science Center, School of Nursing, Houston, Texas; [2]Department of Neuro-Oncology, The MD Anderson Cancer Center, Houston, Texas; [3]Department of Symptom Research, The MD Anderson Cancer Center, Houston, Texas

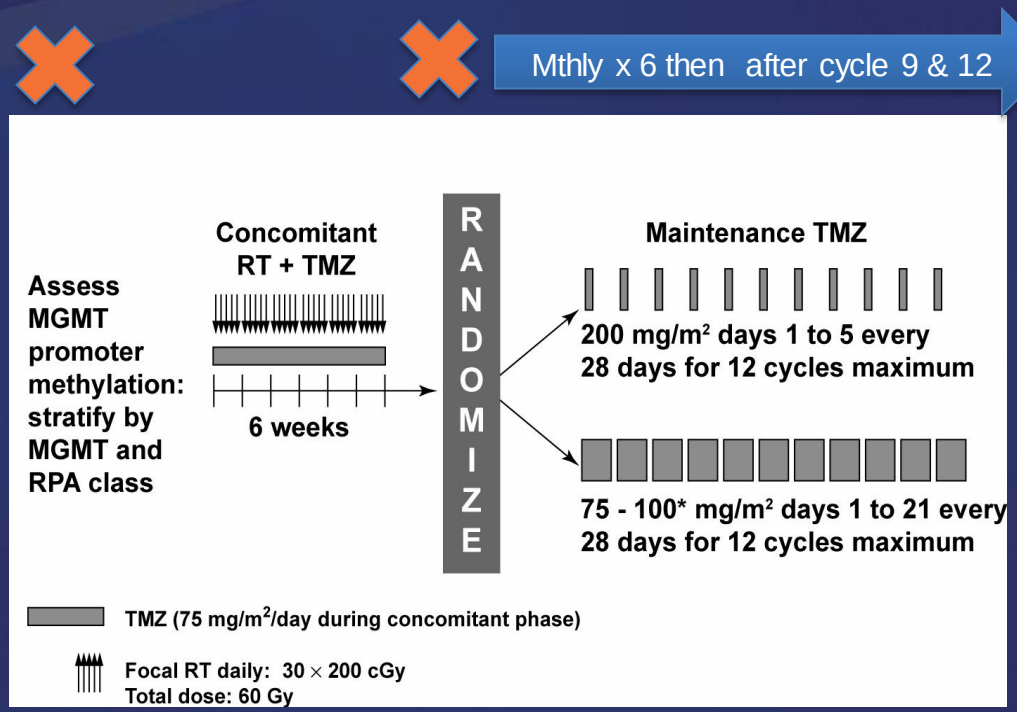
This study was presented at the Society for Neuro-Oncology Annual Meeting, November 18-21, 2010, Montreal, Canada.

**DOI:** 10.1002/cncr.25892, **Received:** September 2, 2010; **Revised:** November 15, 2010; **Accepted:** November 22, 2010, **Published online** January 24, 2011 in Wiley Online Library (wileyonlinelibrary.com)

# NCB of RTOG 0525


- Primary Study tested efficacy of dose dense adjuvant temozolomide (21 of 28 day cycle)
- Designed to determine if dd chemotherapy impacts because of toxicity or tumor response three distinct parameters: health related quality of life (HRQOL)';Symptoms' neurocognitive function (NCF)
- The goal was to determine if this info coupled with traditional outcome data could be used in important risk-benefit considerations for patients & their health care providers.

Patients completed NCB components (2 PROs, EORTC QLQ30/BN20 and MDASI-BT) at baseline, prior to cycle 1-6 of adjuvant, and then prior to cycle 10 and one month after completion if treatment continued for one year



# Objective 1: Evaluation of Between Arm Differences

Can symptom reportng identify differences in treatment toxicity?

**Overall Symptom severity, overall interference, & activity related interference scores were significantly different, with <u>those patients treated in the dose-dense arm experiencing more symptom burden</u>**

| | Arm 1 Deterioration | | Arm 2 Deterioration | | |
|---|---|---|---|---|---|
| Component | n | % | n | % | p-value* |
| **Symptom** | 5 | 10 | 11 | 27 | **0.03** |
| **Interference** | 7 | 14 | 13 | 32 | **0.03** |
| **--Activity related** | 8 | 16 | 15 | 39 | **0.01** |
| -- Mood related | 12 | 24 | 12 | 30 | 0.49 |

Median and range in Arm 2 Deterioration:

Overall Symptom change (1.6; range 1-2.8),

Overall Interference (2.5; range 1.5-7.7)

Activity Interference (1.5; range 1.0-8.0)

# Evaluation of Prediction of Progression Free (PFS) & Overall Survival (OS)

Do symptoms worsen with tumor progression?

- Calculated a change score (Baseline to prior to cycle 1).
- Evaluated whether larger change score predicted earlier progression and shorter overall survival
- Then added this to traditional markers of survival, including MGMT status, and RPA class to evaluate if additive or more sensitive

## MDASI-BT – Early Changes (RPA, MGMT not forced) Cox Proportional Hazards Model for Overall Survival

Do symptoms worsen with tumor progression?

| Variable Remaining in Model (**Bolded** value has unfavorable outcome) | p-value | Hazard Ratio (95% CI) |
|---|---|---|
| ***Cognitive factor*** (**Deterioration** vs. No deterioration) | **0.017** | 1.88 (1.12, 3.14) |

* MGMT and RPA did not remain in the model

# MDASI-BT – Early Changes (RPA, MGMT not forced) Cox Proportional Hazards Model for PFS

Do symptoms worsen with tumor progression?

| Variable (**Bolded** value has unfavorable outcome) | p-value | Hazard Ratio (95% CI) |
|---|---|---|
| ***Methylation status*** (**Unmethylated** vs. Methylated) | 0.003 | 1.90 (1.24, 2.92) |
| ***Neurologic factor*** (**Deterioration** vs. No deterioration) | 0.008 | 1.90 (1.18, 3.06) |

* RPA did not remain in the model

# Summary-
# The Groundwork for the Science of Assessment

- There is increasing evidence that current standards of response and survival are limited.
- Options exist to allow evaluation of the impact of therapy on the patient
- PROs may provide another method to assess disease and benefit of therapy
- Currently added to upcoming Alliance, RTOG, BTTC, and CERN trials as mandatory secondary endpoints & primary endpoints in symptom control and palliation studies

Topic 2: The Science of Symptoms

# UNDERSTANDING THE BIOLOGIC BASIS TO DESIGN TARGETED INTERVENTIONS

# The Cancer Genome: Basic Premise

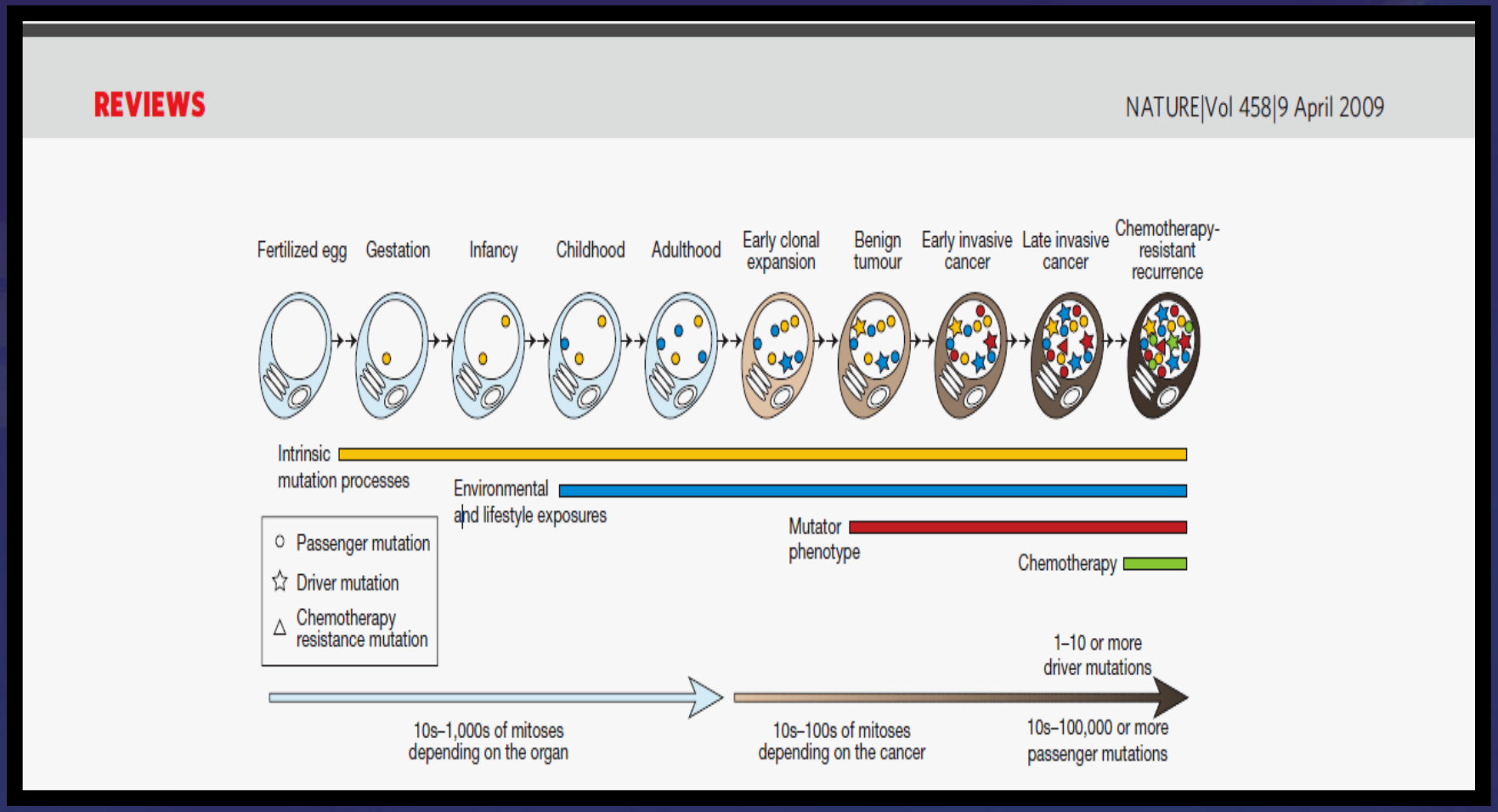
**Stratton, et al. The Cancer Genome (2009). Nature, 458**

- **All cancers are thought to share a common pathogenesis.**
  - Can think of these as a process of Darwinian evolution occurring among cell populations within the microenvironments

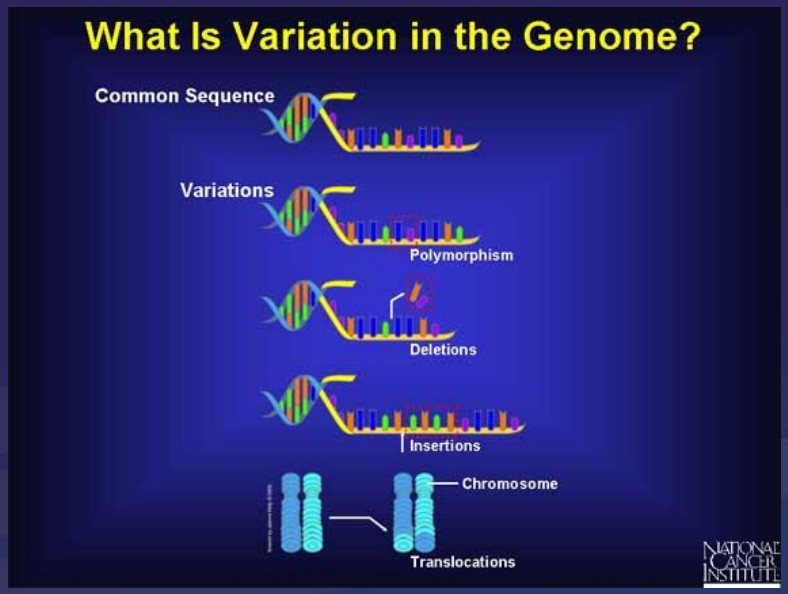
- **Cancer development is based on two constituent processes:**
  - the continuous acquisition of genetic variation in individual cells by random mutation; and
  - natural selection acting on the resultant phenotypic diversity.

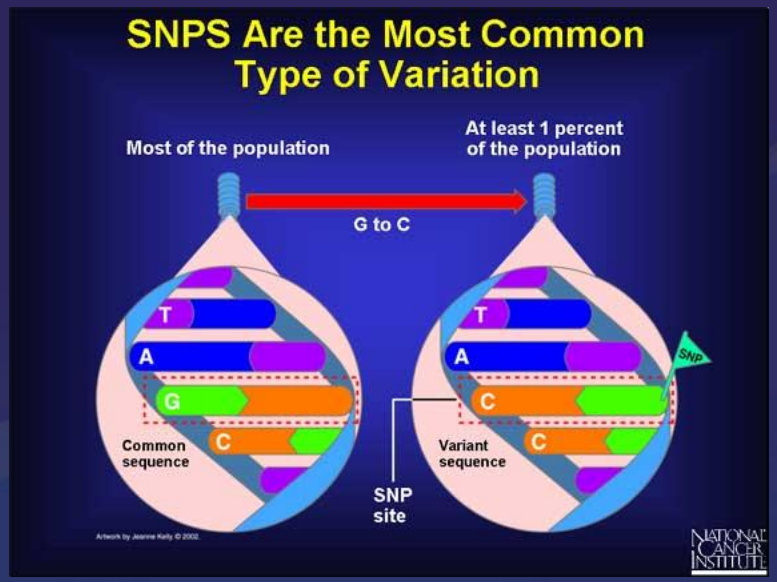
- **The DNA sequence of a cancer cell genome, like normal cells, has acquired a set of differences from its progenitor fertilized egg. These are collectively termed somatic mutations ( vs germline mutations that are inherited from parents).**

# Somatic Mutations & Cancer




Stratton, et al. The Cancer Genome (2009). Nature, 458


What Is Variation in the Genome?
Common Sequence
Variations
Polymorphism
Deletions
Insertions
Chromosome
Translocations
NATIONAL CANCER INSTITUTE


SNPS Are the Most Common Type of Variation
Most of the population
At least 1 percent of the population
G to C
T
A
G
C
Common sequence
SNP site
T
A
C
C
SNP
Variant sequence
Artwork by Jeanne Kelly © 2002.
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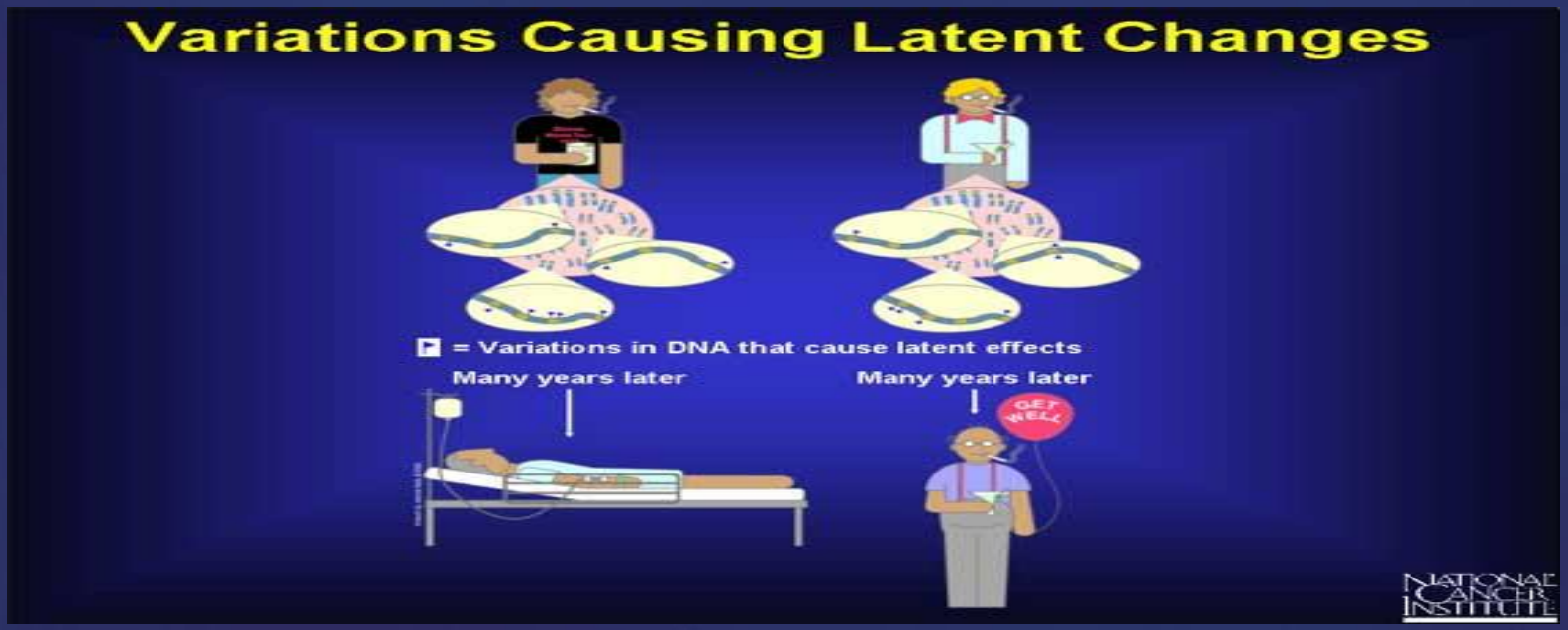
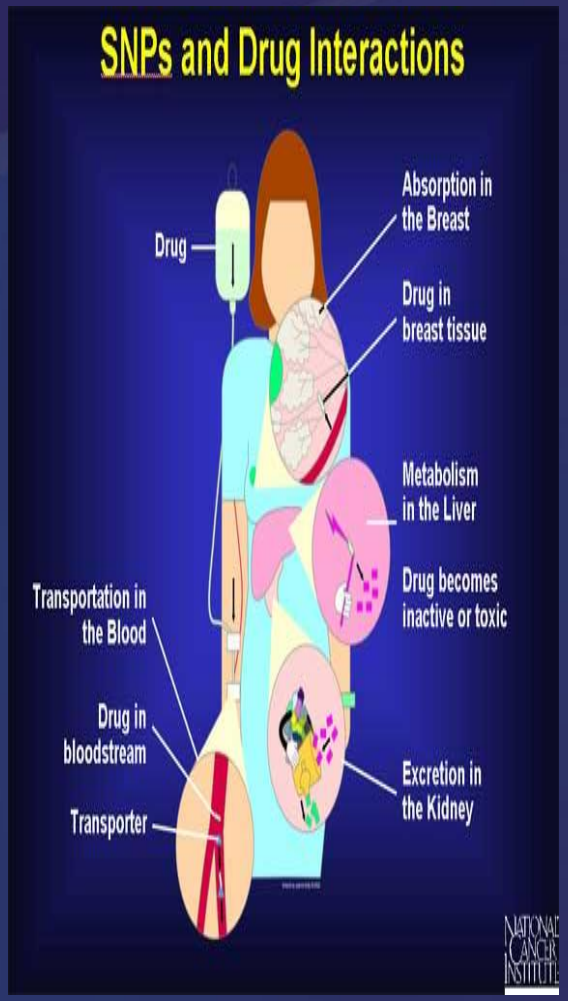
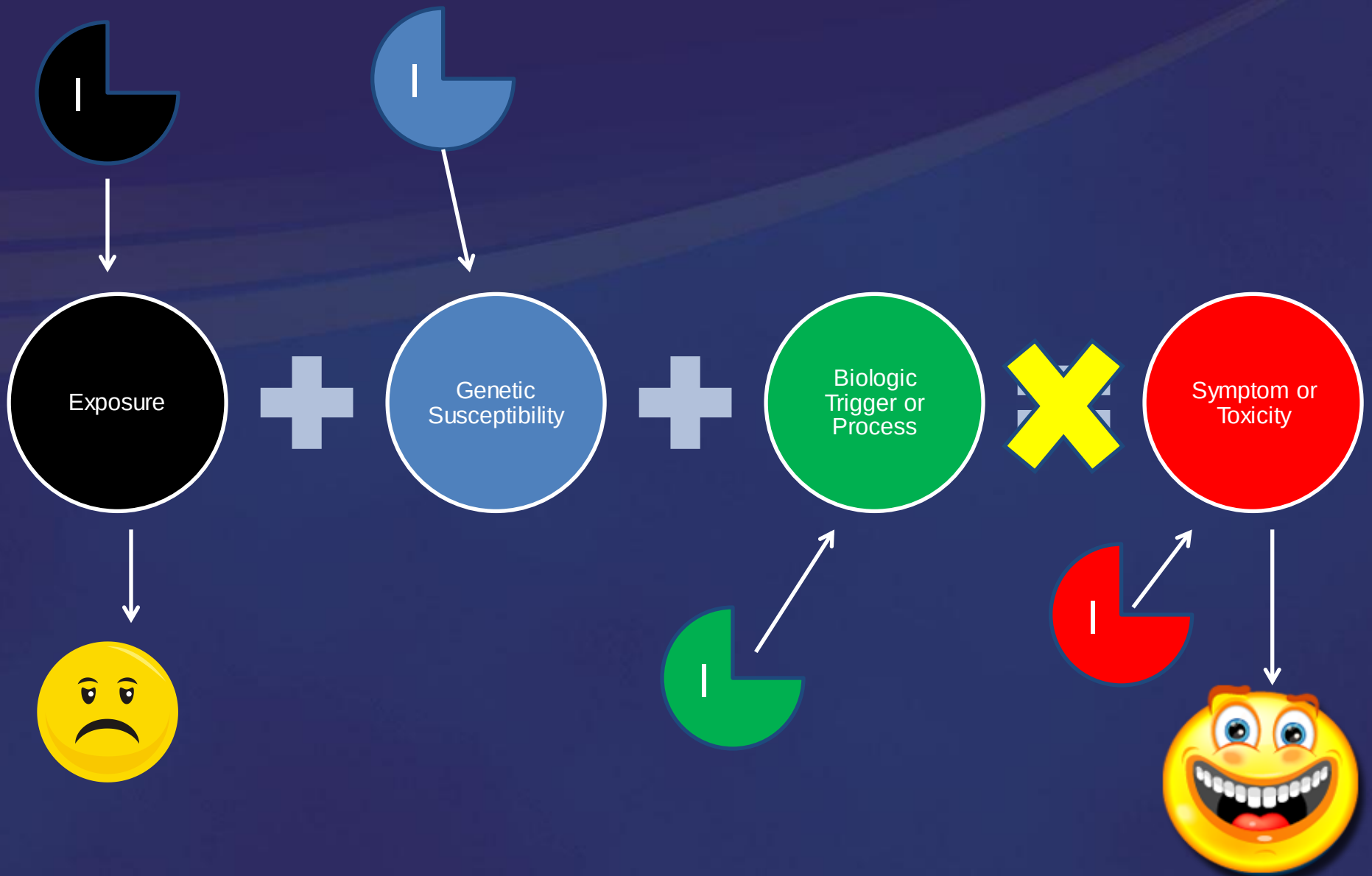

Variations Causing Latent Changes
= Variations in DNA that cause latent effects
Many years later
Many years later
GET WELL
NATIONAL CANCER INSTITUTE

# SNPs and Treatment-Associated Toxicity and Symptoms

- **SNPs may also be involved when patients have different side effects in response to the same drug.**
- **The DNA encodes proteins. Many proteins interact with the drug - involved in**
  - its transportation throughout the body,
  - absorption into tissues,
  - metabolism into more active forms or toxic by-products, and
  - excretion.
- **If a patient has SNPs in any one or more of these proteins, they may alter the time the body is exposed to active forms of the drug or any of its toxic byproducts.**
- **This may lead to increased symptoms & toxicity *or protection against this***



# The Science of Symptom Management



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Cytokine

journal homepage: www.elsevier.com/locate/issn/10434666

# Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression

Julie Illi [a], Christine Miaskowski [a,*], Bruce Cooper [a], Jon D. Levine [b,c], Laura Dunn [b], Claudia West [a], Marylin Dodd [a], Anand Dhruva [b], Steven M. Paul [a], Christina Baggott [a], Janine Cataldo [a], Dale Langford [a], Brian Schmidt [e], Bradley E. Aouizerat [a,d]

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ABSTRACT

Because multiple symptoms associated with "sickness behavior" have a negative impact on functional status and quality of life, increased information on the mechanisms that underlie inter-individual variability in this symptom experience is needed. The purposes of this study were to determine: if distinct classes of individuals could be identified based on their experience with pain, fatigue, sleep disturbance, and depression; if these classes differed on demographic and clinical characteristics; and if variations in pro- and anti- inflammatory cytokine genes were associated with latent class membership.

Self-report measures of pain, fatigue, sleep disturbance, and depression were completed by 168 oncology outpatients and 85 family caregivers (FCs). Using latent class profile analysis (LCPA), three relatively distinct classes were identified: those who reported low depression and low pain (83%), those who reported high depression and low pain (4.7%), and those who reported high levels of all four symptoms (12.3%). The minor allele of IL4 rs2243248 was associated with membership in the "All high" class along with younger age, being White, being a patient (versus a FC), having a lower functional status score, and having a higher number of comorbid conditions.

Findings suggest that LPCA can be used to differentiate distinct phenotypes based on a symptom cluster associated with sickness behavior. Identification of distinct phenotypes provides new evidence for the role of IL4 in the modulation of a sickness behavior symptom cluster in oncology patients and their FCs.



## 1. Introduction

Oncology patients and their family caregivers (FC) report experiencing, with the same frequency and severity, pain, fatigue, sleep disturbance, and depression [1–5]. While these symptoms can occur singly, they often co-occur as a cluster [6–12] and have significant deleterious effects on an individual's functional status and quality of life (QOL) [3,9,13–17]. In addition, several studies have identified distinct subgroups of individuals based on their experiences with these four symptoms [14,17–20]. Across these studies, a consistent finding was a subgroup of individuals who reported high levels of pain, fatigue, sleep disturbance, and depression. These individuals may represent a high risk group with a distinct phenotype.

Recent reviews suggest that inter-individual variability in symptom experiences may result from an individual's genetically determined ability to respond to physical and psychological stressors through changes in pro- and anti-inflammatory cytokines [10,21,22]. In fact, in studies that induced "sickness behavior" through the administration of inflammatory agents [23–29], individuals reported the co-occurrence of lethargy, anorexia, depression, anxiety, sleepiness, and hyperalgesia. For oncology patients and their FCs,

*Abbreviations:* AIMs, ancestry informative markers; BIC, Bayesian Information Criterion; BLRT, bootstrapped likelihood ratio test; CES-D, Center for Epidemiological Studies- Depression Scale; CI, confidence interval; DNA, deoxyribonucleic acid; EM, expectation–maximization; FC, family caregiver; GSDS, General Sleep Disturbance Scale; IFN, interferon; IL, interleukin; KPS, Karnofsky Performance Status; LCA, latent class analysis; LCPA, latent class profile analysis; LFS, Lee Fatigue Scale; MLR, robust maximum likelihood; PCA, principal component analysis; NFKB, nuclear factor kappa beta; NRS, numeric rating scale; OR, odds ratio; QOL, quality of life; RT, radiation therapy; SNP, single nucleotide polymorphism; TGF, transforming growth factor; TNF, tumor necrosis factor; VLMR, Vuong–Lo-Mendell–Rubin likelihood ratio test.

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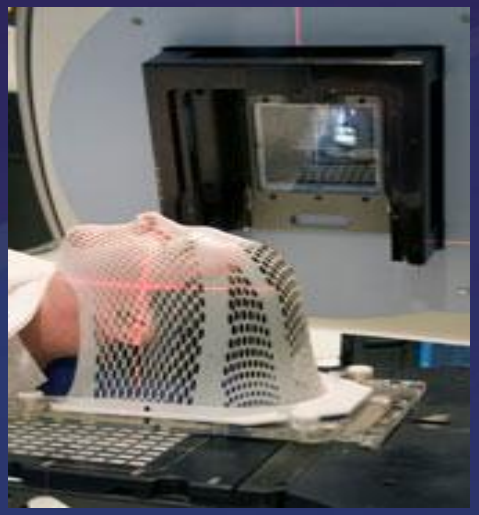
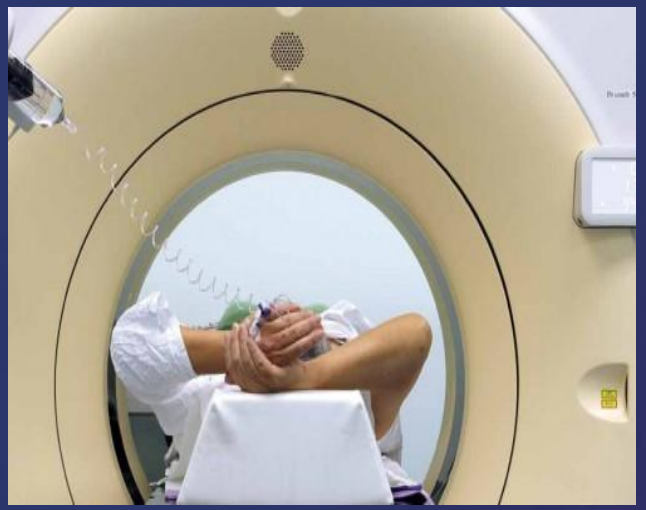
doi:10.1016/j.cyto.2012.02.015

# Common Acute Toxicities

- **The most common therapies of primary brain tumors include radiation therapy and temozolomide chemotherapy**
- **Radiation Therapy:**
  - Worsening of existing neurologic deficits
  - Fatigue
  - Skin Changes/Alopecia
- **Common toxicities of temozolomide are:**
  - Fatigue
  - Nausea
  - Constipation
  - Myelotoxicity



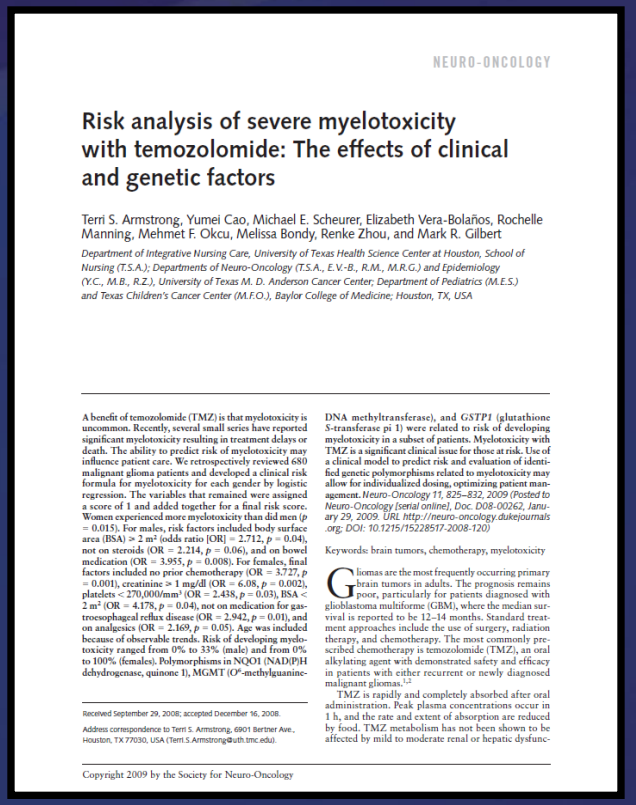


Amelio et al, 2010; Merchant et al, 2010; Armstrong, 2010

# Myelotoxicity Study Background
## Armstrong, et al (2009) *Neuro-Oncology*

Genetic Susceptibility

- **Myelosuppression is a dose-limiting toxicity of most cytotoxic chemotherapies**
  - However, it is relatively uncommon with temozolomide (TMZ) treatment (5-8% overall incidence)
- **Recent case reports and small series indicate problems with clinically significant myelosuppression leading to treatment delays, significant morbidity, and rare reports of death[1]**
- **In our practice, we have observed an even higher incidence of clinically significant myelosuppression in women**
- **The aim of this study was to evaluate the incidence of myelosuppression after the first cycle of TMZ and identify factors that may predict risk for the individual patient**



NEURO-ONCOLOGY

**Risk analysis of severe myelotoxicity with temozolomide: The effects of clinical and genetic factors**

Terri S. Armstrong, Yumei Cao, Michael E. Scheurer, Elizabeth Vera-Bolaños, Rochelle Manning, Mehmet F. Okcu, Melissa Bondy, Renke Zhou, and Mark R. Gilbert

*Department of Integrative Nursing Care, University of Texas Health Science Center at Houston, School of Nursing (T.S.A.); Departments of Neuro-Oncology (T.S.A., E.V.-B., R.M., M.R.G.) and Epidemiology (Y.C., M.B., R.Z.), University of Texas M. D. Anderson Cancer Center; Department of Pediatrics (M.E.S.) and Texas Children's Cancer Center (M.F.O.), Baylor College of Medicine; Houston, TX, USA*

A benefit of temozolomide (TMZ) is that myelotoxicity is uncommon. Recently, several small series have reported significant myelotoxicity resulting in treatment delays or death. The ability to predict risk of myelotoxicity may influence patient care. We retrospectively reviewed 680 malignant glioma patients and developed a clinical risk formula for myelotoxicity for each gender by logistic regression. The variables that remained were assigned a score of 1 and added together for a final risk score. Women experienced more myelotoxicity than did men ($p = 0.015$). For males, risk factors included body surface area (BSA) > 2 m² (odds ratio [OR] = 2.712, $p = 0.04$), not on steroids (OR = 2.214, $p = 0.06$), and on bowel medication (OR = 3.955, $p = 0.008$). For females, final factors included no prior chemotherapy (OR = 3.727, $p = 0.001$), creatinine > 1 mg/dl (OR = 6.08, $p = 0.002$), platelets < 270,000/mm³ (OR = 2.438, $p = 0.03$), BSA < 2 m² (OR = 4.178, $p = 0.04$), not on medication for gastroesophageal reflux disease (OR = 2.942, $p = 0.01$), and on analgesics (OR = 2.169, $p = 0.05$). Age was included because of observable trends. Risk of developing myelotoxicity ranged from 0% to 33% (male) and from 0% to 100% (females). Polymorphisms in NQO1 (NAD(P)H dehydrogenase, quinone 1), MGMT (O⁶-methylguanine-DNA methyltransferase), and *GSTP1* (glutathione *S*-transferase pi 1) were related to risk of developing myelotoxicity in a subset of patients. Myelotoxicity with TMZ is a significant clinical issue for those at risk. Use of a clinical model to predict risk and evaluation of identified genetic polymorphisms related to myelotoxicity may allow for individualized dosing, optimizing patient management. *Neuro-Oncology 11, 825–832, 2009 (Posted to Neuro-Oncology [serial online], Doc. D08-00262, January 29, 2009. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-120)*

Keywords: brain tumors, chemotherapy, myelotoxicity

Gliomas are the most frequently occurring primary brain tumors in adults. The prognosis remains poor, particularly for patients diagnosed with glioblastoma multiforme (GBM), where the median survival is reported to be 12–14 months. Standard treatment approaches include the use of surgery, radiation therapy, and chemotherapy. The most commonly prescribed chemotherapy is temozolomide (TMZ), an oral alkylating agent with demonstrated safety and efficacy in patients with either recurrent or newly diagnosed malignant gliomas.[1,2]

TMZ is rapidly and completely absorbed after oral administration. Peak plasma concentrations occur in 1 h, and the rate and extent of absorption are reduced by food. TMZ metabolism has not been shown to be affected by mild to moderate renal or hepatic dysfunc-

Received September 29, 2008; accepted December 16, 2008.

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1 (Doyle, Middelsen, & Croteau, 2005; Gerbert, et al. 2007; Jalali et al. 2006; Noronha et al. 2006; Singhal, Selva-Nayagam, & Brown, 2007)

# Toxicities of Therapy: Myelosuppression with Standard Dose Temozolomide


- **Retrospective review of 685 patients**
- **Women more likely to experience Grade 3 or 4 leukopenia than men (p = 0.015)**
  - Risk higher in women who received one or fewer prior chemotherapies, weighed less than 50kg, or were on enzyme-inducing anticonvulsants (p=0.0009)
  - Risk in men increased with age, was higher in those who received two or more prior chemotherapy regimens, and was associated with GERD use (p=0.00)
- **Risk of any myelosuppression (Grade III or IV WBC, ANC, or Plts) was also higher in women (18%) then men (7%)**
- **Mathematical formula developed to assign risk based on covariates which either increased or decreased patient risk**

Armstrong, et al. 2006.

# Final Formula for Males

Genetic Susceptibility

**Male tox = Age + BSA + WBC + steroid + bowel + thyroid**

- **Categories of Covariates associated with risk which add +1 to the formula:**
  - Age > 40
  - BSA ≥ 2
  - WBC ≤ 6.5
  - Not on steroids
  - On Bowel medication
  - On Thyroid Replacement

| Division | Calculated Risk Score | % with Toxicity |
|---|---|---|
| No Risk | 0 | 0% |
| Low Risk | 1/2/3/4 | 1.7-16.1% |
| Moderate Risk | 5 | 33.3% |

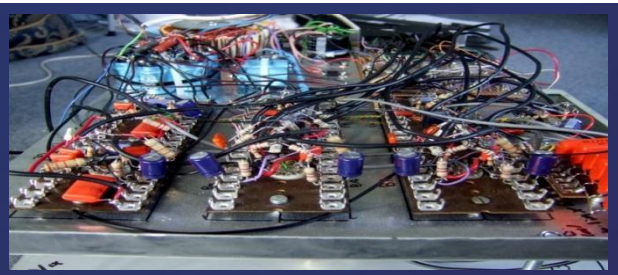
# Final Formula for Females

Genetic Susceptibility

**Female tox = age + no chemo + creatinine + platelet + BSA + anxiety + bowel + GERD + pain**

- **Categories of Covariates Associated with Risk for which +1 was added to the formula:**
  - Age at treatment 31-40
  - No Prior chemotherapy
  - Creatinine >=1
  - Platelet count < 270k
  - BSA < 2
  - Not on Anxiety Medication
  - On Bowel medication
  - Not on GERD medication
  - On Pain medication

| Division | Calculated Risk Score | % with Toxicity |
|---|---|---|
| No Risk | 0/1/2/3 | 0% |
| Moderate Risk | 4/5 | 16.9-20.7% |
| High Risk | 6/7 | 44.4-80% |



# Single Nucleotide Polymorphisms (SNPs)

Genetic Susceptibility

- Performed a case-control evaluation matching those with myelotoxicity to a group of patients without myelotoxicity, in a 3: 5 ratio by gender, and age.
- We evaluated SNPs associated with DNA repair and inflammatory pathways
- Results of this multivariable analysis revealed significant associations between SNPs in MGMT (2.4 increase in TOX), NQO1 *(72% reduction in TOX*), and GSTP105 *(72% reduction in TOX),* and the occurrence of myelotoxicity.

| | | 95% | | |
|---|---|---|---|---|
| Effect | OR | Confidence | Limits | Pr > Chisq |
| MGMT1 | | | | 0.06 |
| G/AG vs AA | 2.32 | 0.95 | 5.62 | |
| GSTP105 | | | | 0.02 |
| MM/MW vs WW | 0.28 | 0.1 | 0.75 | |
| NQO1 | | | | 0.0563 |
| A/AG vs GG | 0.3 | 0.11 | 0.85 | |

# Continued Progress

- Current planned study to validate this model and develop web-based calculator of risk
- Also looking at stroke/thrombosis and hypertension risk with bevacizumab
- Programmatic approach through consortia

"I can't get my positive mind and my fatigued body on the same page. Frustrating. I used to be a jet before cancer and I am still adapting to being a sailboat after diagnosis. I just want to do more, like my old self. CERN EO Survey Participant.

www.cern-foundation.org

# UNDERSTANDING BIOLOGIC CHANGES RELATED TO FATIGUE

# Fatigue

Biologic Trigger or Process

## Overview

- **Fatigue is also one of the most common symptoms reported by patients with brain tumors throughout the disease trajectory.**
  - Overall 42% reported "quite a bit low" or "very low" energy levels[1] and reported **most troublesome[2]**.
  - 39% of low grade glioma patients reported severe fatigue **more than 8 years** after completion of therapy.[3] 2009).
  - We reported 73% had fatigue of any severity, and **40% reported as moderate to severe [4]**

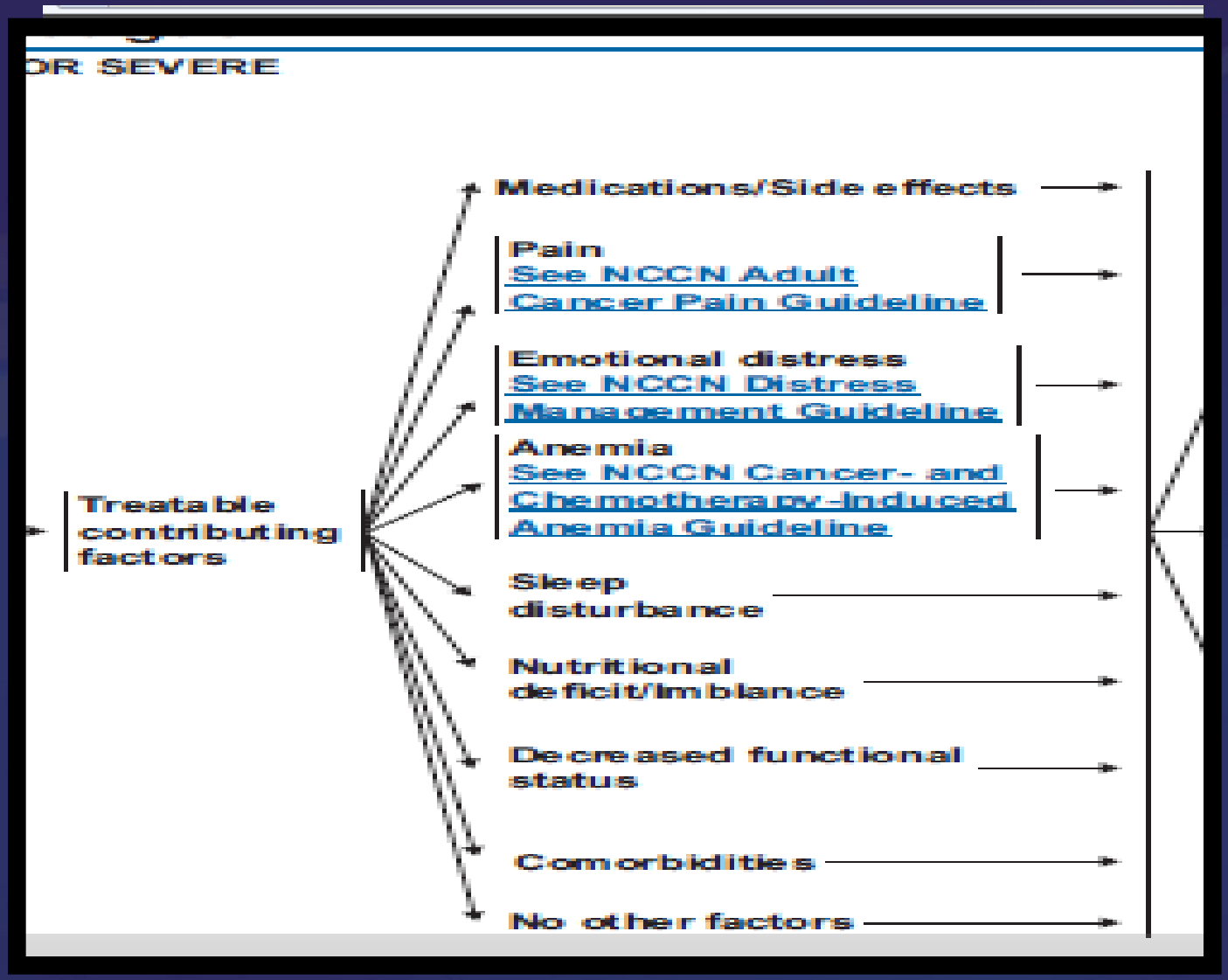
[1]Lovely, 1999; [2]Powell et al, 2011; [3] Struik et al, 2009; [4]Armstrong et al, 2010); [5] Rooney, et al, 2011)

## Contributing Factors

- **Concomitant medications such as anticonvulsants and corticosteroids, have been reported to have a negative impact on fatigue in this patient population[3].**
- **Depression and anxiety has been reported to occur in 16-50% of patients during the early stages of the disease and may be difficult to distinguish from fatigue[5].**

| VARIABLE | Odds Ratio (CI) | P Value |
|---|---|---|
| KPS | 5.73 (2.08, 15.82) | 0.001 |
| Gender | 2.48 (1.32, 4.65) | 0.01 |
| Disease Status | 2.20 (1.18, 4.10) | 0.01 |

# Fatigue Initial Evaluation (NCCN Guidelines)



National Comprehensive Cancer Network®

# NCCN Guidelines™ Version 1.2011
# Cancer-Related Fatigue

NCCN Guidelines Index
Fatigue Table of Contents
Discussion

## INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[a]

### Patient/Family Education and Counseling

Information about known pattern of fatigue during and following treatment

- Reassurance that treatment-related fatigue is not necessarily an indicator of disease progression

### General Strategies for Management of Fatigue

- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Labor-saving devices[f]
  - Postpone nonessential activities
  - Limit naps to < 1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)

### SPECIFIC INTERVENTIONS

#### Nonpharmacologic[g]

- Activity enhancement (category 1)
  - Maintain optimal level of activity
  - Consider initiation of exercise program of both endurance and resistance exercise
  - Consider referral to rehabilitation: physical therapy, occupational therapy & physical medicine
  - Caution:
    - Bone metastases
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Limitations secondary to metastases or other illnesses
- Physically-based therapies
  - Massage therapy (category 1)
- Psychosocial interventions
  - Cognitive behavioral therapy (CBT)[h]/ Behavioral therapy (BT) (category 1)[i]
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies[j]
- Nutrition consultation
- CBT[h] for sleep
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene

#### Pharmacologic

- Consider psychostimulants[k] (methylphenidate or modafanil) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines™ (See appropriate NCCN Supportive Care Guidelines)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

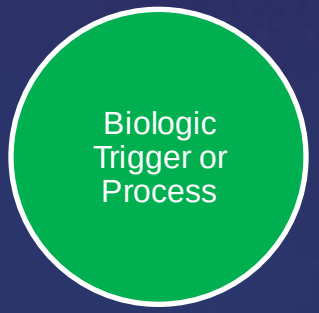
→ Repeat evaluation See (FT-4)

[a] See Discussion for information on differences between Active treatment, Post-Treatment, and End-of-Life treatment. (See MS-1)

[f] Examples include use of reachers for grasping items beyond arm's length, sock-aids for pulling on socks, rolling carts for transporting items, escalators and elevators for traveling between building floors, and electrical appliances for performing common household tasks (eg, opening cans)

The Science of Symptoms

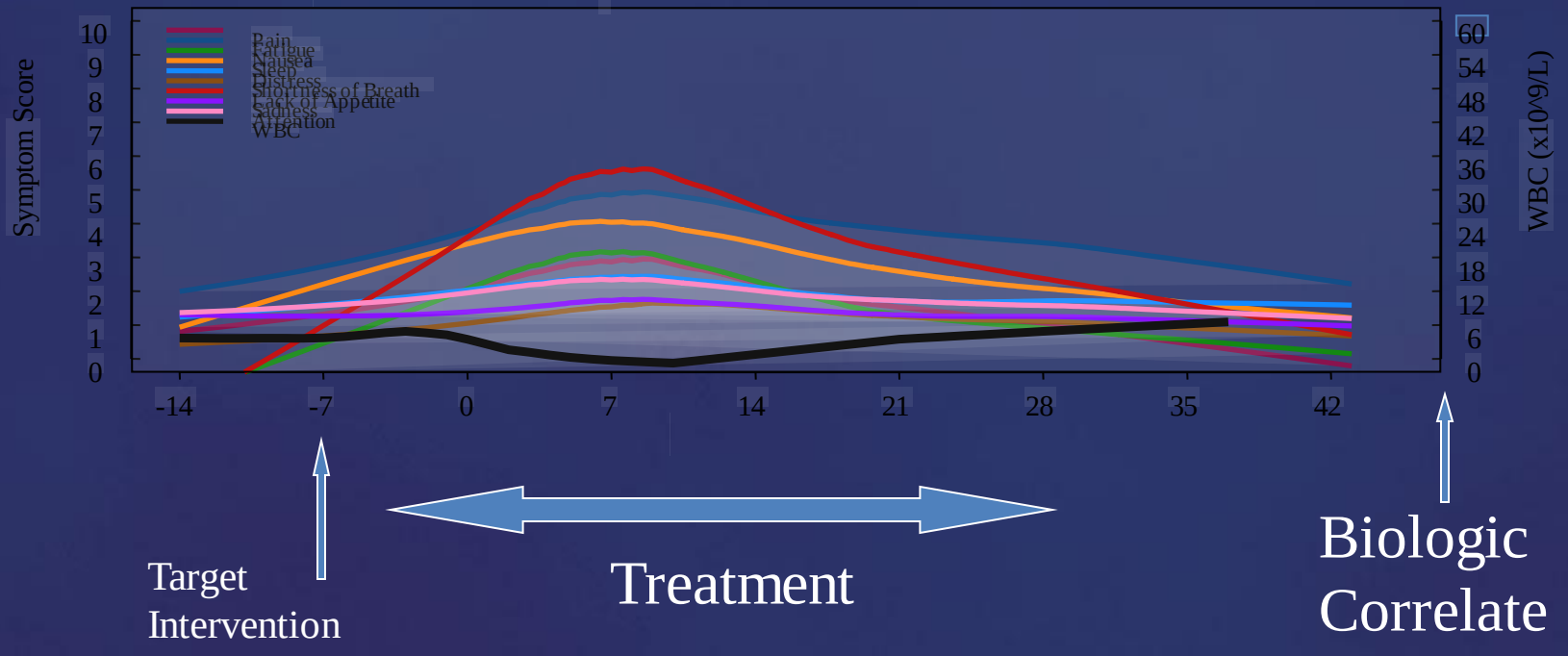
# WHAT IF FATIGUE IS NOT ONE BROAD CONCEPT- BUT DIFFERENT BASED ON THE BIOLOGIC BASIS?



# Fatigue and Radiation

Biologic Trigger or Process

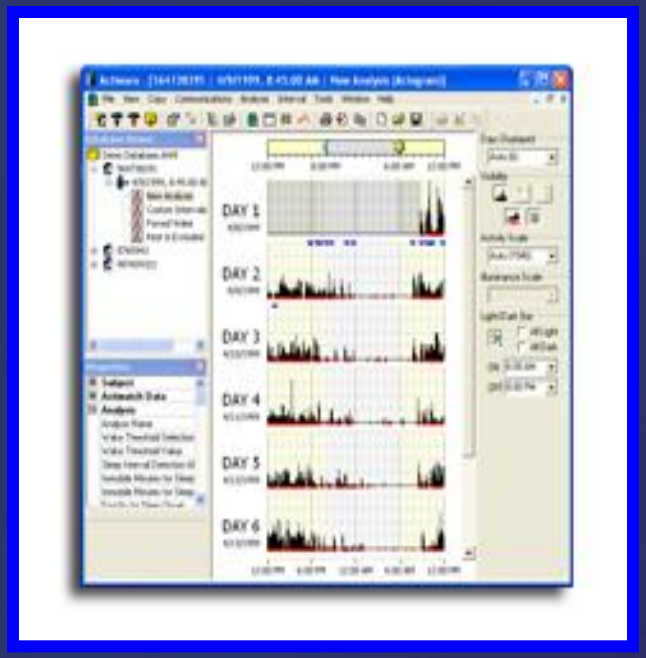
- **80% of primary brain tumor patients report fatigue during radiation therapy (Lovely, 1998).**
- **Specific Pattern**
  - Occurs within 1 week of the first radiation treatment and tends to increase with the number
  - Faithfull and Brandas reported on the occurrence of a somnolence syndrome (fatigue, excessive drowsiness, feeling clumsy, and inability to concentrate)
  - Cyclical pattern, with increased severity between day 1-21 and then day 30-35 after treatment.



# Fatigue, Insomnia & Radiation

- **Symptoms (Fatigue):**
  - MDASI-BT
  - BFI
- **Sleep:**
  - Epworth Sleepiness Scale
  - Pittsburgh Sleep Inventory
  - Actigraphy
- **Biologic Correlates**
  - Actigraphy
  - Urinary epinephrine, norepinephrine, dopamine, serotonin, GABA, Glutamate, PEA, and Histamine)
  - Salivary hormones (melatonin and cortisol)

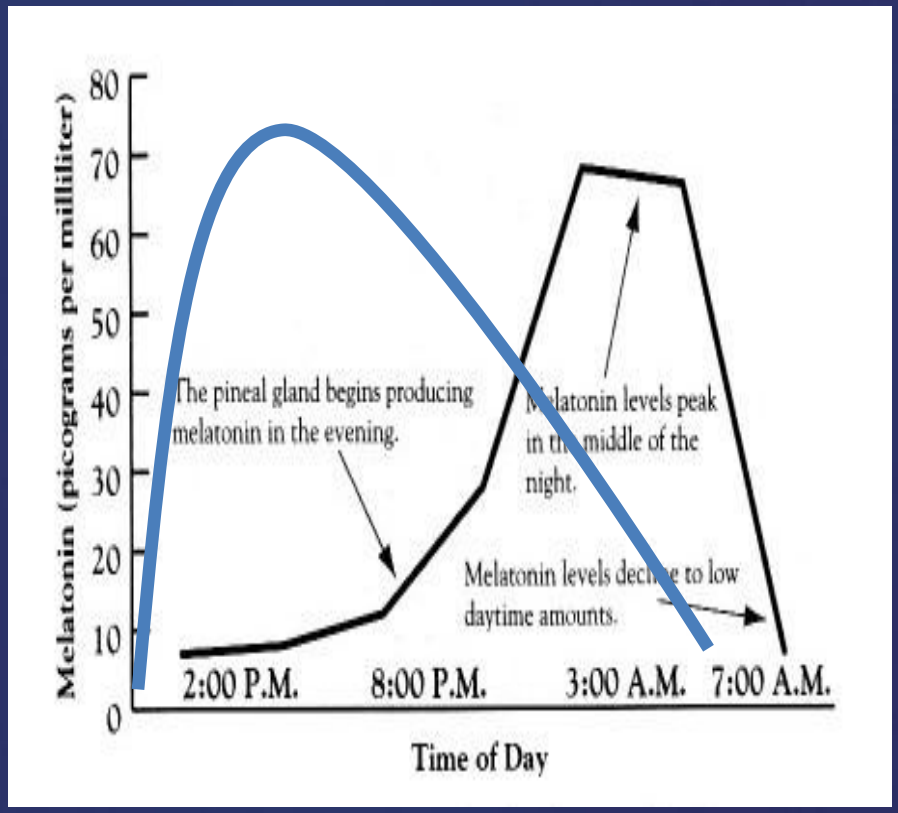
| Pre XRT | Wk1 | Wk 2 | Wk 3 | Wk 4 | W k5 | Wk 6 | Post TX |
|---|---|---|---|---|---|---|---|
| Quest 2 | X | X | X | X | X | X | X |
| Actigraphy (ACT) | X | X | X | X | X | X | X |
| Melatonin Neurotransmitters | | | | | | X | X |



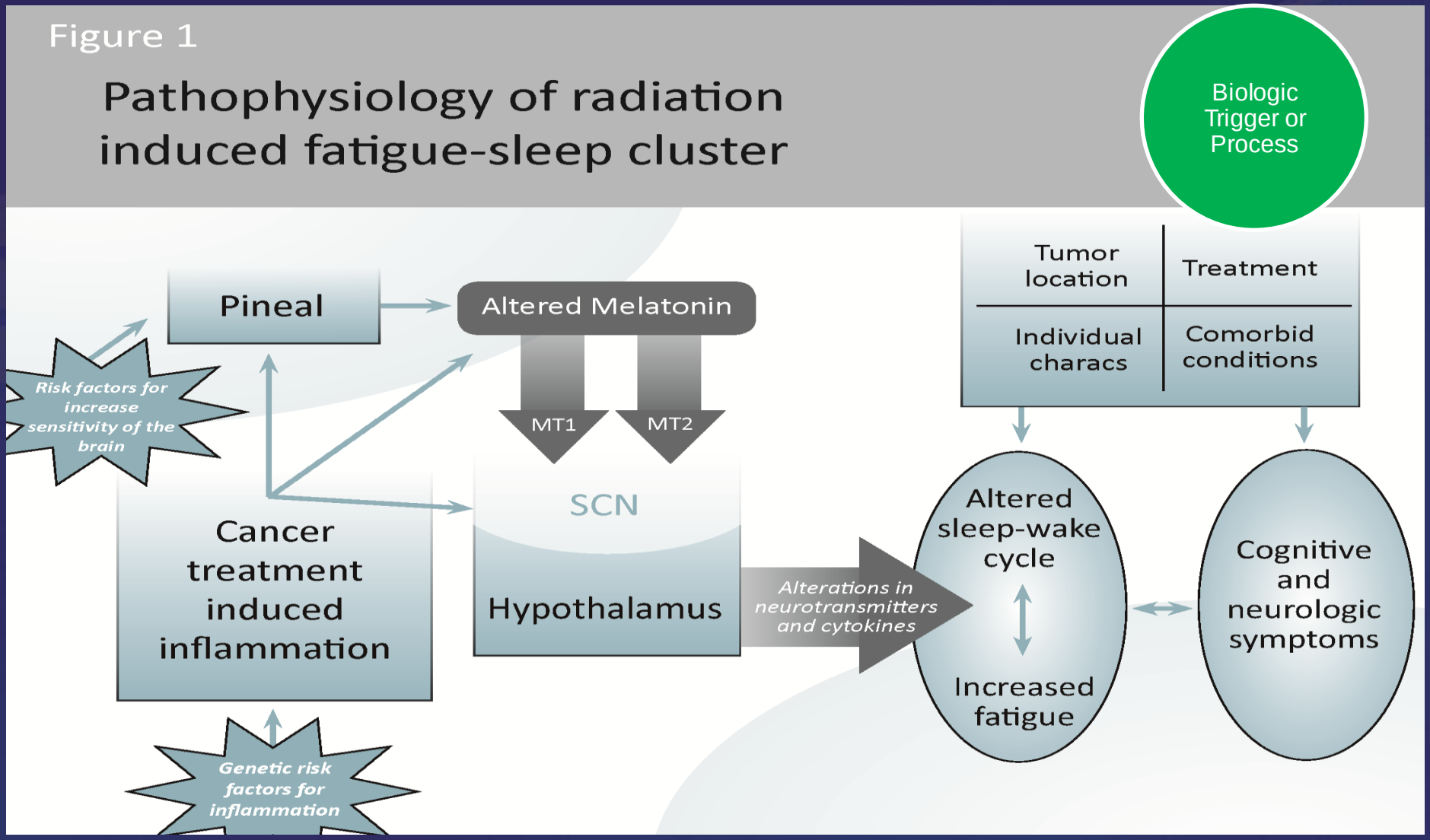
# Results

- **Fatigue severity at WK 6 correlated with:**
  - radiation dose to the pineal gland (dose range 15-60gy, median 35gy; r = 0.86, p = .07),
  - altered sleep, including change in self report sleep (r= 0.849, p =.016), &
  - as determined by ACT from WK 0 to WK 6 (r = 0.70, p =.07).
- **Change in melatonin (MLT) levels strongly correlated with**
  - the change in fatigue score (r = 0.90, p = .036), and
  - change in wake time after sleep onset (WASO) by ACT (r = 0.97, p = .033).
- **Fatigue severity at WK 6 was also correlated with**
  - the severity of reported neurologic (r = 0.72, p = .043) and cognitive symptoms (r = 0.94, p = .01) at WK 6.
- **Pilot study characterizing change in circadian pattern of melatonin production demonstrated 'shift in melatonin to earlier in the day & excess production**

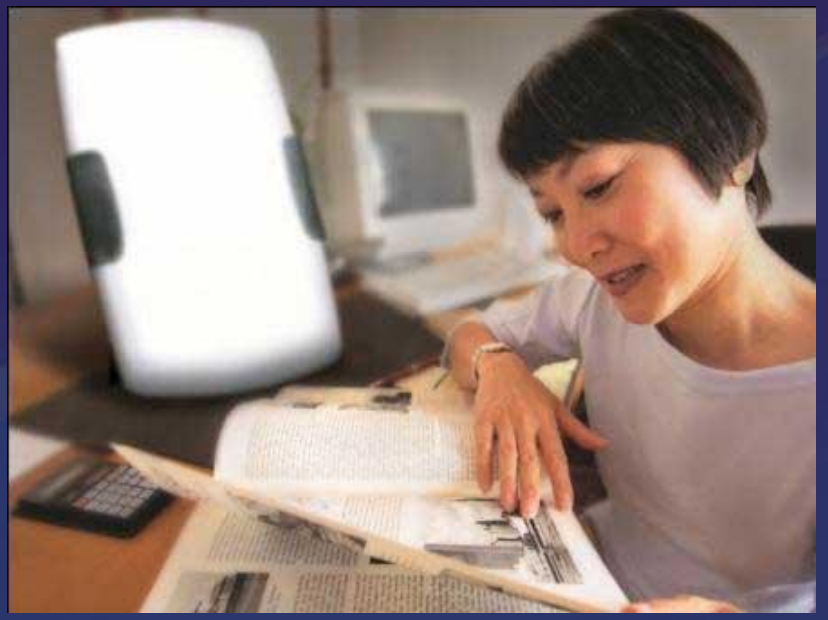
| | | Mean dose pineal gland (Gy) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 18 | 28 | 50 | 52 | 60 | Total |
| BFI worst fatigue right now at week 6 | 2 | 1 | 0 | 0 | 0 | 0 | 1 |
| | 4 | 0 | 1 | 0 | 0 | 0 | 1 |
| | 7 | 0 | 0 | 1 | 1 | 0 | 2 |
| | 10 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | | 1 | 1 | 1 | 1 | 1 | 5 |

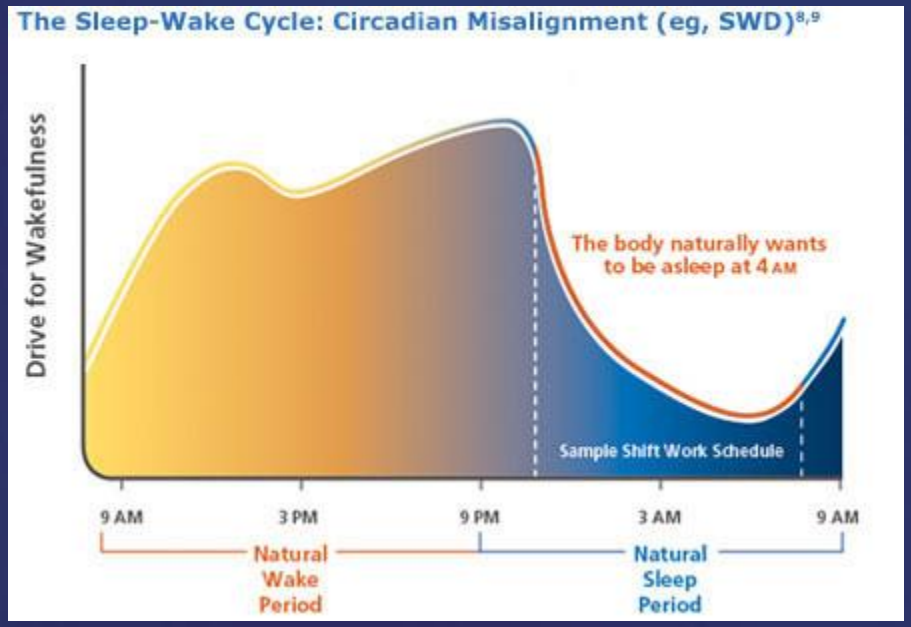


# Model of Radiation-Induced Fatigue
## (Armstrong & Gilbert, 2012)

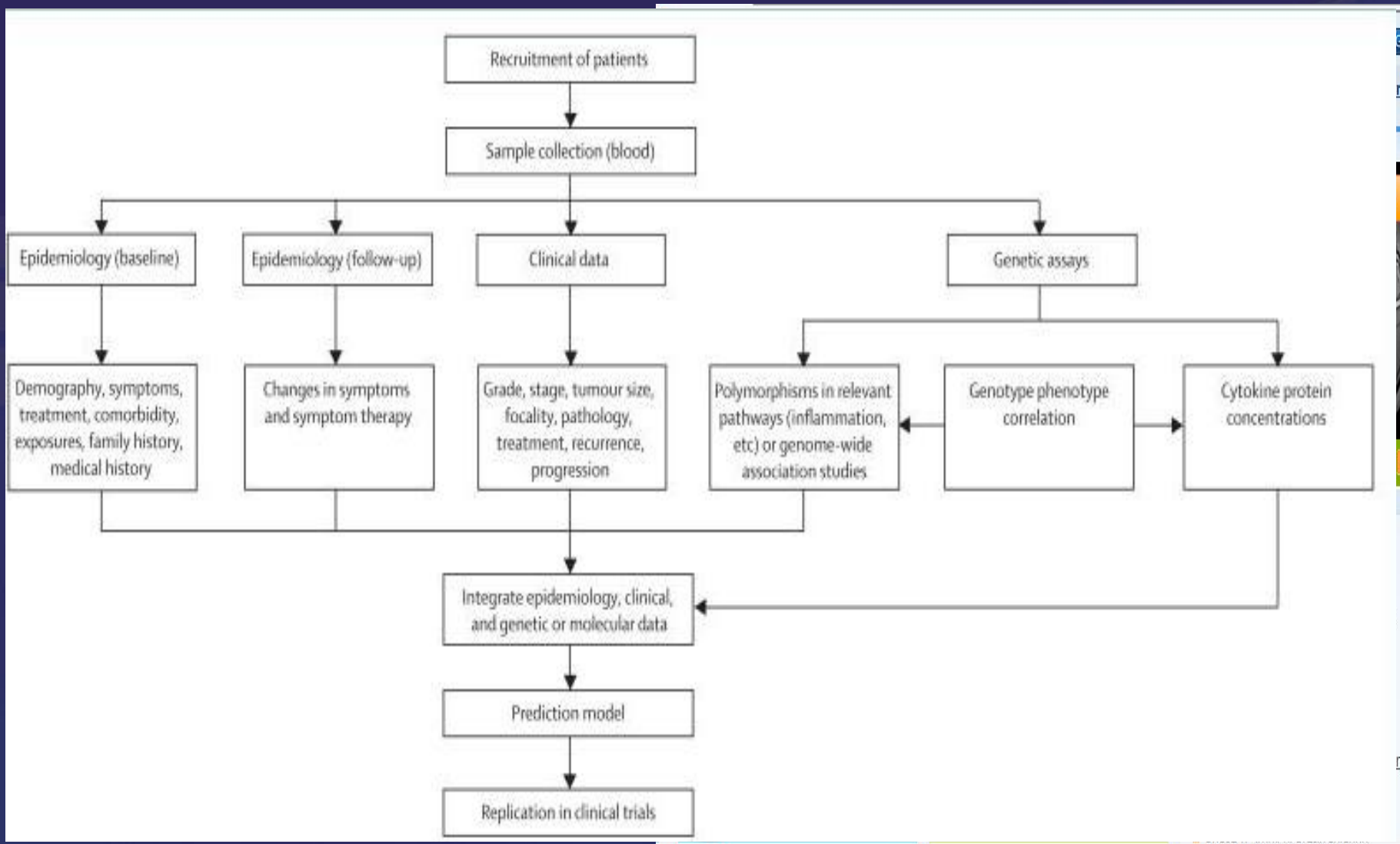


# Biologically Based Intervention? Light Boxes!






# Programmatic Approach: Collaborative Ependymoma Research Network



# Ultimate Goal - Futility: Approach to Patients!

- **Changing paradigm of symptom mgt to identify risk & biologically based approach to symptom prevention**

- **Real Lessons:**
  - Reality is what it is, not what you think that it should be!
    - Pushing your reality ("I would go on a cruise")
    - The informed patients reality should guide treatment
  - Statistics are *just statistics!*
    - Novel treatments with unknown impact on survival
  - Educate *but don't* Dictate
  - Choose Words Wisely *(Larry Burkett):*
    - you are going to die in two months
    - There are some treatments, but they probably won't work
    - This is what I can offer you

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