

An up-to-date and  
essential guide to

Tools for getting organized

Understanding brain tumors

Molecular markers

Your medical team

Questions to ask

Standard-of-care treatment

Clinical trials

Alternative and complementary  
treatments

Common medicines for treating  
symptoms

“Real world” and online support  
groups

Insurance management

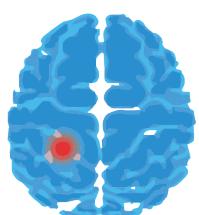
**Al Musella, DPM**

Twelfth  
edition

# BRAIN TUMOR GUIDE

*for the*

**NEWLY  
DIAGNOSED**



**MUSELLA**

FOUNDATION FOR BRAIN TUMOR  
RESEARCH & INFORMATION, INC.

# Brain Tumor Guide for the Newly Diagnosed

Twelfth edition

A comprehensive and essential guide to  
understanding:

Brain tumors and their diagnoses

Genetic markers

Your medical team and questions to ask

Standard-of-care treatment

Clinical trials

Alternative and complementary treatments

Common medicines for treating symptoms

"Real world" and online support groups

Insurance management

AI Musella, DPM  
The Musella Foundation



**MUSSELLA  
FOUNDATION**

FOR BRAIN TUMOR  
RESEARCH & INFORMATION

## **About the Musella Foundation**

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The Musella Foundation for Brain Tumor Research & Information, Inc., is a 501(c)3 nonprofit public charity dedicated to accelerating the search for the cure of brain tumors and to helping families deal with a brain tumor diagnosis. We create and distribute educational materials, provide help matching patients to clinical trials, give emotional and financial support to brain tumor patients, support awareness and advocacy for brain tumor issues, and give grants for brain tumor research. We maintain a website, [virtualtrials.org](http://virtualtrials.org), that is focused on brain tumor information and treatment; a co-pay assistance website, [braintumorcopays.org](http://braintumorcopays.org); and a fundraising website, [walktoendbraintumors.org](http://walktoendbraintumors.org).

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## **Dr. Henry Friedman and Dr. Linda Liau reviewed and approved the contents of this guide.**

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Henry S. Friedman, MD, is deputy director of the Preston Robert Tisch Brain Tumor Center at the Duke University Medical Center in Durham, North Carolina. An internationally recognized neuro-oncologist, Dr. Friedman has a long-standing career in the treatment of children and adults with brain and spinal cord tumors. He has written hundreds of research articles, and his work has been showcased on several segments of the CBS program *60 Minutes*. Dr. Friedman strongly believes that there is hope for patients who are being treated for brain cancer.



Linda Liau, MD, PhD, MBA, is the chair of the Department of Neurosurgery at UCLA in Los Angeles, California, and director of the UCLA Specialized Program of Research Excellence (SPORE) in Brain Cancer. She is a neurosurgeon with a clinical expertise in intra-operative functional brain mapping for resection of brain tumors. Dr. Liau's research is focused on clinical neuro-immunology, immunotherapy, and brain cancer vaccines. Her work has been published in major journals and textbooks and has been highlighted on several television shows. She is an elected member of the National Academy of Medicine.

## Table of Contents

<b>INTRODUCTION</b>	<b>xii</b>
<b>ABOUT THIS EDITION</b>	<b>xiv</b>
Forward	xiv
Applicability	xiv
Personalized Help	xiv
Glossary	xv
Internet Links	xv
Scientific Advances/Studies	xv
Survivor Stories	xvi
Informational Only	xvi
<b>CHAPTER 1: WHAT YOU NEED TO KNOW WHEN A BRAIN TUMOR IS FOUND</b>	<b>1</b>
Discovery of a Cranial Mass	1
Diagnostic Process	2
<i>Neurological Exam</i>	3
<i>Imaging</i>	3
<i>Molecular Evaluation</i>	4
Biopsy	5
<i>Overview</i>	5
<i>Biopsy During Surgery</i>	5
<i>Needle Biopsy</i>	5
<i>Alternate Biopsy</i>	6
Diagnosis Scope/Delays	7
<i>Overview</i>	7
<i>Scope of Evaluation</i>	7
<i>Key Genetic Markers That Enable and Stimulate Tumor Growth</i>	8
<i>Timing/Delays</i>	13
Diagnosis Results	14
<i>Get the facts about your cancer diagnosis</i>	15
Primary Versus Metastatic Tumors	16
<i>Primary Tumors</i>	16
<i>Metastatic Tumors</i>	16
Most Common Primary Brain Tumors	17
<i>Overview of Gliomas</i>	17
<i>Astrocytomas</i>	18
<i>Glioblastomas (GBM)</i>	20
<i>Oligodendrogiomas</i>	21
<i>Medulloblastomas</i>	22
<i>Ependymomas</i>	22
<i>Meningiomas</i>	23
<i>Pediatric Brain Cancers/DMG/DIPG</i>	23
How Long Has The Tumor Been There?	24
Grade Levels (Defined)	25
<i>Classification Summary Table</i>	26
Grade Levels (How Determined)	26
<i>Overview</i>	26
<i>Factors in Grade Determination</i>	27

What are Survival Statistics for Those with Brain Tumors?	28
Coping with a Brain Tumor Diagnosis (Practical)	29
Coping with a Brain Tumor Diagnosis (Emotional)	32
Hope	37
SURVIVOR STORY #1	40
KEY TAKEAWAYS TO REMEMBER	42
<b>CHAPTER 2: TREATMENT FACILITIES</b>	<b>43</b>
Brain Tumor Centers	43
<i>Major Clinic Benefits</i>	43
NCI Designated Cancer Centers	44
Brain Cancer SPORE Locations	45
<i>Travel and Housing Discounts</i>	45
Clinics Offering Alternative Treatments	46
<b>CHAPTER 3: DOCTORS</b>	<b>51</b>
Overview of Your Medical Team	51
Typical Types of Doctors	52
Additional Specialists	53
Need for Expertise	53
Patient-Medical Team Communications	54
Criteria for Selecting a Doctor	55
What questions should I ask my medical team?	55
Second Opinions (Diagnosis/Genetic Study)	56
Second Opinions (Treatment)	57
SURVIVOR STORY #2	59
KEY TAKEAWAYS TO REMEMBER	61
<b>CHAPTER 4: PROTECTING YOURSELF AND FAMILY DURING TREATMENT</b>	<b>63</b>
Health Maintenance Vaccines	63
Fertility Protection	64
Insurance Management	65
<i>Effects of the Affordable Care Act (ACA)</i>	65
<i>Understanding your insurance</i>	66
<i>Medicare coverage</i>	69
<i>Insurance Paperwork Organization</i>	70
Financial Matters	71
<i>The Costs Of Cancer Care</i>	71
<i>Financial Assistance</i>	72
<i>Social Security (When Unable to Work)</i>	75
<i>Benefits for Children of Disabled Parent</i>	76
<i>Crowd Funding</i>	76
Legal Matters	76
<i>Overview</i>	76
<i>Documents to Have in Place</i>	77
SURVIVOR STORY #3	80
CHECKLIST OF TOP TEN FIRST THINGS	82
<b>CHAPTER 5: TREATMENTS OVERVIEW</b>	<b>87</b>
General	87
Patient Navigation Program	88

# Brain Tumor Guide for the Newly Diagnosed

<i>Program Overview</i>	88
<i>How to Access the Program</i>	89
<i>Privacy Protection</i>	89
<i>Service Levels of the Program</i>	90
Treatment Development Challenges	90
<i>NCCN Guidelines for Treatment</i>	91
Standard Of Care (SOC)	93
<i>Considerations Regarding SOC for High Grade Tumors</i>	94
General Treatment Considerations	95
Family/Friends Considerations	96
Work Considerations	96
Financial Considerations	97
Quality of Life Considerations	97
Making Hard Treatment Decisions	98
Long Term Treatment Side Effects	99
SURVIVOR STORY #4	101
KEY TAKEAWAYS TO REMEMBER	105
<b>CHAPTER 6: SURGERY</b>	<b>107</b>
Overview	107
Need for Expertise	108
Selected Definitions	109
When Surgery is Necessary	111
Pre-Surgery	112
<i>Pre-Surgery Health Checks</i>	112
<i>Pre-Surgery Treatments</i>	112
<i>Pre-Surgery Discussions, Prep and Check-In</i>	113
<i>Post-Surgery Preparations</i>	113
<i>Pre-Surgery Anxiety</i>	114
Types of Surgery	115
<i>Emergency Surgery</i>	116
<i>Craniotomy</i>	116
<i>Awake Surgery/Intraoperative Brain Mapping</i>	117
<i>Debulking/Partial Resection</i>	119
<i>LITT Laser Surgery</i>	120
<i>Neuroendoscopy/ Key-Hole Surgery/ Neurosurgical Tubular Retractor System</i>	121
<i>Photodynamic Therapy</i>	122
<i>Shunt Implantation</i>	123
<i>Ventricular Access Device Installation</i>	124
Treatment Implants During Surgery	124
<i>Gliadel Wafers (also called Carmustine Wafers)</i>	124
<i>GammaTiles (also called Surgically Targeted Radiation Therapy or STaRT)</i>	125
Neuroplastic Surgery	126
Length of Brain Tumor Surgery	126
Hospital Stays	126
Risk of Complications	126
Immediate Post Surgery Care	127
Post-Surgery Home Care and Other Topics	128
SURVIVOR STORY #5: BEN WILLIAMS	130
KEY TAKEAWAYS TO REMEMBER	132

<b>CHAPTER 7: RADIATION</b>	<b>133</b>
Overview	133
Radiation Approaches	134
Radiation Technologies	135
<i>Stereotactic Radiosurgery (SRS)</i>	135
<i>EBRT Radiation (Proton, 3D-CRT, IMRT)</i>	139
<i>Brachytherapy</i>	141
Treatment Schedule	143
What to Expect During Treatment	144
<i>Planning Session</i>	145
<i>Radiation Sessions</i>	145
<i>Weekly Checks</i>	146
<i>Post-Radiation MRIs</i>	146
Pre-Radiation Therapy Questions to Ask	146
<i>Questions About Treatment Equipment &amp; Techniques</i>	146
<i>Questions About Side Effects Of Treatment &amp; Management Of Side Effects</i>	147
Side Effects to Expect From Radiation Treatment	148
Post-Radiation Self Care Tips	149
Radiation Limits	150
SURVIVOR STORY #6	151
KEY TAKEAWAYS TO REMEMBER	153
<b>CHAPTER 8: CHEMOTHERAPY</b>	<b>155</b>
Overview	155
Is My Chemo Working?	156
Temozolomide (Temodar or Temodal)	156
<i>Overview of Temodar</i>	156
<i>Dosage and Frequency</i>	157
<i>Length Of Maintenance Phase</i>	158
<i>Side Effects and Toxicity</i>	159
<i>How To Take Temodar (Sample Protocols for Information Only)</i>	160
<i>FDA Data Sheet</i>	162
Lomustine/CCNU/Gleostine	162
Carmustine/BCNU	163
<b>CHAPTER 9: IMMUNOTHERAPY</b>	<b>165</b>
Overview	165
Personalized Vaccines	166
<i>Selected Definitions</i>	166
<i>Overview</i>	167
<i>DCVax-L Vaccine</i>	167
<i>Other Personalized Vaccines</i>	168
Monoclonal Antibodies/Immune Checkpoint Inhibitors	168
<i>PDL/PD-L1 Checkpoint Inhibitors</i>	169
<i>CTLA-4 Inhibitors</i>	169
<i>LAG-3 Inhibitors</i>	169
Chimeric Antigen Receptor T-Cell Therapy/ CAR T Therapy	170
Oncolytic Viral Therapy	171
<i>Polio-Rhinovirus Chimera (PVSRIPO)</i>	171
<i>Adenovirus</i>	172

# Brain Tumor Guide for the Newly Diagnosed

<i>Retroviral Replicating Vectors (RRVs)</i>	172
Vaccines	172
<i>Survivin-Targeting Vaccines</i>	172
SURVIVOR STORY #7	174
KEY TAKEAWAYS TO REMEMBER	176
<b>CHAPTER 10: OPTUNE/TTFIELDS DEVICE</b>	<b>177</b>
Overview	177
How it Works	177
Initial Testing Results	178
Latest Results and Trials	178
Optune Availability and Use	179
<b>CHAPTER 11: BEVACIZUMAB (AVASTIN AND BIOSIMILARS)</b>	<b>181</b>
How it Works	181
<i>Avastin Administration</i>	183
<i>When Best to Use Avastin</i>	183
<i>Side Effects</i>	184
<b>CHAPTER 12: HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)</b>	<b>187</b>
<b>CHAPTER 13: MEDICATIONS FOR SYMPTOM MANAGEMENT</b>	<b>189</b>
Common Medications	191
<i>Medications for Heartburn/Acid Reflux</i>	191
<i>Medications For Pain Relief</i>	192
<i>Medications For Swelling</i>	193
<i>Medications For Reducing Seizures</i>	194
<i>Medications For Reducing Nausea</i>	196
<i>Medications For Improving Mood</i>	198
<i>Medications For Reducing The Formation Of Blood Clots</i>	198
KEY TAKEAWAYS TO REMEMBER	201
<b>CHAPTER 14: CLINICAL TRIALS</b>	<b>203</b>
Importance of Clinical Trials	203
Understanding Clinical Trials	203
Why Should You Consider Participating In A Clinical Trial?	205
When Should You Consider A Clinical Trial?	205
How Do You Assess A Clinical Trial?	206
How Do You Find Clinical Trials?	207
<i>Musella Foundation Resources</i>	207
<i>National Cancer Institute</i>	208
<i>Clinicaltrials.gov</i>	208
<i>DIPG/DMG Trials</i>	208
<i>The Brain Tumor Virtual Trial</i>	208
Treatments, Trials and the Food and Drug Administration	209
<i>FDA Approved Treatments for Brain Tumors</i>	209
<i>Repurposed / Off Label Drugs</i>	212
<i>The Right to Try law and Expanded Access Program</i>	212
Alternative And Complementary Treatments	214
<i>The Mainstream Path Of Treatment Development</i>	214
<i>How Alternative Treatments Are Developed</i>	215

<i>Natural Treatments/ Supplements</i>	218
SURVIVOR STORY #8	220
KEY TAKEAWAYS TO REMEMBER	222
<b>CHAPTER 15: DIET</b>	<b>223</b>
Overview	223
The Inflammation Factor	224
First Fix	224
Proteins	225
<i>Red Meat</i>	226
<i>Fish</i>	226
<i>Eggs</i>	226
<i>Yogurt</i>	226
<i>A Word About Soy</i>	227
<i>Carbohydrates</i>	227
<i>Antioxidants</i>	228
<i>Fats</i>	229
<i>Keto Diet</i>	229
<i>Sugars</i>	230
<i>Hydration</i>	230
<i>Alcohol</i>	230
<i>What To Avoid</i>	231
<i>Strange And Useless</i>	231
<b>CHAPTER 16: IMAGING AND MONITORING</b>	<b>233</b>
Overview	233
CT Scan	233
Magnetic Resonance Imaging (MRI)	234
<i>Overview</i>	234
<i>Frequencies</i>	234
<i>How an MRI Works</i>	234
<i>Contrast Agents</i>	235
<i>Considerations for Use</i>	236
<i>Types of MRIs</i>	237
<i>MRI Interpretation Basics</i>	237
<i>Common Findings</i>	238
<i>Perfusion MRI</i>	239
<i>Magnetic Resonance Spectroscopy (MRS)</i>	239
<i>Pseudo-Progression/ Treatment Effects</i>	240
<i>PET Scan</i>	240
Blood Tests	241
SURVIVOR STORY #9	243
KEY TAKEAWAYS TO REMEMBER	245
<b>CHAPTER 17: SIDE EFFECTS</b>	<b>247</b>
Memory and Cognitive Effects	247
Tumor Side Effects	249
<i>Karnofsky Performance Status</i>	249
<i>ECOG Performance Status Scale</i>	250
<i>Seizures</i>	251

# Brain Tumor Guide for the Newly Diagnosed

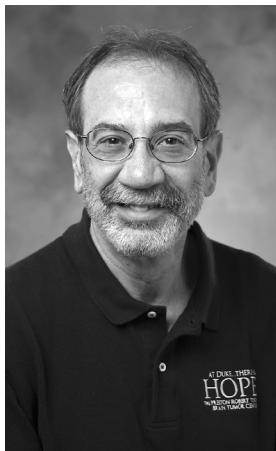
<i>First Aid for Seizures</i>	252
<i>What To Do About Seizures</i>	252
<i>What Causes Seizures</i>	252
<i>Tips For How To Avoid Seizures</i>	253
<i>Hiccoughs/Hiccups</i>	254
Side Effects of Treatment	255
<i>Fatigue</i>	255
<i>Behavioral Changes</i>	256
<i>Hair Loss</i>	257
<i>Effects Of Treatment And Medication On Libido and Sex</i>	260
<i>Birth Control</i>	261
<i>Sex, Surgery, And Brain Tumor Treatment</i>	261
SURVIVOR STORY #10	263
KEY TAKEAWAYS TO REMEMBER	264
<b>CHAPTER 18: CAREGIVING AND SUPPORT GROUPS</b>	<b>265</b>
Caregiving	265
Caregivers Fatigue	266
First Aid for Caregiver's Fatigue	267
Mind, Body, Soul: Faith In Healing And Emotional Wellness	268
<i>Table 1: Organizations that provide support for caregivers</i>	270
Palliative Care	271
Impairments And Strategies For Coping	272
Support Groups	274
<i>“Real-World” Support Groups</i>	274
Online Support Groups	276
<i>Common Sense Cautions about Support Groups</i>	276
SURVIVOR STORY #11: YARON BUTTERFIELD	278
KEY TAKEAWAYS TO REMEMBER	282
<b>CHAPTER 19: LATE STAGE</b>	<b>283</b>
Intubation and Ethical Considerations	283
Hospice	284
<i>Deciding When To Start</i>	284
<i>Practical Tips</i>	285
<i>Emotional Support</i>	285
<i>Pain/Discomfort Control</i>	285
<i>Mobility Management</i>	286
<i>Managing Hospice</i>	287
<i>Miscellaneous Topics</i>	288
<b>CHAPTER 20: PASSING</b>	<b>291</b>
<i>Few Months Before Passing</i>	292
<i>6-8 Weeks Before Passing</i>	293
<i>About A Month Before Passing</i>	294
<i>Days Before Passing</i>	295
<i>Hours Before Passing</i>	296
Where Has My Loved One Gone?	298
Disposal of Unused Medications	298
<i>Disposal of Federally Controlled Substances</i>	298

<i>Disposal of Medications NOT a Federally Controlled Substance</i>	299
Identity Theft of Deceased	300
<i>What To Look For</i>	300
<i>What To Do If You Suspect Identity Theft Of A Deceased Person</i>	300
<i>How to Prevent Identity Theft Of A Deceased Person</i>	300
Brain Donation	302
<b>CHAPTER 21: GRIEVING</b>	<b>303</b>
Overview	303
Anticipatory Grief	304
Grief After the Passing	305
Prolonged Grief Disorder	307
<b>GLOSSARY OF TERMS AND ABBREVIATIONS</b>	<b>309</b>
<b>AL MUSSELLA'S STORY</b>	<b>323</b>
Recent Grants Made By The Musella Foundation	326
<i>2022 (to date) Grant Awards</i>	326
<i>2021 Grant Awards</i>	327
<i>2020 Grant Awards</i>	328
<b>APPENDIX A: MOLECULAR CHARACTERISTICS OF A GBM</b>	<b>331</b>
<i>Subtypes of GBMs</i>	331
<i>Immunosuppressive Environment Differences in GBMs</i>	332
<b>APPENDIX B: BRAIN FUNCTIONS AND DYSFUNCTIONS BY LOCATION</b>	<b>333</b>
Hemispheres Of The Brain	335
Diagnosing Dysfunctions	335
<i>Frontal Lobe Damage</i>	336
<i>Parietal Lobe Damage</i>	337
<i>Temporal Lobe Damage</i>	338
<i>Occipital Lobe Damage</i>	339
<i>Limbic Lobe (Limbic System)</i>	339
<i>Other Locations</i>	340
Rehabilitation	340
<b>APPENDIX C: CAUSES OF BRAIN TUMORS</b>	<b>342</b>
<i>Immune System Escape</i>	342
<i>Triggers that May Lead to Immune System Escape</i>	343
<b>ACKNOWLEDGMENTS</b>	<b>349</b>
<b>SITE MAP OF VIRTUALTRIALS.ORG</b>	<b>350</b>



## Introduction

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Henry S. Friedman, MD

If you have this book in your hands, it is possible that you or someone close to you have just received one of the biggest shocks of your life: the diagnosis of a brain tumor. And as if that shock were not enough, let me add another: you now have to make immediate and important decisions about your brain tumor treatment.

The medical team who made the diagnosis will provide advice and guidance.

But because so many options exist — what doctors to choose, where to be treated, what treatments are available, what clinical trials can be entered — you need to become as informed as much as possible as soon as possible in order to make the best and most rational decisions.

The goal of this ***Brain Tumor Guide for the Newly Diagnosed*** is to provide you, your family, and your friends with a basic primer on the “brain tumor” terrain. This book provides tools for getting organized and delivers information about brain tumors, your medical team, brain tumor treatment, clinical trials, and sources of support. This book can be a vital first resource as you begin the fight against your brain tumor by providing context for the world of brain tumor treatment.

A special feature of this Guidebook is that it is written with explicit reference to the [virtualtrials.org](http://virtualtrials.org) website run and managed by the Musella Foundation for Brain Tumor Research and Information. The [virtualtrials.org](http://virtualtrials.org)

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website was begun in the 1990s to list clinical trials and host online support groups for brain tumor patients. Since then, the website has grown steadily. There were over 150,000 visitors in the past year, from 217 different countries. For many people, the website has become an essential portal to brain tumor information and a place of shared experience. The website lists brain tumor centers, hosts and manages online support groups, keeps an up-to-date catalog of brain tumor clinical trials, and describes current and experimental brain tumor therapies. The website also provides links to, and actually gives, financial assistance.

A final word. Although it might feel otherwise right now, you are not alone. However difficult your next months or years will be as you fight your brain tumor, there are others who have lived through the experience and have a lot to share with you. Please reach out. There is a community that can support you — that wants to support you — beginning with the wonderfully resourceful Musella Foundation.

We wish you peace and health.

Henry S. Friedman, MD  
Preston Robert Tisch Brain Tumor Center  
Duke University Medical Center  
Durham, North Carolina

## **ABOUT THIS EDITION**

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### **Forward**

We are sensitive to the fact that if you are reading this Guidebook, you could be experiencing some of the most stressful and difficult days of your life. We have produced this Guidebook to let you know you are not alone in your challenges. We are here to help you sort through various treatment options and to be a resource for you so that you can further understand your disease. It is our hope that this Guidebook will somehow make the path ahead of you smoother.

### **Applicability**

This Guidebook is intended to primarily address adult malignant brain tumors. Infant and early childhood brain tumors are of different types, and have different characteristics, symptoms, and prognoses. Because of these differences, individuals caring for children with brain tumors are encouraged to access doctors, facilities and resources that specialize in such brain tumors.

For parents whose child has received a diagnosis of DIPG (Diffuse Intrinsic Pontine Glioma) or DMG (Diffuse Midline Glioma), an excellent resource to reach out to for comprehensive information about research, treatment and the latest clinical trials is DIPG.org at this link:

<https://dipg.org>

### **Personalized Help**

If you have any questions or comments, or if you have just been told that you need brain surgery, please call us at the Musella Foundation at 888-295-4740 at any time during normal business hours, US Eastern time zone. You can also submit questions by means of our website. Go to:

<https://virtualtrials.org>

## Glossary

We understand that you are likely to encounter a number of unfamiliar terms and abbreviations. At the back of this Guidebook is a glossary of terms and abbreviations as well as a link to the National Cancer Institute's Dictionary of Cancer Terms.

## Internet links

This twelfth edition of the ***Brain Tumor Guide for the Newly Diagnosed*** contains many up-to-date Internet links to different sections of the virtualtrials.org website of the Musella Foundation and to other websites.

Due care has been taken to ensure that the Internet links are accurate. But as we know, such links are sometimes changed by the organizations that originally posted them. At the virtualtrials.org website of the Musella Foundation, a PDF version of this book is available, which is both searchable and has activated Internet links. There is also a separate webpage on which all the website links in this book are routinely kept up to date. To access that page to see a complete listing of the website links in this book, go to:

<https://virtualtrials.org/booklinks.cfm>.

## Scientific Advances/Studies

This Guidebook is based on the most up-to-date information known at the time. However, the field of medicine is constantly expanding and improving its knowledge about brain tumors such that what may be standard today is considered obsolete later. This is why treatment by a doctor specializing in brain tumors is so important; specialist doctors are on the leading edge and are themselves driving the direction of advanced treatment against brain tumors.

You should also know that one or even a few studies contradicting a current standard practice does not necessarily warrant a change in medical direction. Often, more studies are needed to completely check all factors and verify the data found in the contradictory study. Your best resource for resolving any apparent conflicts in medical thought is your doctor.

## Survivor stories

The survivor stories in this book are real but have been edited for this book format to highlight general themes and the specific interests of book chapters in which they appear. You can find the full stories for these survivors — as well as stories for other survivors — at the virtualtrials.org website of the Musella Foundation: <https://virtualtrials.org/survive.cfm>.

The Musella Foundation is deeply appreciative of all the people who have shared their stories at our website and in this Guidebook. Please share your story, too.

## Informational Only

The information provided in this ***Brain Tumor Guide for the Newly Diagnosed*** (the Guidebook) and at the virtualtrials.org website (the website) reflects the diverse opinions of many different people, most of whom are not physicians or nurses trained to practice oncology, neuro-oncology, or neurosurgery.

Neither this Guidebook nor the website provides any medical advice from any person at the Musella Foundation or associated with the Guidebook or website.

The information in this Guidebook and at the website should, therefore, be considered simply as ideas for further exploration with your personal doctors. You should never ignore professional medical advice in seeking treatment because of something you have read in this Guidebook or on the website. Always consult your doctor for your care.

If you find any errors, disagree with what we say, or have suggestions to improve it, please contact us by email at [musella@virtualtrials.org](mailto:musella@virtualtrials.org) or phone toll free at 888-295-4740.



## What You Need To Know When A Brain Tumor Is Found

### Discovery of a Cranial Mass

It may have been persistent headaches, blurred vision, an episode of confusion, loss of balance, even back pain, a seizure, or some other unusual symptom, all of which might be caused by a brain tumor but could also be caused by something else, that made you concerned enough to visit a doctor or hospital emergency room. Most brain tumors are found after symptoms appear, although some may even be discovered during a routine physical or eye examination.

Upon presentation of the possibility of a tumor the doctor may first order a CT or MRI scan and, if it is detected, return with the news that a "mass" has been found in the brain. The next step is obtaining a tissue sample by surgery or biopsy for histopathologic and molecular analysis by a neuropathologist. Without examination of a tissue sample by a neuropathologist, a brain tumor cannot always be definitely diagnosed.

You may feel a flood of emotions, such as disbelief, fear, and anger at this news because it may sound life-threatening to you. While any mass in the brain is likely to produce the same symptoms, they are not all the same.

There are around 120 different types of brain tumors. All tumors start with defective cells that acquire the ability to rapidly grow in an uncontrolled manner, forming the lumps we call tumors. Just because the doctor may use the term "tumor" does not mean it is cancerous. Tumors in the brain can be non-cancerous (benign) or malignant (cancerous).

Benign tumors most commonly stem from the meninges (layers of tissue that cover the brain), from nerve sheaths (layer surrounding nerves), or from the

pituitary gland. Roughly 70 percent of masses will turn out to be benign (non-cancerous) growths that do not spread and may not even require surgery.

However, even a benign tumor can cause serious symptoms and damage within the brain. Because the brain is enclosed in a rigid container (the skull), there is no space for a tumor mass to grow. As a tumor (even a benign tumor) grows, it builds up intracranial pressure and compresses everything around it, and this process can lead to neurological problems and even death, so getting medical management is important. Fortunately, there has been a lot of progress in the treatment of benign brain tumors.

Meanwhile, although malignant brain tumors may also originate from the same tissues as a benign tumor, malignant tumors more commonly arise from glial cells (comprising neuronal supportive tissues) and are named according to their cell of origin. These tumors typically grow rapidly, invade surrounding healthy brain tissue and are life threatening.

No matter what your tumor turns out to be, please know that you are not alone, even though a brain tumor is considered a rare condition. The chance that a person may develop a cancerous tumor of their brain or spine is less than 1%. And yet, every year around 25,000 adults will be diagnosed in the US with a tumor that originates in the brain and many more will be diagnosed with a cancer that has spread to the brain from another organ such as the lung or breast. In addition, each year about 5,000 parents will hear those two devastating words — brain tumor — about one of their children.

Since by the time most brain tumors are found, they have become well entrenched, researchers are attempting to develop techniques to screen for brain tumors during routine physical exams to find and treat them early before the tumor spreads and may become harder to contain. Clinical tests based on liquid blood or urine biopsies are under study. Researchers in Japan believe that microRNAs (tiny molecules of nucleic acid) found in urine could be a promising biomarker for diagnosing brain tumors.

## Diagnostic Process

When a mass is found by a doctor, the doctor will recommend several tests to determine if it is benign or cancerous, and if cancerous what form of cancer it is. The evaluation of a patient with a suspected brain tumor should include a detailed patient history, a comprehensive neurological examination, and a general

examination of other body systems. Most patients with high-grade malignant gliomas will have no family history of brain tumors or identifiable risk factors for glioma.

An official diagnosis is based principally on the molecular evaluation of the tumor tissue, but the diagnostic procedure typically follows these steps:

## **Neurological Exam**

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The doctor will perform a neurological exam that will consist of items like those listed below. Issues with any of these areas help the doctor understand the scope of effect of the mass.

- Tests for eye movement, pupil reaction, and eye reflexes
- Vision tests and examination of the optic nerve
- Hearing tests
- Tests of involuntary muscle reflexes
- Balance and coordination tests
- Tests for sense of touch using sharp and blunt objects
- Tests of facial muscles, tongue movements, and gag reflexes
- Mental status examination and memory tests

When there is a growth on the brain, symptoms can arise from excessive fluid (edema) or from increased intracranial pressure within the skull. Specific symptoms may also arise from the location of the growth. The most common presenting symptoms of high-grade gliomas include:

- Headache (50% to 60% of patients)
- Seizures (20% to 50% of patients)
- Focal neurologic deficits such as memory loss, motor weakness, aphasia (difficulty speaking or understanding speech), visual symptoms, and cognitive and personality changes (10% to 40%)

Focal neurologic deficits are more common with high-grade than with low grade gliomas. In contrast, seizures are less common with high-grade than with low-grade gliomas.

## **Imaging**

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Imaging studies help to identify and localize brain masses and offer clues as to

what type of mass is present. They are also useful in diagnosing certain complications of brain masses, such as hydrocephalus and hemorrhage. A brain magnetic resonance imaging (MRI) scan with contrast is often the only study required prior to surgery. Patients who should not have an MRI should undergo head computed tomography (CT) with contrast.

The doctor may ask that your whole body be scanned to check if there is cancer elsewhere in the body. A dye called gadolinium may be injected during the MRI, which improves the visibility of inflammation, the tumor and blood vessels.

The urgency of a neurosurgical evaluation for a suspected brain tumor depends on the clinical stability of the patient, symptom severity, and tumor size and location. Patients with large symptomatic tumors, including those with signs and symptoms of elevated intracranial pressure, require emergent evaluation and neurosurgical attention.

Patients with smaller tumors or with minimal symptoms can often be safely and effectively evaluated in the outpatient setting.

For more detailed information about imaging please see the Section entitled "Imaging and Monitoring".

### **Molecular Evaluation**

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The diagnosis of a brain tumor is based principally on the molecular evaluation of tumor tissue. The molecular evaluation and classification of brain tumor tissue is the cornerstone upon which the medical diagnosis and treatment rests. In this evaluation, the pathologist's goal is to determine the tumor's growth pattern (circumscribed versus infiltrative, solid versus cystic), enhancement pattern (non-enhancing versus enhancing), and the presence or absence of edema, necrosis, and calcification.

The tumor tissue required for the molecular evaluation is made available currently to the pathologist by two methods: biopsy or surgery. The biopsy technique is described below. For more detailed information about surgery please see the Section entitled "Surgery".

## Biopsy

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### Overview

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Biopsies are performed by highly specialized doctors called neurosurgeons.

Prior to the biopsy, your neurosurgeon is likely to request that you cease the use of all blood thinners including aspirin, ibuprofen, as well as all herbs and supplements that thin the blood.

### Biopsy During Surgery

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When the tumor is considered operable based on the neurosurgeon's review of the MRI image, the surgery to remove the tumor becomes the biopsy. Before removing the tumor, the neurosurgeon will usually obtain a frozen-section biopsy to provide a working diagnosis. This tissue sample is rapidly frozen and stained so that microscopic examination may be completed while the patient is still under anesthesia. Following this, the neurosurgeon will continue to remove as much of the tumor as possible.

After surgery, the entire resected tumor is sent to the neuropathologist for final examination, during which tissue samples are permanently preserved in paraffin (a petroleum-based wax) or frozen for future use.

A craniotomy and removal of your tumor typically takes 4 to 6 hours. For more information, please see the section in this Guidebook entitled "Surgery."

### Needle Biopsy

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Where the tumor is considered inoperable by the neurosurgeon or there is a location or condition that makes surgery not feasible, the neurosurgeon will recommend a needle biopsy. A needle biopsy may also be referred to as a stereotactic biopsy or guided needle biopsy, depending on the specific technique planned.

It should be noted that pathologists tend to get less data about the tumor from tissue obtained by a needle biopsy than from the greater quantity of tumor tissue taken during a surgery.

In a needle biopsy, your neurosurgeon drills a small hole into the skull and

inserts a thin hollow needle into the tumor. A tiny amount of tissue is extracted through the needle. The incision is very small – only a few millimeters long.

To ensure stability and accuracy of the procedure, your head may be secured with a frame. In a frameless biopsy, the neurosurgeon will use a neuronavigational system like a CT or MRI to identify the exact location of the tumor within the brain.

The CT or MRI images and coordinates are used to guide a needle to the tumor through a small opening in the skull. The neurosurgeon will extract several samples from various locations within the tumor for ensuring maximum diagnostic accuracy.

Many patients can tolerate this form of biopsy while only under light sedation with local anesthesia as opposed to general anesthesia.

A needle biopsy typically takes 2 to 3 hours.

The greatest risk of a biopsy is bleeding in the brain, and about 5% of cases may have some bleeding. Bleeding can cause symptoms ranging from mild headache to serious stroke-like effects. To manage any risks, most neurosurgeons will ask their patients to remain overnight following a biopsy, but a few individuals may be asked to stay for a couple of days. The majority of people are discharged after the one-night stay.

After the biopsy, you may be given a steroid (e.g., dexamethasone) to help minimize swelling caused by the biopsy and an antibiotic or antimicrobial to help guard against post-operative infection.

## **Alternate Biopsy**

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If a biopsy is considered too dangerous (e.g., the individual is fragile/has underlying health concerns, or could be susceptible to a brain bleed or stroke due to the biopsy) then the doctors may turn to evaluation of the cerebral spinal fluid (CSF). This would be done by a lumbar puncture (also called a spinal tap). The theory is that elements of the tumor may be found in the CSF and aide doctors in determining what the mass is. Note that this evaluation would not necessarily provide the level of biomarker detail for the mass that a biopsy would.

# Diagnosis Scope/Delays

## Overview

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The molecular evaluation is a complex process and can take many days, even a few weeks to complete. The World Health Organization (WHO) classification of tumors is the standard and universally used diagnostic system. The basis of the information used in this Guidebook is the fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS), which was published in 2021.

## Scope of Evaluation

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The most recent WHO guidelines require histology with molecular testing to create a “layered” integrated diagnosis. The three layers that are combined to make an integrated diagnosis are:

**Histologic type:** This means the type of cell from which the cancer most likely originated. Cell type is normally ascertained by microscopy of stained biopsy tissue sections, immunohistochemistry analysis, and examination of the inner cell structure. A section below entitled Types of Primary Tumors provides further details.

**Histologic grade:** This means a description of a tumor based on how abnormal the cells and tissue look under a microscope and how quickly the cells are likely to grow and spread. The histologic grade is a measure of malignancy. Low-grade cancer cells look more like normal cells and tend to grow and spread more slowly than high-grade cancer cells. The histologic grading system is used for planning treatment. A section below on Grade Levels provides further details.

**Molecular characterization:** Cancer cells typically contain some changes to the DNA of the cells that helps them grow out of control. These changes, or more technically “genetic alterations”, hijack the cell’s regulation of growth and division. These alterations may involve making multiple copies of a gene (so called “amplification”) or fusing different unrelated genes together (called “translocations” or “fusions”) or changing the sequence of a gene (called “mutation”). When proteins are then produced based on this altered genetic blueprint, the control of the cell lifecycle is disturbed, and the cell can learn survival behaviors that lead to cancer.

Genetic alterations range in size; they can affect anywhere from a single DNA building block to a large segment of a chromosome that includes multiple genes. Using a normal phrase as a baseline the examples below give an idea of the various possible alterations to DNA coding:

THE BOY PLAYED WITH THE DOG – normal gene coding

THC BOY PLAYED WITH THE DOG - missense

THE PBYL OAY DWE ETH OGD TI – mutation

THE YO ADP TH HEW GT – deletion/loss

Plus, there can be an amplification of a gene. Gene amplification is an increase in the number of copies of a gene without a proportional increase in other genes. This can result from duplication of a region of DNA that contains a gene through errors in DNA replication and repair machinery as well as through fortuitous capture by selfish genetic elements.

Part of the molecular characterization will be the identification of any epigenetic alteration. These are changes in how your behaviors and environment can cause changes that affect the way your genes work. Unlike the genetic alterations described above, epigenetic changes are reversible and do not physically change your DNA sequence, but they can change how your body reads a DNA sequence. For example, a person's diet and exposure to pollutants, can impact their epigenetics.

For purposes of performing a molecular evaluation, the pathologist will seek to identify any epigenetic signatures (e.g., DNA methylation, mRNA, and microRNA expression, etc.) which may help with disease classification (and may later provide potential targets for therapy.)

### **Key Genetic Markers That Enable and Stimulate Tumor Growth**

Different tumors will have different molecular and genetic profiles. There are two major classes of genes critical for the development and diagnosis of brain tumors:

Tumor Suppressor Genes: these are genes that are supposed to inhibit cell proliferation and tumor development, but go awry opening the path to tumor development, and

Oncogenes: these genes produce the proteins that stimulate tumor activ-

ties important for invasion, the growth of new blood vessels to support the growth and nourishment of the tumor (a process called "neoangiogenesis"), the ability of the tumor to escape the functions of the immune system, and other characteristics.

Generic alterations in tumor cells that include mutations in certain genes, deletions of chromosomal regions, and epigenetic changes to DNA structure can identify the status of these tumor suppressor genes and the oncogenes, which drive the characteristics of the tumor. By testing for these genetic alterations in your brain tumor, your medical team can generate a genetic and epigenetic profile of your tumor to achieve a "layered" integrated diagnosis that can guide treatment choices.

To this end, these are the certain, basic genetic alterations that are routinely tested for an integrated diagnosis:

## **Mutations in IDH-1 and IDH-2**

Mutations in the isocitrate dehydrogenase 1 and 2 (IDH-1 and IDH-2) genes cause the production of flawed enzymes that interfere with cell metabolism and promote the growth of tumors. Studies have shown that IDH-1 mutations are present in approximately 85-90% of secondary GBMs (i.e., glioblastomas arising from a progression of a lower Grade astrocytoma) but are rarely present in primary GBMs. Despite being a cause of tumors, mutations in IDH-1 and IDH-2 are associated with longer survival.

Although certain tumors contain IDH1/2 mutations, in astrocytic gliomas, IDH mutations are typically associated with mutations in TP53 and ATRX genes. In fact, the absence of the ATRX protein and the abundance of p53 protein are required for the diagnosis of an astrocytoma.

## **Modification of MGMT Gene and Methylation**

The status of the MGMT gene predicts, at least to some degree, the sensitivity of the tumor to treatment with some of the standard brain cancer chemotherapies. Knowing the MGMT status provides the doctor with some insights as to best treatments and course of the disease. Here's how that happens.

An important brain cancer treatment drug is temozolomide (often called Temodar), which is a standard chemo for high-grade malignant gliomas. Temodar works by stopping the replication of a cancer cell's DNA. If the cancer cells can-

not make more DNA, it cannot split into 2 new cells and, therefore, the cancer cannot grow. What the chemo is actually doing is putting alkyl (referred to as a methyl group by biochemists) on the O6 atoms of guanine on the DNA strand. This change severely damages the DNA of the cancer cells and if this change is not repaired, the cancer cells will die, which is what we want.

However, a protein (enzyme) produced by the MGMT gene is designed to protect the DNA of cells against damage from things like ionizing radiation, but it also protects cells from damage done by alkylating chemos. That repair enzyme is called O6-methylguanine-DNA methyltransferase or just "MGMT" for short. In short, the DNA repair enzyme produced by the MGMT gene can cause resistance to alkylating chemos like Temodar. This MGMT repair enzyme does its repair work by transferring the methyl group it finds at the O6 site of guanine to its cysteine residues. This avoids the desired genetic mutation of the cancer cell and its inevitable death. Clearly, this repair enzyme un-does at least some of the beneficial effects of Temodar or another alkylating chemo.

In some people with high-grade malignant gliomas, there are decreased levels of this MGMT repair enzyme because the DNA elements that promote the production of the MGMT repair enzyme have been changed due to an epigenetic modification of the MGMT gene. Many studies have shown that the loss of MGMT expression and decrease in repair enzyme production is not due to gene deletion, mutation, rearrangement, or unstable RNA, but rather to an epigenetic modification.

An epigenetic modification can be caused by exposure to environmental mutagens, such as UV radiation and N-nitroso compounds (e.g., foods containing sodium nitrites like processed meats and imported beers); these exposures are thought to account for 80% of the human cancer incidence.

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For more information about epigenetic modifications, please go to this CDC site:

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<https://www.cdc.gov/genomics/disease/epigenetics.htm>

The epigenetic modification to the MGMT gene impairs its production of repair enzyme. That is a good thing in the context of gliomas being treated with Temodar. When the tumor is said to be methylated, that means the amount of the DNA repair enzyme normally produced by the MGMT gene is reduced. Less MGMT repair enzyme = less interference with the cancer cell killing effects of

Temodar or other alkylating chemo.

It then can be understood why tumors said to be unmethylated were twice as likely to progress during radiation as those with a mutated MGMT gene. Plus, the median time interval between resection and tumor progression of unmethylated tumors was also nearly half that of methylated tumors. IN other words, unmethylated MGMT tumors generally tend to progress sooner following tumor resection than methylated MGMT tumors.

Even knowing all this, the routine use of Temodar in patients with an unmethylated GBM is still justified. Randomized studies show a modest improvement and a few patients with unmethylated tumors do experience prolonged survival if treated with Temodar. Since doctors and researchers cannot yet identify which patients might do unexpectedly well, Temodar is being prescribed to most patients with unmethylated tumors.

The presence of MGMT promoter methylation, which can be determined by molecular testing, is thus one of the most important predictors of response to treatment with alkylating agents in those over the age of 65 and is used to guide treatment choices. It is, however, prognostic in all ages. Because the MGMT methylation status varies within each glioma, reliance on this factor is not advisable.

## **Codeletion of 1p/19q Chromosomes**

During cell division, pieces from two different chromosomes sometimes switch places with each other. In some cases, when this rare event occurs, the chromosome pieces are jointly deleted. Codeletion of 1p/19q is an example of this type of chromosomal abnormality; part of chromosome 1 is switched with chromosome 19, and then both parts are removed.

In the 2021 WHO classification, codeletion of 1p/19q serves as a diagnostic biomarker for oligodendrogliomas. Tumors that have codeleted 1p/19q are more sensitive to chemo than those that lack the codeletion, and the presence of codeleted 1p/19q is associated with longer survival times.

## **Mutations of CDKN2A, CDKN2B**

Among the mutations known to increase the risk of glioma development in adults are cyclin-dependent kinase inhibitor 2A and B (CDKN2A, CDKN2B). CDKN2A loss is considered the most common mechanism for cell cycle dysreg-

ulation. Such a loss occurs in slightly more than 50% of GBM cases. Variants to three tumor suppressor genes close to both the CDKN2A and CDKN2B genes (on the chromosomal locus 9p21) are known to increase the risk for glioma, basal cell carcinoma, and melanoma. Untreated, a cancer exhibiting this biomarker can ultimately accelerate in growth.

## Mutations of EGFR

Epidermal growth factor (EGF) is a protein that stimulates cell growth by binding to a receptor — conveniently called the epidermal growth factor receptor (EGFR). Many different types of cancer produce abnormally high levels of EGFRs, and when these EGFRs are stimulated by EGF proteins, they cause the cancer cells to divide and grow excessively. EGFR has been identified as a known oncogene for some forms of brain tumor. In an estimated 57% of GBMs, the EGFR gene is amplified. This means that there is an abnormally high number of copies of the EGFR gene in a cell, a situation that can lead to overproduction of the EGFR protein, signaling the tumor to grow.

High levels of EGFR are not found in normal cells, so controlling EGFR has been identified as a path to slowing down tumor growth. Because stopping the production of excessive amounts of EGFR or preventing EGF from binding to excessive amounts of EGFR could restrain the growth of tumor cells, EGFR has long been a target of several potential therapies for brain cancer.

There is a variant called EGFR Variant III (EGFRvIII) for which there are targeted treatments. EGFRvIII positive tumor cells are known to be resistant to cell death, have a faster growth rate and tend to be more invasive. About 30% of glioblastomas contain this variant, so researchers are targeting this factor in their treatment development efforts.

## Mutations of TERT

TERT stands for telomerase reverse transcriptase. It is a gene that increases telomerase expression. The prevalence of TERT promoter mutations has been found in about 70-80% in GBMs of adults. The presence of TERT helps to confirm the fact that the tumor is primary (i.e., originating in the brain.) TERT mutations at 124C and 146C are considered “hot spots” for mutations and have been known to give rise to other cancers (i.e., ovarian, thyroid, melanoma). It is currently thought that the presence of TERT is not an early event in the development of a brain tumor. Primary GBMs without TERT mutations appear to behave more like high-grade astrocytomas, which generally lack TERT muta-

tions. This possibility is supported by the observation that those primary GBM patients without TERT mutations had a longer survival, on average, than other primary GBM patients.

## Mutations of p53

A tumor suppressor gene frequently identified in the development of astrocytomas is p53 (sometimes referred to as TP53), located on chromosome 17p. The p53 protein has been found to influence multiple functions including progression through the cell cycle, DNA repair after damage, gene stability, and the tendency for a cell to undergo cell death (apoptosis) following treatment. One of this gene's major functions is to prevent abnormal cells with damaged DNA from reproducing. It does so by releasing a protein referred to as p53. When the p53 gene is mutated, the p53 protein is inactive. Since mutant p53 cannot bind to the DNA in an effective way, cells with damaged DNA are allowed to proliferate without check and form tumors. p53 mutations have been reported in approximately 40% of astrocytic tumors of all grades.

A certain, rare variant of TP53 has been implicated in the development of Li-Fraumeni syndrome. Li-Fraumeni predisposes carriers to a variety of cancers, including brain cancer, throughout their lifetime. More than half of all families with Li-Fraumeni syndrome have inherited mutations in the TP53 gene.

## H3K27 mutations

There are mutations in histones — specialized proteins around which the DNA in our cells are wound — that can contribute to the pathogenesis of cancer and other genetic diseases. These mutations are found in most of the diffuse gliomas arising in midline brain structures, such as the thalamus, brainstem, and spinal cord. Tumors in these locations occur primarily in children but also sometimes in adults. These tumors have a Grade 4 classification. If your pathology report indicates that you have this mutation, please contact the Musella Foundation to learn about experimental therapies targeted to this mutation.

## Timing/Delays

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Depending on the checks to be done on the harvested tissue, the results of the evaluation (and therefore the diagnosis) may take anywhere from a few days to even a few weeks to be complete. The uncertainty and anxiety waiting for results can be stressful, so it is helpful to discuss with the doctor some notion of when

you might expect to have a diagnosis.

Some reasons for delays include but are not limited to the need to use special stains to differentiate cellular components which may have to be freshly acquired, the need for larger samples than were initially provided to the lab (these will be obtained from the stored biopsy or surgical sample), or advanced tests like flow cytometry and electron microscopy. In the case of rare or unusual findings, the pathologist may seek a second opinion before entering their conclusion in the record to ensure maximum accuracy of the conclusions.

Many of the premier brain tumor hospitals will convene, either actually or virtually, a "tumor board". A tumor board consists of several doctors of differing disciplines who will weigh all the evidence (e.g., pathology findings, MRI/CT Scan images and medical history) to agree on the diagnosis and proposed treatment.

The rate for accurately determining the diagnosis of a brain tumor is at least 95%. Occasionally, there can be uncertainties. In those cases, it is highly advisable to request a second opinion from a highly rated brain cancer clinic. (To locate highly rated clinics please see the Section below entitled "Treatment Facilities".)

## Diagnosis Results

The diagnosis will provide the name of the type of tumor (out of the 130+) available and the grade level.

Even though a brain tumor may have the same name as another, each brain tumor is unique with a highly variable molecular design and its own equally unique immune system environment. Understanding both the molecular composition of the tumor and the various immune infiltrates (or lack of them), are pivotal in treatment selection.

Owing to the diversity among tumors, being overly distracted by what worked for the uncle of a friend, or what is written in some long-term survivor's blog may turn out to be a disservice to you because it is highly unlikely that the two tumors are an exact match in their molecular/DNA structure and the immunosuppressive environments. Then when one considers other factors like age, tumor location and operability, gender, health, etc., the differences between one tumor and another grows even more.

Based on these various studies, the best strategy appears to be to ensure the characteristics of your unique tumor is defined with the most appropriate level of detail and clarity as recommended by the attending doctor, and that this definition is the basis for treatment selection.

Your unique tumor will be described to an extent in a pathology report, which formed the basis of your diagnosis. If you don't have a copy, you may wish to ask for it for your files and future reference.

For more information about the genetic structure of GBMs please see Appendix A entitled "Molecular Characteristics of GBMs" at the back of this Guidebook.

## Get the facts about your cancer diagnosis

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Try to obtain as much basic, useful information about your cancer diagnosis as you need to make decisions about your care. Write down your questions and concerns beforehand and bring them with you. Consider asking:

- What kind of cancer do I have?
- Where is the cancer?
- Has it spread?
- Can my cancer be treated?
- What is the chance that my cancer can be cured?
- What other tests or procedures do I need?
- What are my treatment options?
- How will the treatment benefit me?
- What can I expect during treatment?
- What are the side effects of the treatment?
- When should I call the doctor?
- What can I do to prevent my cancer from recurring?
- How likely are my children or other family members to get cancer?

Consider bringing a family member or friend with you to your first few doctor appointments to help you remember what you hear.

You might also want to consider how much you want to know about your cancer. Some people want all the facts and details, so they can be very involved in the decision-making process. Others prefer to learn the basics and leave details and decisions to your doctor. Think about which approach works best for you.

Let your health care team or caregiver know what you'd prefer.

## Primary Versus Metastatic Tumors

If conclusive, the diagnosis would identify if the tumor originated in the brain or elsewhere in the body. A tumor originating in the brain is considered primary; those originating elsewhere are identified as metastatic.

### **Primary Tumors**

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Primary brain tumors start from brain cells, nerves, glands (like the pituitary) or from the membranes that surround the brain (called the meninges). Not all primary brain tumors are cancerous.

93% of primary brain tumors are diagnosed in people over 20 years old; people over 85 have the highest incidence. The average age at diagnosis is 57.

Medical professionals widely believe that primary, malignant brain tumors do not metastasize outside the central nervous system. However, there are exceptions in approximately 0.5% of cases.

### **Metastatic Tumors**

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A metastatic brain tumor is a tumor that develops from cancer cells originating elsewhere in the body that have spread to the brain. Metastatic brain tumors are named for the location in which they originate and are all considered cancerous. Approximately 20-40% of people with cancer will see their cancer spread to the brain, often depending on the originating cancer. For instance, close to 40% of people with lung cancer will develop metastatic brain tumors.

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The likelihood that a brain lesion is metastatic should be assessed before proceeding to biopsy or surgery.  
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Metastatic brain tumors are four times more common than primary brain tumors in adults. Although metastatic brain tumors usually occur in the context of known systemic cancer, they can also occur as the first sign of a systemic cancer. If any aspect of the clinical or neurodiagnostic evaluation suggests that a

brain tumor is a metastatic rather than a primary lesion, systemic evaluation, including CT scan of the chest, abdomen, and pelvis or a PET scan of your entire body should be performed.

Treatment for metastatic brain tumors is dependent upon the treatment of the originating, primary cancer. As a result, an individual with a metastatic brain tumor will need the support of a closely coordinated team of doctors to include the oncologist for the originating, primary cancer, and a neuro-oncologist for guidance in treating the brain tumor.

Recently, trying to understand why a tumor in one part of the body will transition to another, researchers have learned that cancers are able to hijack a metabolic pathway that breaks down fats and proteins, which boosts the levels of a byproduct called methylmalonic acid. We have also learned that as people age, their bodies produce more methylmalonic acid. This methylmalonic acid drives cancer progression and invasion in another location. In that process, the cancer must suppress the activity of a key enzyme and when that suppression happens, the cancer becomes more aggressive and invasive.

Metastasis is responsible for the majority of cancer-related mortality, so researchers are working on finding ways to predict who might have the tendency to produce metastatic lesions and on developing new therapeutics to discourage the metastasis in the first place.

Additionally, more sophisticated diagnostic tools are available today, in addition to innovative surgical and radiation approaches, which have helped survival rates expand in the last years. These improvements also provide for better quality of life for patients following diagnosis.

## Most Common Primary Brain Tumors

### **Overview of Gliomas**

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In this Guidebook, the focus is on gliomas, a category of CNS tumors that arise from glial cells. Glial cells are the “support cells” of the CNS, helping neurons and nerve cells do their jobs. Glial cells are subdivided into astrocytes, ependymal cells and oligodendroglial cells (or oligos). Primary tumors are identified by the predominance of the type of cells found in the tumor tissue.

Gliomas are the most common type of primary brain tumors, accounting for 78 percent of malignant brain tumors. These are serious tumors with the capability of producing a combination of problems for people ranging from memory loss to seizures resulting from the compression of brain tissue as the growing tumor competes for space and from tumor infiltration into the surrounding healthy brain tissue, so they require expert medical intervention.

A landmark publication in The New England Journal of Medicine (NEJM) distinguished three genetic subsets of gliomas: (1) IDH wild-type gliomas, the most common and lethal type; (2) IDH mutant astrocytomas, which have longer survival; and (3) oligodendrogiomas, with both IDH mutations and 1p/19q co-deletions, which have the longest survival.

A description of some of the most common glial tumors follow below.

### **Astrocytomas**

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Astrocytomas are the most common primary tumor. Most occur in men and women older than 45. About 50% of primary brain tumors are astrocytomas. This type of tumor originates from astrocytes, which are star-shaped glial cells found in the supporting tissue of the brain. Astrocytes can be readily identified histologically since they have a filament called a glial fibrillary acidic protein (GFAP). Astrocytes are very busy cells in the brain. They are involved with the biochemical support of neurons and other brain cells, support of certain cells which form the blood-brain barrier, a major role in the repair and scarring process of the brain and spinal cord following mechanical / inflammatory injuries and providing a "guidance" for growing neurons / axons during the development of the brain.

Astrocytomas may occur in many parts of the brain but are most commonly found in the cerebrum. People of all ages can develop astrocytomas, but they are more prevalent in adults, particularly middle-aged men. Astrocytomas in the base of the brain are more prevalent in children or younger people and account for most children's brain tumors. In children, most of these tumors are considered low-grade, while in adults, most are high-grade.

Based on their histological features, astrocytomas are classified based on their structural abnormalities and the speed of their growth. Commonly occurring astrocytomas include:

WHO Grades 1 through 4: Pineal astrocytoma (a tumor that forms in

the pineal gland). This form can have any Grade, depending on its aggressiveness.

WHO Grades 1 and 2 (Low grade): These occur more frequently in children or young adults and include:

- Pilocytic astrocytoma (Grade 1): are slow-growing, benign brain or spine tumors that often take the form of fluid-filled sacs called cysts, although they can also take on solid forms. They generally occur in the lower half of the brain including the cerebellum, brain stem, and around the pituitary gland or hypothalamus. They tend to not infiltrate surrounding tissues; however, they can increase pressure on brain tissue and block the flow of cerebrospinal fluid (CSF). This may cause symptoms of headaches, personality changes, disequilibrium, and nausea.
- Diffuse or Fibrillary astrocytoma (Grade 2): this is the most common form of low-grade astrocytoma. It occurs in the brain stem. Diffuse astrocytoma most often occurs in young male adults. Although these tumors grow slowly and have low cell-division activity, they can infiltrate into neighboring brain structures. In 40% of cases, this type of tumor causes seizures. It may also cause headaches, hydrocephalus, and personality changes.

WHO Grade 3 and 4 (High grade): These occur more frequently in adults and include:

- Astrocytoma (Grade 3): This is a rare form of malignant brain tumor. They often occur in the cerebral hemispheres but can arise anywhere in the central nervous system, particularly the frontal and temporal lobes. This type of tumor responds better to treatment than GBM, however, response truly depends on the tumor cell structure.
- Astrocytoma (Grade 4): is a fast-growing tumor. It is different from a Glioblastoma in that the Astrocytoma Grade 4 has a mutated IDH-1 gene, whereas a Glioblastoma does not. It is also differentiated from a Grade 3 Astrocytoma owing to its greater aggressiveness in growth and invasiveness due to its CDKN2A/B deletions.

## Glioblastomas (GBM)

Glioblastomas (GBM) are the most common, fastest growing and the most invasive type of brain tumor in adults. GBMs account for nearly 50 percent of all primary brain tumor cases. In a few rare cases, a secondary GBM may progress from a lower grade astrocytoma. GBMs can occur anywhere in the brain, but most typically forms in the frontal or temporal lobes.

Like Astrocytomas, GBMs develop from astrocytic cells, but eventually may be composed of several different kinds of cells, also including oligodendrocytes.

Slightly more men develop GBMs than women, and the risk of occurrence increases with age. Most people are diagnosed between the ages of 50 and 70, but they can occur at any age. Doctors diagnose about 15,000 glioblastoma cases in the U.S. each year.

These tumors are:

- aggressive, fast growing.
- diffuse; GBMs spread into nearby regions of the brain erratically and sometimes to the opposite side of the brain. They can be surgical challenges.
- likely to return, even if totally removed and intensively treated.
- have a distinctive appearance that helps neuropathologists distinguish them from a lesser Grade tumor.

Prior to the 2021 WHO classification update, Grade 4 astrocytomas (not in the pineal gland) were all classified as a Grade 4 Glioblastoma. With the 2021 classification, tumors classed as Grade 4 Glioblastomas are limited to tumors found to be negative for mutations in the IDH-1 gene, owing to the substantial differences in the course of the disease and treatment challenges. As a result of this change, aggressive astrocytomas with a mutated (positive) IDH-1 gene are no longer classified as Grade 4 Glioblastomas, but rather are classified as Grade 4 astrocytomas.

Based on the 2021 WHO classification, a typical GBM has alterations in EGFR, no mutations in the IDH-1 gene, and alterations (even losses) in chromosomes 7p and 10q or the TERT promoter.

GBMs can be resistant to treatment. One of the reasons for that resistance is that a GBM is a very complex cancer. As its full name - Glioblastoma Multiforme-suggests, this tumor is multiforme in its gross structure; it has not just tumor tissue, but necrosis (clumps of dead cells) and areas of hemorrhage. The tumor is multiforme in its microscopic structure; it has regions of elongated and compressed necrosis and tumor cells, plus cell nuclei of substantial variation in size and shape. The tumor is multiforme genetically with a variety of genetic alterations, deletions, and amplifications.

One of the challenges in treating GBMs is that a GBM is not a homogeneous tumor. A GBM has been described as a cluster of different cancers. Cells within the same tumor will display distinct characteristics that affect their growth rate, survival, migration, and therapy-response.

These cells have the ability to change depending on factors within a tumor and outside of the tumor. Analysis shows that GBM cells exist in at least four different cellular states and can change between them. As a result, treating a GBM is like trying to shoot a moving target. One treatment that might shrink and contain the GBM for a few months, killing susceptible cells, may leave surviving cells that are resistant to that treatment.

At the present time, GBMs are classified into four different subtypes, based on their most common genetic characteristics: classical, neural, proneural, and mesenchymal. For more information about GBMs please see Appendix A entitled "Molecular Characteristics of a GBM."

The challenges presented by GBM are motivating researchers to find new and sophisticated ways of treating this cancer. One promising new treatment approach for cancer is microRNAs (miRNAs). One miRNA can target multiple miRNA transcripts, which allows the targeting of multiple cancer-producing pathways using a single drug. This will not just enhance the effectiveness against the whole GBM but will reduce the chances the GBM regrows.

## **Oligodendrogiomas**

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Oligodendrogiomas account for less than 10% of all primary brain tumors. This type of tumor also accounts for 4% of primary brain tumors in children. They originate from oligodendrocytes, which are cells with a cross-section that look like trees with only a few branches. Oligodendrocytes are the myelinating cells of the central nervous system (CNS), so they are quite vulnerable. (Myelination is the insulation wrapping found around the axon, which is a long and spindly

part of nerve cells.)

Oligodendrogliomas can be low or high grade:

- WHO Grade 2 (low grade): are slow-growing tumors with relatively better prognosis than the same grade astrocytomas (pilocytic and diffuse astrocytoma) and roughly the same symptoms as low-grade astrocytoma.
- WHO Grade 3:(high grade): as referred to as oligodendrogliomas. These are rapid growing and often consist of a combination of cancerous astrocytes and oligodendrocytes.

Oligodendrogliomas can occur anywhere within the CNS but are primarily found in the frontal and temporal lobes of the cerebral hemispheres.

## **Medulloblastomas**

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A medulloblastoma is the most common pediatric brain cancer, accounting for 10% to 15% of pediatric central nervous system tumors. They are high-grade (Grade 3 or 4) tumors and are thought to originate in embryonic tissue. Owing to that, they are likely to be discovered in the first five (5) years of life and be exceptionally rare in adults. More boys have this type of tumor than girls.

Almost all medulloblastomas arise in the cerebellum at the back and base of the brain. They are typically treated with surgery, chemo, and radiation.

## **Ependymomas**

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Ependymomas, which originate from a transformation of ependymal cells, which line the ventricular system of the brain and have numerous small hair-like structures called cilia. These cells secrete cerebrospinal fluid that fills the ventricles in the brain and beat their little cilia to keep that fluid properly circulating.

Ependymomas account for two to three percent of all brain tumors. Most are well-defined, but some are not. There are three grades of ependymoma:

Low grade Ependymoma (Grade 1): The cells reproduce slowly. There are two subtypes:

## One: What You Need To Know When A Brain Tumor Is Found

- Subependymoma: a rare form that develops in glial cells in the spinal cord and brain.
- Myxopapillary ependymoma: typically develops in the lower spine.

Low grade Ependymoma (Grade 2): These ependymomas can occur in the brain or the spine.

High grade Ependymoma (Grade 3): Known as anaplastic ependymomas, these are malignant tumors that mostly occur in the brain (versus the spine).

## **Meningiomas**

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Meningiomas are not gliomas but are among the most common brain tumor in adults, accounting for 20-30% of all primary brain and spinal cord tumors. A meningioma develops on the brain's meninges (the tissue around the outer part of the brain and spinal cord) and is a tumor of leptomeningeal origin.

The meninges consist of the outer three layers (dura mater, arachnoid mater, and pia mater) of a thin tissue designed to protect the brain and is found just under the skull. Meningiomas commonly form in areas populated with heavy amounts of arachnoid villi (located in the second layer which covers the brain).

Meningiomas are almost invariably benign, but some can be cancerous. Elderly patients are more frequently affected. It is believed that meningiomas might be caused by a genetic abnormality or chromosomal defects (e.g., partially or completely missing chromosome 22), however, other studies show that meningiomas reacts to hormonal changes or trauma. Ultimately, we are not sure what causes these tumors. However, those diagnosed with Neurofibromatosis Type 2 may be affected by multiple meningiomas and bilateral vestibular schwannomas. Neurofibromatosis Type 2 has been proven to be hereditary.

The risk of developing a meningioma increases with age, and they occur about twice as often in women.

## **Pediatric Brain Cancers/DMG/DIPG**

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Brain cancer is the second-most common type of cancer in children, surpassed only by leukemia and is the leading cause of deaths among children.

Diffuse Midline Glioma (DMG) is a serious pediatric glioma that arises at the critical connection point linking the brain cortex—an area responsible for com-

plex information processing, logical reasoning and thinking—to the spinal cord. A DMG in the pons is referred to as a Diffuse Intrinsic Pontine Glioma (DIPG). Because those tumors are buried deep inside the brain, surgery is often impossible, and they are usually non-responsive to radiation. However, there is a lot of research going on for this type of tumor in the areas of immunotherapy and targeted treatments.

Recently, researchers have discovered that DMG's are uniquely dependent on methionine. Methionine is one of nine amino acids that our bodies use to make proteins. Since we are unable to make methionine, we must obtain our methionine from foods with this amino acid, such as poultry and legumes. Researchers are now understanding that controlling methionine in the diet may help extend survival of the children with this disease and may make other therapies more effective.

For more information about different specific types of CNS tumors and how they are treated, visit the section on brain tumors on the website of the National Cancer Institute (NCI). The NCI is the principal agency for cancer research and training of the United States federal government. The section on CNS tumors is located at: [www.cancer.gov/types/brain](http://www.cancer.gov/types/brain).

## How Long Has The Tumor Been There?

Nobody really knows how long you have had your particular tumor. Slow-growing tumors can be present for years without causing any symptoms. Fast-growing tumors can occur and cause symptoms within a span of six months or less.

Recent research has found that, on average, a GBM may develop for up to seven (7) years before it becomes symptomatic, a surprising discovery given the aggressiveness with which these tumors will grow once they have reached a certain stage in their development.

## Grade Levels (Defined)

Brain tumors are given grades, as opposed to stages. Tumor grade is not the same as a cancer stage. Cancer stage refers to the size and/or extent (reach) of the original (primary) tumor and whether cancer cells have spread in the body. The grade of a brain cancer is indicative of its current speed of growth and the potential to interfere with brain function. Grading is a determination of what stage the tumor is at, or how advanced (bad) it may be in its development.

The WHO classifies all cancers on a grade of 1 to 4. Brain cancer tumors vary in their malignancy, from Grade 1 (least aggressive) to Grade 4 (most aggressive). The grade levels are as follows:

- Grade 1 means a very slow growing tumor that is "well differentiated" and is unlikely to spread much, if at all. They can often be cured with surgery. This is the grade level meant when a tumor is called benign. Long term survival is likely.
- Grade 2 means a tumor that has slightly abnormal characteristics and is slow growing. It is considered "moderately differentiated." It is considered a cancerous tumor, but of a low grade. This tumor might regrow after treatment at a more life-threatening grade.
- Grade 3 means a tumor whose cells look abnormal. It is actively growing but may have little or no dead cells. This tumor is considered a "poorly differentiated" high grade cancer. This tumor tends to regrow after treatment at a more life-threatening grade.
- Grade 4 means an "undifferentiated", high grade tumor where its cells are abnormal and actively dividing. Plus, the tumor has abnormal blood vessel growth and areas of dead tissue (sometimes called necrosis). Grade 4 tumors can grow and spread quickly.

## **Classification Summary Table**

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The table below displays a summary of the WHO classification of brain tumor grades and their general characteristics.

<b>Grade</b>	<b>Tumor Types</b>	<b>Characteristics</b>
<b>Low Grades</b>		
Grade 1	Craniopharyngioma Chordomas Ganglioglioma Gangliocytoma Pilocytic astrocytoma	Possibly curable via surgery alone Long-term survival Least malignant (benign) Non-infiltrative
Grade 2	Pineocytoma “Diffuse” astrocytoma Pure oligodendrogloma	Slightly infiltrative Relatively slow growing Can recur as higher grade
<b>High Grades</b>		
Grade 3	Anaplastic ependymoma Astrocytoma Anaplastic oligodendrogloma	Malignant Infiltrative Tend to recur as higher grade
Grade 4	Glioblastoma multiforme/ GBM Astrocytoma Medulloblastoma Ependymoblastoma Pineoblastoma	Most malignant Rapidly growing and aggressive Widely infiltrative Recurrence is common Tendency for necrosis

## **Grade Levels (How Determined)**

### **Overview**

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Grading a specific tumor type has been described as a process that is as much an “art form” as a science and typically involves a determination made by a pathologist after a biopsy or surgery.

If the tumor tissue has been obtained by biopsy, grading can be somewhat

controversial depending on the size of biopsy specimen obtained. One part of the tumor may have smaller lower-grade cells, while larger more aggressive cells may be present in a different location in the tumor.

Furthermore, tumors initially assigned a low grade can become aggressive in growth, changing the status of the grade even during treatment. It is important to have your biopsy examined by a neuropathologist who sees a large number of brain tumors, always requesting a copy of the report for your records and comparison.

## Factors in Grade Determination

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The determination of Grade level is based on factors that include, but are not limited to these:

- The presence or absence of mutations of the IDH-1, MGMT Promoter and TP53 genes.
- The presence or absence of other mutations that will contribute to the doctors' understanding of the aggressiveness of the tumor. If a pathologist has access to sufficient tumor tissue, the presence of a couple dozen mutations/ biomarkers can be checked (e.g., EGFR, GFAP, PTEN, MDM2, H3K27M, PDL1, NF1, PIK3CA, etc.).
- Mitotic index (or MIB factor or Ki-67 index). This index offers a view in terms of the rate at which the tumor cells replicate/grow. This is often shown on the pathology report.
- Tumor size and observable diffusion through the brain based on contrast MRI images. Experienced neurosurgeons and neuro-oncologists can often accurately predict the official diagnosis from the images but are obliged to withhold final judgment until the pathology report is issued.
- Histological factors. Sometimes when the slides of the tissues are examined under the microscope, certain characteristics are observed that provide some important clues as to aggressiveness. For instance, if granins (crumbles of acidic proteins), synaptophysins (little glycoproteins) or cytokerotins (small filaments) are observed in the tissues, then those give the doctors vital clues about the type and aggressiveness of the tumor.

For a detailed discussion about the molecular characteristics of a Grade 4 Glioblastoma, please see Appendix A entitled "Molecular Characteristics of a GBM".

## What are Survival Statistics for Those with Brain Tumors?

Nobody knows how long you are going to live with your brain tumor. Statistics are a tool used for comparing treatments and for describing what has happened in the past to groups of people with your tumor type. Statistics cannot predict how long any individual person will live.

There are two important survival statistics that you will commonly see in research about brain tumors:

- Overall survival (OS): OS is the average survival time of a group under study — such as 1 or 2 years. Just because a 1-year or 2-year survival statistic is reported does not mean that you will live for 1 or 2 years. Rather, it means that on average the people described in that particular research lived for that length of time; and
- Progression-free survival (PFS). PFS is reported either as the percentage of people who reach a milestone without having tumor progression — such as 6 months or 1 year — or as the average number of months before tumor progression for the entire group. Progression means tumor growth or regrowth.

The survival statistics of OS and PFS are commonly used in medical research, and you can compare treatments by looking at either number. We feel that PFS is the more important survival statistic because after people experience tumor progression, they usually move on to other treatments. In that case, relying on the OS survival statistic to evaluate a treatment may be misleading. As you read about survival statistics, keep in mind that they fail to take into consideration many factors that are extremely important on a case-by-case patient basis — such as age, general health, tumor size and location within the brain, the extent of tumor surgical removal, and much more, including access to the care of brain tumor experts.

Surgical technologies and the ability to accurately diagnose brain tumors have improved dramatically, and ongoing clinical trials are leading the way to new

and better treatments. Your ability to challenge survival statistics will greatly depend on surrounding yourself with a medical team that is not influenced negatively by such numbers.

Try to avoid those within the medical community who have an unfortunate and bleak outlook and may not be current in their understanding of advanced, new treatments. Physicians associated with, and in consultation with, leading brain tumor medical centers are your best defense against negative survival statistics and will enhance your ability to remain positively engaged during your journey through treatment.

Look for people with your tumor type who are leading normal lives. These people prove that no tumor type is completely hopeless. Participate in online and real-world support groups, discussed later in this book, to meet others who have gone through the same medical crisis as you but are now many years out and doing well. It is important to see and acknowledge that there are people with brain tumors who do well.

If you want to see brain tumor survival statistics, go to the website of the Central Brain Tumor Registry of the United States:

<https://cbtrus.org/cbtrus-fact-sheet-2021/>

## Coping with a Brain Tumor Diagnosis (Practical)

The diagnosis of a brain tumor can leave patients and their loved ones in a mental fog, a fog so thick with questions that simply determining where to begin can be debilitating. There are ways in which you can regain control, step out from the fog, and achieve some much-needed clarity.

**Ask Your Doctor for a Case Manager (or Nurse Navigator).** Not all the brain tumor clinics have them, but some do, and if you can get one assigned to you, they can be a major asset for you. A case manager serves as a link between you, the doctors, and other service providers (e.g., insurance companies) throughout your care, and can be especially helpful when one of the thousand questions emerge for which you need guidance but not necessarily from the doctor. They cannot treat you or provide medical direction, but they can provide education and information to enable you to obtain your medical services more efficiently and effectively.

**Organize A Binder.** Organization is your key to obtaining the information you will need for finding the proper treatment necessary for your specific type of tumor. The following are approaches that have helped other brain tumor patients:

A three-ring binder can become your best friend and treatment partner for safeguarding and promptly retrieving all the necessary information about your tumor type and treatment plan. Referrals to specialists or for second (or third) opinions are often delayed by the need to obtain records sometimes caused by records that have been lost along the way. Maintaining your own copies of the items described below items will ensure that your consulting physicians have access to all of your important documents at the time of your appointment.

Items to keep in your treatment binder include:

- Medical history. Start with a copy of the first medical history form you are asked to fill out. This will list past medical problems, such as diabetes or heart problems, which may affect the treatment choice, as well as any allergies you have. An important allergy to note is one to either iodine or shellfish, as the dyes (contrast agents) used in some brain scans contain iodine. Having a copy of your first medical history will be helpful when you have to fill out similar forms. Keep your medical history updated as things change. You can also ask your doctor for a copy of your examination records.
- Copies of imaging films and reports. Most radiological centers today can provide you with a copy of your imaging scans on a CD that can be viewed on any computer. When you check in at the MRI radiology facility, it is very important to request a copy of the film or a CD along with the written report of the radiologist's findings. (Most office supply stores carry special three-hole vinyl pages that hold multiple CDs safely within a binder.)

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Ask for a CD of your images BEFORE you go into the scanner, as it is easier for the staff to handle the request than if you tell them afterward.  
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- All routine laboratory reports (e.g., blood tests) and pathology reports from biopsies. Different members of your medical team will benefit from receiving recent laboratory results that may have been initially ordered by another physician. Having your own personal copies of all routine laboratory reports as well as pathology reports from biopsies, so that

they are available for review on demand, will save time, increase your own understanding, and in some cases eliminate the need for unnecessary blood work. As a bonus, if you are computer literate, keep track of lab results in a spreadsheet so you can graph results over time and see how you are doing.

- **List of Medications.** It is important to disclose all the medications you take to your doctors and care team members. Keeping an up-to-date medication record in your treatment binder (including all vitamins, herbal supplements, and over-the-counter items) can provide a quick and clear snapshot of your daily meds at a glance, reducing the chance of error when more than one physician is involved with your care. Without this information, you may experience symptoms that are medication-related or side effects of a medication that one member of your medical team may not realize you are taking, with the consequence that you may be incorrectly diagnosed or treated.

Take your treatment binder to every appointment with every doctor and request that this list be reviewed before any new medication is prescribed. You should also request a copy of the drug formulary — a list of covered medications — from your insurance company and keep it in your treatment binder. Knowing in advance about the need for prior authorization can save you time and expense.

Many people maintain their binder virtually on their computer, stored the data on a flash drive, and occasionally print the data out and store them in the binder as needed — since it is easier to carry a binder around.

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Please note that the Musella Foundation's Patient Navigation Program (as described earlier in this Guidebook) can help you organize your medical records.  
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**Emergency Note.** You should produce and print out a list of your current medications and allergies to store in your wallet or pocketbook in case of emergency.

**Know The Location.** Knowing the exact location of your tumor will assist you in many ways. By researching the functions of that part of the brain, you can more clearly understand — and be prepared for — many of the symptoms you are experiencing or might expect to experience. Ask your physician to be

specific about the location. Perhaps he or she can provide you with a diagram of the brain with a penciled-in identification of the tumor site. For a detailed discussions of what symptoms can be expected from what location, please see Appendix B “Brain Functions and Dysfunctions by Location” at the back of this Guidebook.

**A Personal Diary.** Beginning on day one, keeping a diary is very important as you review various treatment options with specialists. Recording your specific questions and concerns will help ensure that your medical team provides the answers you and your loved ones or caregivers need. You may want to create a separate section for each team member, writing down which doctor is responsible for the various aspects of your care, medication refills, routine lab work, referrals, and what was discussed at appointments. Questions can often arise after you leave an appointment and being able to refer to these pages later may be helpful. It is critical that you maintain monthly calendar pages to record the start of new medications or therapies and any bad reactions to them. The starting times of symptoms and side effects may be difficult to recall at a later date, but it is important to distinguish their origins.

**Phone Numbers.** Record the names, addresses, phone numbers, email addresses, and a short description of all of your important contacts. Be sure to include your family members who should be contacted in an emergency, all of your doctors, your lawyer, your financial advisor and/or insurance agent, and any clergy.

## Coping with a Brain Tumor Diagnosis (Emotional)

**Love.** When you are diagnosed with a brain tumor, especially a high-grade tumor, those closest to you are also diagnosed. Everyone is affected in some way. The way to move through this journey with as much strength and stability as possible is to make kindness and love a central part of the daily routine with each other.

**Avoid Isolating.** Keep the lines of communication open. Maintain honest, two-way communication with your loved ones, doctors, and others after your cancer diagnosis. If needed, try to find a new openness with loved ones. You may feel particularly isolated if people try to protect you from bad news or if you try to put up a strong front. If you and others express emotions honestly, you can all gain strength from each other. Communication can help reduce the anxiety and fear that cancer can cause.

**Let Family and Friends Help You.** Often friends and family can run errands, provide transportation, prepare meals, and help you with household chores. Learn to accept their help. Accepting help gives those who care about you a sense of contributing at a difficult time. Also encourage your family to accept help if it's needed. A cancer diagnosis affects the entire family and adds stress, especially to the primary caregivers. Accepting help with meals or chores from neighbors or friends can go a long way in preventing them from developing caregiver fatigue.

**When Family/Friends Fall Short.** Don't be shocked or dismayed if some dear friend or a certain family member doesn't call, doesn't help, changes the topic when you are talking. Plenty of people do not know how to handle this kind of diagnosis or don't have the strength. Don't press them. Take heart because friends and family might not act the way you think they should, and you will be left bruised in the middle of the road if you expect too much from them. Don't worry. Perfect strangers often show up and help in meaningful ways.

**Anticipate possible physical changes.** Now — after your cancer diagnosis and before you begin treatment — is the best time to plan for changes. Prepare yourself now so that you'll be better able to cope later. Ask your doctor what changes you should anticipate. If drugs will cause hair loss, advice from image experts about clothing, makeup, wigs and hairpieces may help you feel more comfortable and attractive. Insurance often helps pay for wigs, prostheses, and other adaptive devices. Members of cancer support groups may be particularly helpful in this area and can provide tips that have helped them and others.

**Fear of Being a Burden.** Especially if you have a high-grade tumor, you may be looking at periods in your future where you are dependent on others to care for you. Many people in that situation develop a fear of being a burden. That thinking is stunningly flawed.

When you have periods of dependency, it is an act of tremendous generosity on your part to allow the people who love you to take care of you. If you ask caregivers who have done this, even in intense and demanding situations, they will describe their time with their dependent loved ones as "poignant", "special" or even "sacred". The opportunity to comfort and care for an ailing loved one resonates at the deepest parts of the human heart and soul and the experience adds to the lives of people who would care for you; it does not diminish it.

So, every moment you fight this disease and live to your fullest extent within the bounds of this disease, even if it means you need lots of help from others, is an act of love from you that matters in the deepest ways.

**Review your goals and priorities.** Determine what's really important in your life. Find time for the activities that are most important to you and give you the most meaning.

**Consider potential lifestyle changes.** Maintain your normal lifestyle but be open to modifying it as necessary. Consider how treatment will impact your daily activities. Ask your doctor whether you can expect to continue your normal routine. You may need to spend time in the hospital or have frequent medical appointments. If your treatment will require a leave of absence from your normal duties, plan for this.

**Maintain a healthy lifestyle.** This can improve your energy level. Choose a healthy diet consisting of a variety of foods and get adequate rest in order to help you manage the stress and fatigue of the cancer and its treatment. Exercise and participating in enjoyable activities also may help. Continuing study data suggest that people who maintain some physical exercise during treatment not only cope better but also may live longer.

**Questioning.** You must learn to question your doctors what you are told initially and, as treatment plans are put into place, to ask what qualifying factors your diagnosis and treatment plan are based upon.

However, we understand that some of the first questioning you will do has to do with how this could have happened in the first place. In short: why you? and how is it that you have a brain tumor. This is an especially urgent question if the brain tumor turns out to be malignant. At the back of this Guidebook is Appendix C entitled "Causes of Brain Tumors" which describes what is known about the complex conditions that lead to the formation of a brain tumor.

**Reaching And Internet Researching.** Because not all brain tumors are the same, when confronted with wildly encouraging or wildly discouraging statements about this drug or that treatment, just recognize that the statement might not be true in your loved one's case. Anything that sounds too good to be true – in either direction – should be treated with suspicion and followed with rational fact-finding, including especially consultation with the doctor.

Also know that statements and statistics on the Internet may be old, irrelevant

for the specific type of brain tumor, and without benefit of the results of the latest treatments. It is recommended that you avoid searching about this disease on the Internet as much as possible.

Since our society is increasingly dependent on Internet searches, when you do your searches, seek trustworthy content. Signs that the site/article you are reading is trustworthy are:

**Recently Dated.** Look first to see how recent the information is. Any worthy article will be dated; if you can't find a date, the information risks being bogus. Brain tumor research changes constantly; if the article was written several years ago, the data is likely obsolete.

**Written/Reviewed by Experts.** Verify that the article was written and reviewed by qualified experts. You should be able to easily find the names and professional qualifications of the author or reviewer.

Some papers are written by people who have themselves tackled a brain tumor. While these papers or sites are a fantastic source for inspiration and practical tips on your day-to-day journey, the experiences of others should not be taken as sound medical advice for you.

Be aware that in certain countries, candidates for medical certifications must publish a paper to complete their certification process and some of those candidates will employ papermills to produce unverified "medical" papers that then can be found online.

**Contents Based on Well-Respected, Independent Research.** You should look for the sources of the research that forms the basis of the paper. The sources you want to see are respected and independent medical journals, government health sites, academic institutions, hospitals, or expert health organizations.

Certain companies, particularly those selling home remedies or supplements, will produce papers extolling the benefits of their products and get those papers published online as a marketing ploy. These papers may sound very detailed and scientific, but the underlying data will not have been verified by any independent research.

Making sure the data you find on the Internet is trustworthy will help you have more useful and satisfying conversations with your doctor.

A good way to ensure you are looking at trustworthy data is to sign up for the Musella Foundation brain tumor news blasts, which presents the latest news about brain tumor research with knowledgeable comments to help you keep that news in proper perspective. You can sign up at this link:

<https://virtualtrials.org/newsblast.cfm>

**Depression.** Depression is probably the first symptom of this disease, but we tend to look at depression as "normal" and overlook it. If your loved one is depressed, you should bring it up with the doctor (privately if need be). Brain cancer patients can be depressed because the tumor changes the chemistry of their brain. During treatment, anti-depressants are often prescribed, and some of those anti-depressants can sometimes help in the fight against the cancer by making the cancer cells more sensitive to the chemo.

**Quality Of Life.** When the treatment plan is being discussed (especially after Standard of Care), make sure that your loved one's objective for quality of life (QOL) is considered. There may be trade-offs. Your loved one might prefer to get to play in a golf tournament with friends rather than schedule a certain phase of treatment.

The preferences of the loved one with the brain tumor needs to be your #1 priority, even if you might disagree for whatever reason. It's your loved one's disease, your loved one's skin and is the one who would endure the side effects. The one with the disease needs to be provided with the dignity and compassion of handling treatment the way they want. It is hard sometimes to stand back and just be the advocate of the wishes of a loved one with this disease, but that may be what is required.

**Prayer.** If you have a religious tradition, recruit prayer warriors. You will be praying for your loved one, but it's wonderful to have little (or big) armies of people praying for you and your loved one, too. If your loved one is or has been religiously engaged, get their priest, minister, spiritual director involved NOW. Have that person visit regularly. This journey is deeply spiritual in nature.

**Future.** Do not think about the future any more than you have to. Do everything you can to live in the present moment. This is harder to do than to say because the nature of a human being is to be focused on the future; however, you do not want to give up your time with your loved one today by worrying excessively about tomorrow.

**Feelings.** Just know that it is perfectly okay for you to feel overwhelmed, angry, sad, alone, confused, anguished, in denial, and really angry all in the space of an hour and then do it all over again 2 hours later. That's pretty normal.

**Telling People.** After the diagnosis, you might feel compelled to share it with others. It's a good idea to start sharing slowly. Many people who hear of the diagnosis will have their own opinions, suggestions, anecdotes, and feelings they will then flood you with when you are still trying to absorb all sorts of new thoughts and information yourself. When you have given yourself the chance to find your own equilibrium, start sharing with those caring people closest to you first and ask them for their support. Then, share the diagnosis with those in the next layer of your life. Avoid feeling as though you have to share every detail; just remember that you can always provide more details later.

## Hope

Any of us confronting a brain tumor, especially a high grade one, feel a strong need to find any reason to be hopeful. This craving that exceeds anything we have experienced in the past. We hope the treatments will work; we hope the tumor will stay gone after surgery or if it is not removable, we hope the radiation kills it. We hope to qualify for a clinical trial that we hope will be that special, silver bullet that destroys the disease. Above all, we hope that our lives can get back to the way it was before the diagnosis.

All these hopes turn to an externally driven source. They are dependent upon test results, treatment response, treatment research and availability, etc. and if they do not come to fruition as all of us might like, we can find ourselves in a deep emotional ditch. To be clear, these are all good goals, but these forms of hope are simply insufficient for this journey. Individuals relying on these factors can set themselves up to experience a crushing anxiety if they are told what they have hoped for has not happened.

The challenge of hope must include the realization that there just is no such thing as a Life without its challenges, and brain cancer is one of those challenges, certainly one of its fiercest. So, pinning one's hopes to external factors over which we have only the barest control (if any) in the face of such a serious challenge like brain cancer is simply not enough to sustain a person – at least not well.

The option to an externally driven hope is an internally driven one. This is hope that comes from our deepest, most authentic parts, and is the fruit of our attitudes and philosophy of Life. It is not as dependent on what happens. It rests instead on an understanding of our lives as being a part of the huge tapestry of Life, which includes an understanding that no physical life is infinite and a recognition of our place in human history and in this wide, awesome universe. For the religiously inclined, it includes a recognition of our valued place in God's unfolding plan.

Central to an internally driven hope is the development of new attitudes and probably a new meaning to a person's Life. This form of hope, obviously to be developed within the context of a person's personal philosophical/spiritual/religious views, is vital for this sort of a journey. Because of the powerful connection between our minds and our bodies, an attitude of hopelessness can actually predict a poorer outcome against the disease. Of course, feeling hopeful in the face of all the obstacles throughout diagnosis and treatment is truly difficult. Therefore, devoting some time and effort to pursuing and nurturing hope is a worthy endeavor.

Only a hope based on a deep, personal philosophy will produce the resilience necessary to allow a person to face the challenges of brain cancer with the strength and sturdiness that will offer future opportunities to undergo continued treatment and live longer.

Good places to start or continue the process of developing a strong, internal hope for this journey include:

- Discussions with clergy or spiritual counselors, especially those associated with the chaplain's office at your hospital.
- Discussions with palliative care counselors or social workers at your hospital.
- Logotherapy. Logotherapy derives from the works of Viktor Frankl, a neurologist and psychiatrist, who survived severe suffering in the Holocaust and concluded that "Everything can be taken from a man but one thing: the last of the human freedoms—to choose one's attitude in any given set of circumstances, to choose one's own way." Finding a counselor with competency in logotherapy can help with hope.

## One: What You Need To Know When A Brain Tumor Is Found

1

- Reading stories of brain cancer survivors - people who have faced the same types of challenges you are facing and have learned to cope. This Guidebook contains many such stories.



## SURVIVOR STORY #1

It started with small things in 1999, mostly visual. My wife thought I was experiencing a stroke.

I called my doctor at home on a Sunday. He had a scan set for Wednesday; my wife and I saw the neurologist and neurosurgeon on Thursday, and surgery was on the following Tuesday. I had glioblastoma. I received radiation and chemotherapy as well as stereotactic radiation. I was very fortunate to be at a teaching hospital. I had a recurrence in 2001 with successful resection during which Gliadel Wafers were implanted.

In 2002, they thought I had another recurrence, but it was only scar tissue and radiation necrosis.

I am currently a 19-year survivor of glioblastoma. I still deal with several medical issues associated with my tumor treatment, including some loss of peripheral vision and neuropathy in my right foot, which affects my balance. Most important to me are conversations I have with brain tumor patients and their caregivers. On average, I talk to two or three patients in a given month. I always point them to the [virtualtrials.org](http://virtualtrials.org) website as the best resource for all things brain tumor. I do not give medical advice, but I do answer questions as best I can. What I hear quite often is the hope they feel when they meet someone who has survived glioblastoma for as long as I have. I make sure they know that there are many long-term survivors and that there is hope based on new treatments and research.

I have learned a lot of things from my experiences; these are just a few of them:

- You will learn quickly who is comfortable and who is not comfortable in dealing with issues of mortality.
- Have someone with you to listen, ask questions, and remember. Several times the neurosurgeon told my wife that no one had ever asked him a particular question before.
- Don't fear knowledge. As my wife said many times, "There is nothing you can tell us that is worse than we can imagine."

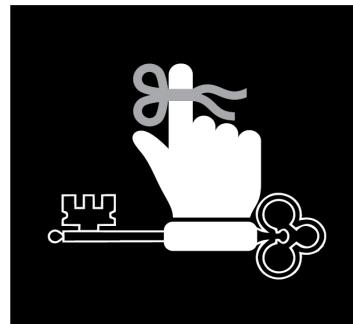
## One: What You Need To Know When A Brain Tumor Is Found

1

- God gave us the gift of life that brings uncertainty. When tough times hit, He can comfort us much as we can comfort each other.



## KEY TAKEAWAYS TO REMEMBER



About 70% of masses in the brain are benign (non-cancerous) growths that do not spread and may not even require surgery.

Metastatic (secondary) brain tumors are about four times more common than primary brain tumors. The likelihood that a mass in the brain is metastatic should be assessed by the doctor before biopsy or surgery.

An integrated diagnosis consists of a full neurological exam, imaging of the site, and a molecular evaluation of tissue obtained by biopsy or surgery.

The molecular evaluation can take up to a few weeks to complete.

By testing for molecular markers, your medical team can generate a profile of your tumor cells that achieves a reliable diagnosis and can help guide treatment choices.

If diagnosed with a brain tumor, especially a malignant one:

Get organized from Day #1 with a binder to keep track of everything, including especially your medications, and

Know the exact location of your tumor.

Survival statistics do not necessarily consider all factors; your ability to challenge survival statistics will greatly depend on surrounding yourself with a medical team that is not influenced negatively by such numbers.



## Treatment Facilities

### Brain Tumor Centers

For a list of major brain tumor centers by state and country, please go to:

[https://virtualtrials.org/Brain\\_Tumor\\_Centers.cfm](https://virtualtrials.org/Brain_Tumor_Centers.cfm).

If possible, all brain tumor patients should receive at least one second opinion from a brain tumor center.

### Major Clinic Benefits

The most accurate diagnoses and resources for the best, most expert treatment across the multiple medical disciplines you will need on your medical team is most often found at a brain tumor center. Any brain tumor is complex, but Grade 3 or Grade 4 tumors are exceptionally complex diseases requiring the high level of expertise available at a brain cancer center.

The reasons you want to go to a brain cancer center are these:

- The neurosurgeons and team members at brain cancer centers perform over 50 brain surgeries annually (as many as five surgeries per week at some centers) and may offer the most technologically advanced procedures with higher rates of survival and lowest postoperative deficits. Your choice of surgeon and post-surgical treatment team can profoundly affect the out-

come of your care. In addition to having the best neurosurgeons and neuro-oncologists, the top brain clinics also have the latest technologies and equipment to help those expert doctors.

- The most advanced clinical trials are for GBMs, but the majority of openings for those trials are available at the well-resourced, top brain clinics. So, if your loved one has a high-grade brain tumor, you want to set them up in a system where they may get access to advanced treatments when they are needed.

Many of these specialized centers allow you to directly submit imaging scans and even tissue samples, if you have them, for further examination without a referring physician.

If the nearest brain tumor center is far from where you live, the staff there should be able to coordinate some of your treatment with doctors more local to you, so that extended stays near the brain tumor center may not be necessary.

## NCI Designated Cancer Centers

The United States is fortunate to have a number of superb brain cancer centers with world-class capabilities. The National Cancer Institute (NCI) has designated cancer centers in the U.S. Most of these centers are part of a university or large medical center; all have a high degree of cancer competency. You can locate a NCI designated cancer center at this website:

<https://www.cancer.gov/research/infrastructure/cancer-centers/find>

.....  
For information about consultations with the neuro-oncology branch of the National Cancer Institute, go to: [ccr.cancer.gov/Neuro-Oncology-Branch](http://ccr.cancer.gov/Neuro-Oncology-Branch). Then, select the box on the left marked "Information for Patients," and click "Read more."  
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## Brain Cancer SPORE Locations

In 2002, the NCI established the Brain Cancer Specialized Programs of Research Excellence (SPORE) program. The Brain Cancer SPORE program objectives include improved prognostic testing, tumor vaccines, and other immunotherapeutic approaches, as well as enabling the rapid and efficient movement of scientific findings into clinical settings.

Current Brain Cancer SPORE grant clinics are:

Brigham and Women's Hospital  
Duke University Medical Center  
Northwestern University at Chicago  
University of California at Los Angeles  
University of California at San Francisco  
University of Texas MD Anderson Cancer Center

### **Travel and Housing Discounts**

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Those needing to travel to a medical facility should ask about available discounts for travelers.

Air carriers may offer a discount to those traveling for medical reasons. Generally, this discount is obtained at the time the reservation is being made, so you should ask at the time you make flight arrangements.

Many of the top brain cancer clinics have discounts at local motels and hotels. In addition, most of the largest brain cancer centers have supportive and affordable facilities geared for their cancer patients. Examples:

Near Duke University's Cancer Institute is a facility called the Caring House which has affordable housing for patients and their caregivers that travel to Duke for their outpatient treatments. The website for this facility is:

<https://caringhouse.org>

Near MDAanderson, where about 150,000 people each year get cancer treatment,

there is the Jesse H. Jones Rotary House International, the Hope Lodge from the American Cancer society, the Halo House, the Aishel House, Joe's House, Matthew's Miracle House, the ASCF (A Shelter for Cancer Families), plus Comfortable Home (furnished apartments), not to mentioned reduced rates at the nearby luxury hotels like Marriott, Hilton, or Wyndham.

In short, if you know you will need to be treated as an outpatient at one of the brain cancer centers, it is advisable to ask if they have facilities that may reduce the costs of the stay.

## Clinics Offering Alternative Treatments

A diagnosis of a high-grade brain cancer can be devastating. The panic and anguish that ensue may cause a person to look beyond established medical facilities.

There are private clinics that will present very compelling assurances. Their personnel seem compassionate, understanding, and competent. Their clinic has a reassuring, restful, spa-like ambiance to it. Testimonials are published online by very enthusiastic, grateful clients. The treatments often blend unusual drugs that not otherwise available with innovative "healthy" approaches to diet and elevate hope.

These private clinics are typically but not exclusively outside of the US; they operate under laws or loopholes in laws that enable the clinic to provide compassionate care to patients who have been diagnosed with a terminal illness. Doctors with variable qualifications are allowed to provide unproven or disproven treatments without any regulations or requirements to report on their results.

All of these clinics charge exorbitant prices, which insurance companies generally do not cover, in the range of \$60,000 to \$120,000 for their treatments. Also, treatments may require the patient and family to remain in the clinic's country for several weeks at a time, incurring not just the basic treatment costs, but also the costs of travel, ground transport, hotels, and meals during the stay. Treatments will often need to be repeated at another round of similar charges.

Amid other concerns is the potential that a patient may experience a medical crisis while abroad. Standard commercial air carriers may not accept transporting a medi-

## Two: Treatment Facilities

cally fragile person, which will then necessitate a medical evacuation flight. Getting back home by "med-evac" plane may easily run into the tens of thousands of dollars, and most insurance companies, including travel insurance companies are not likely to cover such costs.

It is highly advisable that if you are seriously considering seeking treatment at a clinic offering alternate treatments that you thoroughly investigate everything about the clinic. No one can presume to make crucial decisions for a person when they or their loved one is ill but having one's eyes wide open is the best path to the best outcome.

Some questions to ask to identify clinics that are not likely to provide treatments supporting the best outcome are these:

- Is the clinic regulated by the relevant government or an independent, rigorous medical oversight agency? Do they report results? If not, why not?
- If the clinic describes its treatment as a "miracle," "scientific breakthrough", or containing "secret ingredients", please read the section in this Guidebook entitled "Alternative Treatments."
- Where does the clinic get the drugs used in their treatments? (Clinic may use drugs harvested from failed, terminated clinical trials and will not be keen to disclose that.)
- Does the clinic use the same treatment for all types of cancers? (There is no such thing as one size fits all with cancer.)
- How does the clinic ensure the safety of the treatment? Some clinics will claim the treatment is "natural." Not everything that is natural is safe, especially for cancer patients.
- Does the personnel and marketing videos and literature use a lot of medical jargon and talk about "curing" the disease or other strong words appealing to the emotions? How reliable are the testimonials in their marketing brochures? (If researched, you may find that some of the patients in the testimonials have either been deceased for years or were simply paid actors.)

- What is their explanation for why their products are not supported by conventional doctors? (A questionable clinic may claim that their treatment challenges modern practices and, therefore, the medical industry conspires together to silence them.)
- Can they back up their claims of outcomes? (Questionable clinics may make claims of impressive outcomes but can provide no specifics even if they claim people have been "cured" of brain cancer using their treatment.)
- Will you have to sign a non-disclosure? Many questionable clinics require clients to sign a non-disclosure agreement prohibiting them from talking about the clinic and their treatment outcome.

Before proceeding, and certainly before giving a clinic offering an alternate treatment any money, it is wise to strongly consider the factors described above and speak to your neurosurgeon or neuro-oncologist. Contact the Musella Foundation to see what we know about the particular treatment.

## Two: Treatment Facilities

2



# Brain Tumor Guide for the Newly Diagnosed





## Understanding brain tumors

3

### DOCTORS

#### Overview of Your Medical Team

Typically, the physician discovering your tumor will refer you to a doctor with expertise in neuro medicine for a consultation regarding treatment.

Treatment of brain tumors often consists of a number of different types of interventions: brain surgery to biopsy or remove the tumor and obtain a tissue sample; radiation therapy; chemotherapy; alternating electric field therapy with a device called the Optune; different drugs for managing symptoms caused not only by the tumor but also by the tumor's treatment; and even enrollment in a clinical trial.

This large number of different possible treatments means that you will need a team of specialized doctors—preferably associated with a single medical center experienced in treating brain tumors—that will be able to coordinate and administer the most up-to-date treatments with precision and care.

Your medical team should include several experts experienced in different medical specialties. The make-up of your medical team will vary depending on the type and location of your tumor, and it may include specialists representing a variety of different medical cross-specialties.

It is essential that your medical team include experts with current and comprehensive experience in the treatment of your specific type of brain tumor and that have a communication process to remain inter-connected about your care.

## Typical Types of Doctors

Among the doctors you may encounter are:

**Neurosurgeon.** A neurosurgeon is someone who performs biopsies and surgery involving the nervous system, typically specializing in one particular area or system, such as the brain or the spine. Before considering any surgical procedure, it is important to establish that your neurosurgeon has substantial and up-to-date experience in your condition. It is also wise to obtain a second opinion from a similarly qualified neurosurgeon associated with a major brain tumor center.

While some neurosurgeons also practice neuro-oncology and oversee the administration of chemotherapy treatments, most confine their practice to surgical therapy and follow-up care.

**Neuro-oncologist.** If the tumor is found to be cancerous, you will need a neuro-oncologist on your team.

A medical board-certified oncologist treats many forms of cancer; however, not all oncologists are experts in treating brain tumors. As part of your medical team, your general oncologist can assist you with obtaining second opinions and researching available treatment options, but he or she should refer you to a neuro-oncologist experienced specifically in the treatment of brain tumors.

Many neuro-oncologists are also neurologists, doctors who treat disorders of the nervous system (some also started as general oncologists) as well as general cancer. It is important that your selected neuro-oncologist has substantial and up-to-date experience in treating your type of tumor and is up to date on advances in both surgery and alternative treatments.

If your primary brain tumor physician is not familiar with the most current treatments or clinical trials you should request a second opinion. Even if you are diagnosed by a major brain tumor center, you may still wish to get a second opinion from another major brain tumor center to confirm your diagnosis, to confirm a treatment plan, and/or to locate a clinical trial. It is your right to have a second opinion. (See sections below on Second Opinions.)

**Neuroradiologist.** This is a specialist in the area of reading MRI and CT scans involving the nervous system. Your MRI or CT scans should always be reviewed by a neuroradiologist experienced with tumors within the brain.

**Radiation oncologist.** This is a doctor specializing in the administration of radiation therapy (solely and specifically) and should work in cooperation with your neuro-oncologist/ surgeon to develop an appropriate course for the duration and intensity of your radiation therapy.

**Neurologist.** In the event your tumor is benign, you will need a neurologist, a doctor with expertise in treating conditions of the nervous system, such as the brain and spinal cord.

## Additional Specialists

From time to time you may have a requirement for complementary care during your treatment and recovery, such as:

- Rehabilitation specialists (physical/speech therapist, occupational therapist)
- Neuropsychologists and psychiatrists
- Endocrinologists
- Ophthalmologists (eye doctors)
- Dentists (especially important prior to chemotherapy)
- Pharmacists
- Nutritionists
- The group of doctors at your hospital of care who might undertake the tumor board review of your tumor treatment

## Need for Expertise

You must seek out the foremost expert advice. Because diagnosing a specific type of

brain tumor is complicated, it is essential to get confirmation of a diagnosis. Second, third, or even fourth opinions should come from experts within a specific area, such as those who are experts in the removal of brain tumors: neurosurgeons performing at least 25 brain surgeries per year, or experts in neuropathology who can qualify the diagnosis of your tumor biopsy. It is estimated that as many as 25 percent of brain tumor patients will have their diagnosis changed upon further examination by a second, expert opinion, which can drastically alter not only the prognosis but also the recommended treatment plan.

A review of your MRI or CT scans, tests, and pathology reports, along with an overview of new resources and treatment programs can be obtained through many of the leading major brain tumor centers. Your physician can also consult with the National Cancer Institute (see discussion under "Treatment Facilities"). They will also review your case for free. They have excellent adult and pediatric brain tumor specialists available to help you.

Most pathologists do not see enough brain tumors to allow them to make the subtle distinctions that may be necessary for diagnosis. You can also ask for a second opinion on the reading of the biopsy slides from a major brain tumor center.

There is a cost, but the process is easy; your hospital just mails the slides. If you do need to travel for a second or third opinion, there are many organizations that provide financial assistance specifically for brain tumor patients. Please check the information on insurance and financial help in the next section (entitled "Protecting Yourself and Your Family During Treatment") of this book.

## Patient-Medical Team Communications

Brain tumors can change, grow, and recur, so it is important for you to be an active participant by being organized and knowledgeable about your tumor's makeup and location, your medications and their side effects, and symptoms that you might expect throughout your treatment. It is important to maintain an ongoing, open dialogue with your medical care team.

Physicians do not always engage one another in the type of dialogue that patients often assume is transpiring on their behalf. Being organized can assist you by ensur-

ing that all of your team members are on the same page with current information at the time of your appointments and consultations. You and your advocate team must become your own primary-care manager.

## Criteria for Selecting a Doctor

It is advisable that you look for a doctor who:

- **Listens.** It's important to find a doctor who will listen to your concerns. It will be easier for you to ask this doctor questions.
- **Explains.** You want a doctor who can use plain language to explain what you have, what the treatment options are and what your prognosis is in terms you can understand.
- **Understands.** You want that elusive quality of chemistry between you and your doctor — a doctor who understands you. If it isn't there, find someone else. He or she may have all of the credentials, but if the chemistry between you and that doctor isn't positive, you might do well to switch.

3

Make the relationship with your doctor a working partnership. The best treatment relationship is one where you ask questions and participate in your care.

## What questions should I ask my medical team?

Some of the questions you may wish to ask your medical team are:

- What type of brain tumor do I have?
- What is the grade of the brain tumor?
- Are any additional tests needed?
- How many tumor types like this do you treat each year?
- Will the brain tumor board review my case? How often?
- Where would you recommend I get a confirming/second opinion?
- Do you have any written information about my type of brain tumor?
- How will the brain tumor affect my functioning?
- What are my treatment options?
- Which treatment do you recommend? Why?

- Which clinical trials do I qualify for, and which do you recommend?
- Can you recommend a neuro-oncologist who specializes in this type of brain tumor?
- What other specialists will be part of my care?
- What is the timeline for treatment(s)?
- Where will I get the treatment?
- Will I be able to drive myself to and from treatment?
- Will my medical insurance cover this type of treatment?
- How will this type of treatment affect my work schedule?
- Will I need to apply for disability? Social Security disability?
- Will I need to take medications? If so, what kinds and how often?
- Are there any side effects? What kind?
- Are there short-term and long-term side effects?
- How can side effects be managed? By medicines? By physical therapy?
- Will my quality-of-life change? Will I function differently?
- Will I see a change in my personality? Appetite? Sleep habits? Memory?
- What can I expect before, during, and after treatment?
- What is the follow-up plan if this treatment doesn't work?
- How often will I need follow-up imaging scans? What kind of scans?
- Do you think I should attend a support group now? Are there any support-groups nearby?

## Second Opinions (Diagnosis/Genetic Study)

The initial tumor molecular evaluation done following a hospital biopsy or surgery is done to the extent needed to reach a conclusive diagnosis and enable the doctor to commence treatment of the disease.

The key genetic characteristics ("biomarkers") that are of most interest at the initial stage are these: IDH-1 gene status, MGMT promoter gene status, presence/absence of chromosome 1p and/or 19q deletions, and the mitotic index (or Ki-67 index).

These are just the absolute basic data points needed at the commencement of diagnosis and medical treatment. However, should the tumor prove to be resistant to the first-line treatment or regrow, as many high-grade tumors do, an in-depth evaluation of the tumor tissue may enable your doctors to identify more effective, alternate treatments such as those available in a clinical trial.

Your neuro-oncologist should discuss with you the option of having your tumor genetically profiled. If your doctor does not present the topic, you may wish to inquire your doctor about genetic testing.

Companies that do this type of work include:

- FoundationOneCDx (FDA approved in 2011 for tumor mutation profiling; most often recommended)
- CARIS Molecular Intelligence (well-recommended)
- Guardant360CDx (first FDA-approved tumor mutation profiling via liquid biopsy)
- MSK IMPACT (Integrated Mutation Profiling Of Actionable Cancer Targets at Memorial Sloan Kettering) FDA-approved profiling of variants, insertions, deletions, and microsatellite instability
- CeGat (Tubingen, Germany)

Tumor mutation profiling services performed by these companies can be expensive, take time (notionally 4-6 weeks), costs are often not covered by insurance and the attending neuro-oncologist may prefer the results of one service over another. The timing for requesting this second evaluation should be discussed with the doctor, because initial chemo treatments are likely to alter the molecular characteristics of the tumor.

## Second Opinions (Treatment)

It is reasonable and common to obtain a second opinion for treatment from a different neurosurgeon or neuro-oncologist at a hospital other than your current one. See the Section entitled "Treatment Facilities" for suggestions of highly rated options. For a second opinion on your treatment options, you may also turn to the Patient Navigation Program described earlier in this Guidebook.

## Brain Tumor Guide for the Newly Diagnosed

The purposes of a second opinion include but are not limited to: confirming the diagnosis, obtaining recommendations regarding surgery, ensuring the current treatment plan is correct, and learning about opportunities for other advanced treatments relevant to your tumor.

The process for a second opinion typically involves a review of your medical history, current diagnosis and all images that have been taken.

You would initiate a second opinion by calling the appointment desk at the brain cancer clinic you wish to have the second opinion from and informing them you need a second opinion. Appointments for second opinions are usually scheduled promptly.

In the event you do not want to travel to the clinic from which you are requesting the second opinion, you may ask them if they would perform the second opinion by means of a virtual, online visit or by a "desk review" of your files and images. Many clinics will accommodate such a request.

While second opinions are reasonable, it is not advisable to waste time and energy by going to six or seven different cancer centers to see several doctors who may all tell you the same thing. If the two opinions are similar, it's likely that all other neurosurgeons or neuro-oncologists will tell you the same thing.



## SURVIVOR STORY #2

On the night of December 25, 2012, I went to bed and had a grand mal seizure for the first time ever. The only thing I remember was waking up on a stretcher as I was being lifted into an ambulance. I failed to answer basic questions. I was confused and had no idea what was happening. I was rushed to the local hospital to undergo a CT scan. The results showed an 8-cm tumor on the right frontal lobe of my brain.

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This news left my wife and me speechless. It was so much to digest. She cried, and I sat in disbelief. I was then transported by ambulance to another hospital where an MRI scan and another CT scan were performed. Unfortunately, the imaging interpretation at the first hospital was confirmed. I was told that I needed to be operated on as soon as possible. Luckily, one of the best neurosurgeons in the state was on call that night. After quick but thorough research, my family and I decided to go ahead with the surgery. My neurosurgeon and his team were able to remove the entire tumor. During recovery I had several more seizures and received the antiepileptic medication levetiracetam (Keppra). A week or so after discharge, while still recovering in bed, I received the phone call that no one wants. My pathology report was back. I had a grade 3 anaplastic astrocytoma.

My family and I were devastated. Before that first seizure my life was great. I had just turned 31 years old, I had a great job, my wife and I had just purchased our first home, and we had a beautiful one-year-old boy. Life seemed perfect, then the curve ball.

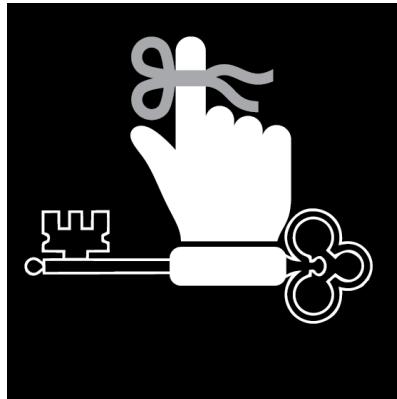
My first reaction was, Why me? What did I do to deserve this? My wife and I went to see the neurosurgeon for a follow-up appointment, and he recommended a comprehensive cancer center. Our appointment came quickly. We received detailed information about my diagnosis and my treatment schedule. I did not like hearing the statistics, especially when they confirmed what Dr. Google seemed to be reporting on the Internet, but we decided to take the brain tumor head on. My treatment was 30 days of radiation therapy with weekends off, 6 weeks of temozolomide (Temozar) every day, and then 12 months of adjuvant temozolomide with the cycle of 7 days on, 23 days off.

The radiation therapy was difficult to tolerate near its end. Because I did not like watching my hair fall out, I shaved all my hair off. Chemotherapy, however, was not too hard to tolerate, and I went back to my job on light duty toward the end of treatment.

## Brain Tumor Guide for the Newly Diagnosed

Throughout all this, I recognized how blessed I am. I had such an awakening. I started to take charge of my health in ways I never thought possible. I no longer procrastinated. I no longer put anything on hold. The experience gave "living life" a whole new meaning to me. I received many miracles on my journey. Although not everything was easy, especially at the beginning, I can say that my diagnosis saved me.

## KEY TAKEAWAYS TO REMEMBER



The single most important decision you have to make is WHERE and by WHOM to have treatment.

The best, most expert treatment is most often found at a major brain tumor center. In addition to having the best neurosurgeons and neuro-oncologists, top brain clinics also have the latest technologies and equipment.

Get copies of your brain scans (or a CD of them) and their interpretations, and share them with other members of your medical team to ensure that they agree with the interpretations.

Understand the different functions of the members of your medical treatment team.

If considering alternate treatment facilities, ask lots of in-depth questions before paying any money.

It is essential that your medical team include experts with current and comprehensive experience in the treatment of your specific type of brain tumor and that have a communication process to remain inter-connected about your care.

It is reasonable and common to obtain a second opinion for treatment from a different neurosurgeon or neuro-oncologist at a hospital other than the one you are currently going to.

# Brain Tumor Guide for the Newly Diagnosed





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## PROTECTING YOURSELF AND FAMILY DURING TREATMENT

### Health Maintenance Vaccines

4

You may want to discuss with your doctor getting certain vaccines that may help you maintain your underlying health. Because the benefits and safety of vaccines vary from person to person, only your doctor can determine the appropriateness and timing of you getting these certain vaccines.

In general, vaccines are not recommended during chemo or radiation therapy. For that reason, the scheduling of vaccines may need to be made prior to the start of those procedures, so discussing the issue of vaccines early is recommended.

The vaccines you may wish to explore with your doctor include the following:

**COVID-19.** Many medical experts recommend that those with cancer should get the COVID-19 vaccine but be sure to talk to your doctor first.

**Influenza.** It is a good idea for patients to be protected from the flu. You can typically get the flu vaccine at least two (2) weeks before chemo or between chemo cycles. Your doctor may have specific instructions for how you get this vaccine. The nasal mist flu vaccine may not be recommended because it contains the weakened flu virus and can lead to an infection. The injectable vaccine has the dead flu virus and is believed by more doctors to be safer for their cancer patients. Unless your doctor suggests otherwise, your family members should also get the injectable flu vaccine instead of the nasal mist. By protecting themselves from the flu, they're also protect-

ing you from getting it from them.

**Shingles.** Shingles is a reactivation of the herpes zoster (chicken pox) virus in patients. Those who have had chicken pox at any time in their life may get Shingles, which produces large, painful welts on the body that can last for weeks. Shingles may occur more frequently with people with compromised immune systems such as those with cancer or those going through cancer treatment. There is a particular vaccine against Shingles that some doctors believe would be safe for individuals with brain cancer to take to prevent Shingles, but other vaccine forms that most doctor agree are not recommended for brain cancer patients. It is important to discuss with the doctor first.

**Pneumococcal Pneumonia.** A person's immune system becomes compromised by the combined assault of the disease and treatments and pneumonia can follow, with consequences that may be serious. The pneumococcal vaccine helps to prevent serious lung, blood or brain infections caused by certain bacteria. As with all vaccines, it is important to discuss this one with your doctor first, as recommendations may vary depending on your particular case. But generally, patients with cancer should receive two types of pneumococcal vaccine. These vaccines should be given 2 weeks prior to chemo.

**Others.** The doctor may recommend that you are re-vaccinated for certain illnesses (e.g., tetanus) or may tell you that you do not need or should not get certain vaccinations (e.g., polio, MMR -measles, mumps, rubella). Ask the doctor also what vaccines your family members should get if they are expected to be around you during your treatment.

## Fertility Protection

Radiation to the head, surgery, and most medications (except chemotherapy drugs) used to treat brain tumors do not pose a threat to fertility. If radiation therapy is aimed at locations other than the head, you should consult your radiation oncologist about fertility concerns prior to beginning treatment. Often, a lead apron can provide adequate protection to sex organs during radiation treatments.

Chemotherapy can have a real and permanent effect on fertility in men, reducing or eliminating sperm production. While this effect is reversible in most cases, it may

be a number of years before sperm counts return to normal. In women, chemotherapy can temporarily halt menstrual periods, but normal menses should resume after treatments are concluded. Alkylating agents, however, can affect egg production (effects worsen for older women).

If your brain tumor requires certain forms of treatment such as chemo, you may have difficulty becoming pregnant or fathering a child. You should discuss with your doctor before starting treatment if you think you may want to have a baby in the future. Men may be able to store sperm and women may be able to store eggs prior to treatment, and then use those stored resources to have a baby once treatment has concluded. These services are not always offered at every hospital, but your doctor's office may be able to recommend a clinic that specializes in this kind of service.

The importance of fertility is a personal choice. While it is not always the priority of the medical team who are basing their treatment on life-saving measures, it should be discussed before beginning any form of chemotherapy. If necessary, you should insist on having that discussion.

Fertility experts can provide advice about the possibility of sperm banking for men or egg harvesting and fertilization techniques for women. Sperm banks typically suggest a minimum sperm count to be frozen for use at a later date, but a low count alone should not discourage you. A fertility expert can give guidance regarding your chances of success in the case of a low sperm count and other options available to you.

Although rarely the result of brain tumor treatments, impotence can occur as a result of depression. If you experience more than the occasional sexual dysfunction that is normal with aging, you should consult your medical team about medications and other available treatment avenues.

## Insurance Management

### **Effects of the Affordable Care Act (ACA)**

Some people with brain tumors are afraid that their health insurance will be can-

celled because they have become sick. Others are afraid that the cost of their medical treatment during a year or over a lifetime will exceed dollar pay-out limits set by their health insurance plan, thereby depleting life savings, or even bankrupting them. Others are afraid that if they lose their job plus the health insurance that goes with the job, while being treated for a brain tumor, they will not be able to find new health insurance because of the preexisting condition. Or they are afraid that they will not be able to afford the health insurance even if they can continue with their existing policy or if they do find new coverage.

The Patient Protection and Affordable Care Act (ACA), the federal law passed in 2010 that is often also referred to as Obamacare, was enacted to help displace such fears. Many national cancer organizations have evaluated the ACA. According to the American Cancer Society, for example, the ACA has helped and will help people with brain tumors in the following ways:

- Upon passage, the law immediately stopped insurance companies from dropping patients from coverage just because they got sick.
- Upon passage, the law immediately banned health insurance companies from having lifetime pay-out limits. In 2014, the law banned health insurance companies from having annual pay-out limits.
- Upon passage, the law immediately banned health insurance companies from denying coverage to children with preexisting conditions. In 2014, the law banned health insurance companies from denying coverage to adults with preexisting conditions, like cancer.
- Upon passage, the law immediately banned health insurance companies from denying coverage to patients who participate in clinical trials.
- Upon passage, the law immediately banned health insurance companies from charging patients for cancer screening tests, such as mammograms and colonoscopies.
- In 2014, the law required all states to create online health insurance marketplaces (usually called “exchanges”) so that people without insurance through employment can compare and buy coverage from health insurance companies.

With passage of the ACA, if you had health insurance through your employment, you kept your current health insurance. However, your health insurance plan now has to abide by the provisions of the ACA law, such as following the ban on lifetime

and annual pay-out limits and providing free cancer-screening tests, among others.

## **Understanding your insurance**

Insurance laws vary from state to state. Also, your health insurance policy may be under state or federal guidelines depending on where you work and whether your employer is self-insured. A large employer who is self-insured is not considered an insurance company but rather writes its own policy that is in turn managed by an oversight organization, which may be a health maintenance organization (HMO) operating within your state. The self-insured policies are governed by federal laws, and even state laws such as in California — with strict HMO laws protecting consumers — are not available to those covered by self-insured federally regulated plans.

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Complicating things even further, plans such as HMOs and preferred provider organizations (PPOs) often fall under different jurisdictions as well. Your human resources department at your employer can often tell you if your plan is self-insured, whether it is governed by state or by federal regulations, and the contact information for the proper agency.

Most insurance plans contain a specific list of “covered” medications and those that are excluded from coverage, called a “formulary,” and by law must provide you with a copy upon request. Many of the drugs used in the treatment of brain tumors are approved by the FDA for other conditions but are not approved for treatment of conditions associated with brain tumors. When a physician prescribes a medication for a condition that falls outside the FDA-approved guidelines, it’s called an “off label” use, and in many cases is not covered.

Many states provide an appeal process for challenging an off-label denial that may assist you in obtaining coverage. You may be required (if for no other reason than your immediate need of the drug) to pay for the prescription out of pocket, as the process may take several weeks for a decision. If your employer or the insurance company will allow you to upgrade your prescription coverage to one that will allow for off-label medication coverage, you would be wise to do so now, regardless of whether or not you require such coverage at this time — it’s likely you will need it in the future.

Request a copy of your insurance plan's formulary and keep it in your treatment binder. Have your physician check the formulary when prescribing a new medication to ensure coverage, or perhaps select a like drug (if available) from the formulary to avoid unnecessary out-of-the-pocket expense.

Information regarding the laws that govern switching plans during treatment or “continuity of care” issues when policies change with new employment can best be answered by calling the office of your state’s insurance commissioner. Many states, such as California, have specific departments for patient advocacy that can help you work through these issues, or direct you to the proper federal agency if your plan is governed by federal regulations. Such patient advocates within your state health insurance department can help you with the necessary paperwork for filing appeals or complaints when your insurance company denies coverage for specific treatments or medications.

- All communications (from making claims to general inquiries) should be in writing.
- When communicating by phone or in person, be sure to record and confirm your understanding of the conversation in a letter sent certified with confirmation of receipt and keep a copy of the letter in your file.
- Scrutinize everything you receive from the insurance company and hospital — for example, bills, payments, and credits for mistakes — they DO happen! Do not be afraid to ask for explanations for items that are unclear or unspecified.
- Read your policy thoroughly so that you are aware of what benefits you are entitled to and what items are excluded, paying special attention to areas involving clinical trials or experimental treatments. Be prepared to ask your physician to write a letter on your behalf explaining why you should be allowed coverage for these items. It is helpful to have an “understanding” with your physician as to when consideration of experimental therapies would take place, rather than waiting for that day to arrive, only to find an unsupportive care partner.
- Health insurance companies can assign a case manager to you so that you can talk to the same person each time you call. Ask your insurance company whether you can be assigned a case manager.
- Do not hesitate to ask to deal with a “superior” of the person handling your

account and keep accurate information regarding the names of all persons (and their positions) involved with your claims.

- Before making a request, make sure that the person you are dealing with has the authority to grant it.
- Do not be intimidated.
- Do not hesitate to challenge anything that doesn't sound right to you.
- If you are unsure about anything, check with the State Insurance Department and then, if necessary, with a lawyer. If you do not think you can afford a lawyer, you may be able to get low-cost or free legal help. Try calling the local bar association to ask about legal aid (available through non-profit organizations in most major communities) or a local law school to ask if they have a student law clinic.
- Most states have nonprofit advocacy organizations that are dedicated to access and continuity of care issues and are able to discuss your legal rights and avenues for contesting insurance decisions on your behalf. You can search the Internet using words like: "insurance denials", "HMO", "continuity of care", or "healthcare access" along with "patient advocates." In California, Citizens for the Right to Know is an excellent resource.
- Set up and keep a file of all correspondence and phone communications relating to your claims. The file should include, but not be limited to: bills, payments, claims, letters you send, letters you receive, checks, contacts, and your policy.
- Be sure that all of your premiums are paid on time. You may have trouble getting insurance again if you let your policy lapse.
- Keep track of all of your unreimbursed medical expenses. You might be able to claim these expenses on your tax returns.

## **Medicare coverage**

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In the United States, Medicare starts at age 65 years for persons eligible to receive it. Medicare comes in several distinct parts. Part A covers hospital expenses, an optional part B covers doctor expenses and outpatient care, and an optional part D covers prescription drug expenses. Part A is free for Medicare patients, but it pays only 80% of hospital inpatient care and has a deductible. Part B charges a means-based monthly fee starting at \$170.10 in 2022 (deducted from Social Security benefits if they are being received), but it also pays only 80% of expenses and has a deductible. Parts A and B are called "original Medicare." Part D requires enrolling in a Medicare prescription drug

plan provided by a private company, which charges a monthly premium.

Because parts A and B pay only 80% of medical expenses, another part of Medicare, the missing part C, is designed to cover much of that 20% gap and lower deductible exposure. These are Medicare Advantage Plans, offered by private companies. A person must be in original Medicare before joining a part C plan. Medicare Advantage Plans often have monthly premiums (in addition to the part B premium), but many of these plans also include part D drug coverage as well as extra benefits, like vision, hearing, and dental coverage. Medicare Advantage Plans, however, typically operate with provider networks — that is, they are either HMOs or PPOs. That means that covered services will be less expensive to you as long as you see doctors or use hospitals that belong to the plan's network.

As an alternative to Medicare Advantage Plans, Medicare supplemental insurance (Medigap) policies are available from private companies to cover the 20% gap that original Medicare leaves. There are a variety of these supplemental plans, offering different benefits. These plans generally cost more than Medicare Advantage Plans, and they are not bundled with a part D prescription drug plan, which will have to be acquired separately. But supplemental plans do not attempt to limit the choice of doctors or facilities, exposing you to more expense if you choose to use doctors or medical care centers outside a plan's provider network.

As a brain tumor patient, you will need to seek out the best care possible for your brain tumor at a comprehensive cancer center — or at more than one center over the course of your treatment — wherever possible in the country. Consequently, if you are enrolled in Medicare, or will soon be, it might be prudent during the next annual enrollment period to seek out the best supplemental insurance (Medigap) policy you can afford because Medicare Advantage Plans are designed to limit choices to a preferred provider network. One place to begin a search for supplemental insurance (Medigap) policies is at the website of the American Association of Retired Persons (AARP) here:

<https://www.aarpmedicareplans.com/shop/medicare-supplement-plans.html>

## **Insurance Paperwork Organization**

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From an insurance standpoint, a brain tumor diagnosis could cover the gamut from surgery to lab reports, chemo, radiation, prescriptions (e.g., for anti-seizure meds, anti-

nausea pills), long term care, hospitalization, palliative/hospice care. Fighting a brain cancer often means touching everything medical.

The insurance and other paperwork might be overwhelming. If you can, find someone competent – like someone in the family or a trustworthy friend - who agrees to be in charge of dealing with the insurance paperwork and insurance companies. The one diagnosed with the brain cancer should not have to deal with any of it.

## Financial Matters

### The Costs Of Cancer Care

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Even with insurance coverage, cancer care can be expensive and result in financial hardship. Many people have insurance plans with yearly deductibles, specified amounts of expenses they must pay out of pocket each year before the insurance plan will begin paying any costs. After the yearly deductible is met, insurance plans also often require co-insurance payments. For example, with a typical 80/20 coinsurance rate, the insurance plan will pay 80% of approved medical costs while the patients must pay the remaining 20% of medical costs out of pocket. Finally, many insurance plans require co-payments. A co-payment is a set fee, like \$30, that an insurance plan requires the patient to pay out of pocket each time the patient visits a physician.

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The Musella Foundation runs a co-pay assistance program for people with health insurance for one or more of the following treatments: Avastin, Temodar, Lomustine (CCNU or Gleostine) and the Optune device. To find out about this program, go to: <https://braintumorcopays.org>.  
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Consequently, considering deductibles, co-insurance payments, and copayments, the amount of out-of-pocket costs for direct medical care — visits to physicians, surgery, radiation therapy, chemotherapy — can add up to a considerable amount even for patients with excellent insurance plans. But in addition to direct medical costs, there are also many nonmedical expenses associated with cancer treatment. These include transportation, hotels, meals, and childcare.

The Centers for Disease Control (CDC) determined in 2021 that out-of-pocket costs per person for medical services were highest in the initial and end-of life phases of care

for brain cancer, among a few other cancers. In the medical journal Neuro-Oncology Practice, investigators analyzed the out-of-pocket expenses for 43 patients diagnosed with malignant glioma between August 2008 and May 2012. Of these 43 patients, 35 (81%) were newly diagnosed with malignant glioma. The majority had private medical insurance, 10 (23%) had Medicare or Medicaid coverage, and 2 (5%) were uninsured.

The investigators found that the monthly median out-of-pocket expense for these patients was \$1342 (remember, the median is the middle value in a set of measurements, with half the values above that middle value and half below). Within that monthly median out-of-pocket amount, the highest components were payments for medication (\$710), hospital bills (\$403), and transportation (\$327). These expenses decreased after 3 months, suggesting that expenses were reduced after the completion of radiation therapy. The investigators also found that median lost wages were \$7500, and that median lost work time was 12.8 days.

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The American Society of Clinical Oncology sponsors a website for patients called Cancer.net. This website has an excellent section on financial considerations related to cancer care, including a video presentation. Especially relevant is the page entitled "Questions to Ask About Cost." Go to: <https://www.cancer.net/navigating-cancer-care/financial-considerations>.

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## **Financial Assistance**

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There are many organizations and even individuals that provide financial assistance to patients with brain tumors and their families. Miles for Hope, for example, provides flight assistance to those participating in clinical trial treatment. Other organizations might not provide direct help with expenses but can help reduce the costs associated with medical care. Angel Flight was created by a group of volunteer pilots to provide for free air transportation for medically related needs when time is important, but the trip is not an emergency. The organization called Mission4Maureen has funds to cover an array of expenses, from travel for treatment, to maintaining a place to live, to paying medical bills not covered by insurance.

The Musella Foundation runs two different programs to help you with treatment costs. For people with insurance, we have a co-pay assistance program for one or more of the following treatments: Avastin, Temodar, Lomustine (CCNU/Gleostine) and the Optune device.

For people without insurance, we have a Musella Foundation Drug Discount Card that can save everyone — not just patients with brain tumors — up to 80% or more off the cost of prescription medicines, over-the-counter medicines (that is, medicines not needing a prescription), and even prescription medicines for pets. There is no cost for the card, there is no risk in using it, and it is immediately available online, with no registration required. You take the card to your pharmacy and ask how much the prescription would cost using this card compared with how much it would cost without it. If using the card is less expensive for the prescription, then use it.

The Musella Foundation Drug Discount Card can also be used by patients who have insurance, but you cannot combine the discount this card provides with the discount your insurance provides. Sometimes the card discount will be greater than your insurance discount.

The Musella Foundation provides a Musella Foundation Drug Discount Card for all patients, but especially those patients without insurance. To get the card immediately, go to: [https://virtualtrials.org/Drug\\_Discount\\_Card.cfm](https://virtualtrials.org/Drug_Discount_Card.cfm)

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Table 1 on the next page provides a list of some of the organizations that can help you. As a reminder, if you receive Medicare or Medicaid benefits from the US Centers for Medicare & Medicaid services, you can also contact those agencies directly for help paying some of your health care and prescription drug costs. For Medicare call 1-800-Medicare (1-800-633-4227).

## Brain Tumor Guide for the Newly Diagnosed

**Table 1: Organizations that can provide financial advice and support**

Organization	Website	Description
Angel Flight Travel Assistance	<a href="http://www.angelflight.com">www.angelflight.com</a>	Arranges free air transportation for any legitimate, charitable, medically related need
CancerCare	<a href="http://www.cancercare.org">www.cancercare.org</a>	Offers financial assistance for cancer-related costs and co-pays, and professional oncology social workers can help guide to additional resources
Darren Daulton Foundation	<a href="http://www.darrendaultonfoundation.org">www.darrendaultonfoundation.org</a>	Provides financial assistance to those who suffer from brain cancer, brain tumors, and brain injuries
Drug Assistance Programs from Pharmaceutical Companies	<a href="http://www.cancersupportivecare.com/drug_assistance.html">www.cancersupportivecare.com/drug_assistance.html</a>	Lists pharmaceutical company programs intended to facilitate access to needed medications for patients who have financial difficulties and are not eligible for Medicare, Medicaid, or private insurance
Glenn Garcelon Foundation	<a href="http://www.glenngarcelonfoundation.org">www.glenngarcelonfoundation.org</a>	Gives grants to people with primary brain tumor of any type (malignant or non-malignant)
Medicare Rights Center	<a href="http://www.medicarerights.org">www.medicarerights.org</a>	Ensures access to affordable health care for older adults and people with disabilities
Mission for Maureen Travel Assistance	<a href="http://www.mission4maureen.org">www.mission4maureen.org</a>	Provides financial assistance to families burdened with the cost of brain cancer treatment. Financial aid is available for medical bills as well as child care, housing payments, utility bills, transportation, medication and other areas of assistance
NeedyMeds	<a href="http://www.needymeds.org">www.needymeds.org</a>	Maintains website of programs that help people who cannot afford medications and healthcare costs and provides a free drug discount card
Patient Advocate Foundation	<a href="http://www.copays.org">www.copays.org</a>	Provides financial assistance to patients, including those insured through plans like Medicare, for co-payments, co-insurance and deductibles required by a patient's insurer

## Social Security (When Unable to Work)

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If, as a result of a brain tumor diagnosis and treatment, you can no longer work, either temporarily or permanently, you may be entitled to Social Security benefits.

These benefits may be Social Security Disability Insurance (SSDI) and/or Supplemental Security Income (SSI).

There is a confidential online tool provided by Social Security that would be able to tell you what benefits you may be eligible for. You can access that tool at the link below. You just answer their questions about your situation and the tool will tell you what benefits may apply:

<https://ssabest.benefits.gov>

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In the case of a high-grade brain tumor, i.e., a Grade 3 or Grade 4 (including GBM), Social Security guidelines (as of this writing) provide for immediate approval for benefits. For that reason, there is no need to secure the services of an attorney to obtain benefits to which you are entitled. These benefits are automatic for high grade tumors and the application process is straightforward.

If a person has earned enough, they may qualify for SSDI, but if they do not have sufficient credits for SSDI, they can still apply for SSI. SSI is not dependent on any earnings history.

You can apply online or by phone. You should know that there is a 5-month waiting period before benefits will start, so you should apply as soon as they realize they cannot work.

It is not required but may speed up the process if you ask the doctor for a letter with the diagnosis to give to Social Security. When Social Security has a doctor's letter with the diagnosis specifically stated, the process seems to be given maximum attention.

You can begin the application with Social Security on-line at this link: <https://www.ssa.gov/applyfordisability/>

OR.... you can start the application process by phone. To do that, you would call 1-800-772-1213. Someone from Social Security will then follow up with a call to complete the application process.

## **Benefits for Children of Disabled Parent**

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As soon as your Social Security benefit is approved, if you have children at home, you should apply for benefits for them. Once you are approved, your children under age 18 (or 19 if still in high school) are eligible for benefits as children of a disabled parent.

## **Crowd Funding**

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Some individuals elect to obtain the funds they need to cover the expenses they incur for brain cancer treatment (e.g., travel to major brain cancer clinic, cost of drugs not covered by insurance).

It is advisable that prior to proceeding, you consider the taxable nature of any funds you might obtain. While some of these sites state that the money provided through their organization are “gifts” and are, therefore, not taxable, this declaration is not binding on the US Internal Revenue Service (IRS).

Crowd funding organizations usually send recipients 1099-Ks if the fund-raising campaign raised more than \$20,000 and had more than 200 donors, which may then attract the scrutiny of the IRS. The proceeds may end up being deemed to be taxable income, so you might want to get competent tax advice before proceeding.

## **Legal Matters**

### **Overview**

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It is important to have certain legal documents in place to protect you, your privacy, and your loved ones, and some of these documents you have been intending to put in place, but they were not a priority at the time. Now they are.

The first time you are admitted to a hospital, you will be asked if you have an Advanced Directive or a Medical Power of Attorney. Most people don’t. If the hospital offers to help you put some of these documents in place, do it and ask for copies and keep them in your binder.

Other ways of getting these documents in place is to access document drafts online for your specific locale (each State has different laws and forms). You may talk to a lawyer or the doctor's/hospital's social worker about how to get these documents in place.

If you do already have the documents in place of most concern to hospitals and doctors, bring them with you, and the staff will make copies for your files and return the originals to you.

## **Documents to Have in Place**

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Other than your Will, financial beneficiary statements, and Financial Power of Attorney, medical service providers will want to see all the rest of these documents:

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**Last Will and Testament.** Make sure your Will is current.

**Financial Beneficiary Statements.** Make sure you have a current designated beneficiary on any 401(k), IRA and life insurance policy. The Will does NOT govern these. If your beneficiary is still the friend you started a rock band with years ago in your garage, that friend will get the 401(k) or life insurance proceeds no matter what the Will says. Remember that accounts like 401(k)s, IRAs, and annuities can often just be re-named in the event of a passing so that someone inheriting those accounts might be able to minimize or avoid paying taxes on the amounts until withdrawn.

**Durable Medical Power of Attorney.** You should execute a Durable Medical Power of Attorney (Medical POA) so that someone you trust can make medical decisions in case you are not capable of making those decisions for yourself. (A power of attorney that is "durable" refers to the fact that the POA will remain in effect for your lifetime unless you revoke it, which you always can.)

It is very important to tell your family who you have designated to be your medical power of attorney and to tell them what your values are and what kinds of medical treatment you would want or not want, including breathing machines and feeding tubes, if your condition were to worsen and you were unable to communicate or were in a coma.

## Brain Tumor Guide for the Newly Diagnosed

Another reason for the Medical POA is that many doctors' offices, MRI centers, etc., will not let a family member fill out the medical history or other pre-procedure forms unless they are the designated Medical POA.

**HIPAA Disclosure.** In order to have enough information about your condition to be able to make good decisions under a Medical POA, whoever you designate under that Medical POA should be designated under a HIPAA disclosure.

Every doctor who treats you will ask you to sign a HIPAA privacy form indicating who you allow to know and discuss details of your case with that doctor (or facility). You will need to list each person by name (e.g., your spouse, parents, children and maybe a friend.) Ask for a copy of the completed form, as the original will be kept by the physician in each case. Having the copy of the executed HIPAA form will help save time when you need to send someone to pick up reports or films or to ask questions for you. When medical personnel tell you they cannot give your children something for you or talk about something to anyone other than you, having the copy of the HIPAA form available for them to see will enable them to meet your request without delay.

**Advance Directive.** You need to express how you want things handled if things get tough. Basically, an Advance Directive and Palliative Care counseling are needed. We all hate to think about these things, but it can save a lot of trouble later if you handle this now. An advance directive, also called a living will, tells your medical team what kind of care you would like to have if you become unable to make medical decisions for yourself. Such decisions include:

- Do you want to be resuscitated?
- Do you want aggressive treatment like ventilation and intubation?
- Do you want tube or intravenous feeding?

Most hospitals will not resuscitate or intubate a person with what is considered a life-threatening diagnosis like a high-grade brain tumor unless that person expresses this desire in writing.

If this very tough and delicate conversation is too much to take on by yourself, it can be facilitated by a social worker or other person experienced in handling these discussions with perhaps the support of clergy, if needed. The person designated under the Medical POA should be present to hear the responses so that he/she can execute your wishes.

- Best rule of thumb: Palliative Care Counseling should occur so promptly after diagnosis that you feel like it is a waste of time.
- In 2010, Massachusetts General Hospital found that patients with life threatening diagnoses who received early palliative care counseling stopped chemo sooner, entered hospice earlier, experienced less suffering at the end of their life, but lived 25% longer than those who received such counseling late (e.g., when ending treatment).

Durable Financial Power of Attorney designates a person of your choice to manage your finances if you become incapacitated and are unable to make financial decisions for yourself. Your financial power of attorney document should not contain any medical directives, which are covered in your Medical POA document. Standard Durable Financial Power of Attorney forms are available online or through an attorney. They are straightforward and easy to complete. If you have special circumstances, you may wish to consult with an attorney.

Please be aware that companies like cable TV, electricity, gas (for cooking/heating), water, etc. will not even speak to anyone else if those accounts are in your name - even if they are told you are in the ICU. You should consider either getting those accounts transferred or make sure you have a Durable Financial Power of Attorney in case you become unable to do whatever is necessary under those accounts.

## SURVIVOR STORY #3

I am now a seven-year survivor of my brain tumor. I remember being seated in the emergency department in May 2009 as a nurse pushed a sedative into my IV line to control my shaking before transporting me into the room with an MRI scanner. The CT image in front of me displayed a lesion that would later be diagnosed as anaplastic astrocytoma. At that moment, I was a 23-year-old biomedical engineer working for a medical device company, I had recently moved in with my girlfriend, and I had always been healthy. Everything changed; I became a cancer patient overnight.

The events following my diagnosis were a blur. After neurosurgery to remove the tumor performed with a procedure called an “awake” craniotomy — during which the neurosurgeon administered verbal tests to see what areas of the brain had been affected by the tumor — I began treatment, which included radiation therapy and concurrent chemotherapy with temozolomide (Temozolamide).

After that initial treatment, I began adjuvant therapy with temozolomide on the cycle of 5 days on, 23 days off. During adjuvant therapy I was fortunate to have no delays due to the emergence of side effects like neutropenia (an abnormally low count of a type of white blood cell).

Fast forward a year and one brain-tumor recurrence scare (a second opinion was invaluable in avoiding a second surgery), I found myself in a completely different state and city with my now fiancé starting medical school. I was looking for a job, continuing my temozolomide regimen, and trying to answer the ever-present question in my mind, “What do I want to do with my life?” Ironically, I had never been much for introspection before I was diagnosed, when my perceived “time” seemed to be in oversupply. The answer I came up with is that I wanted to matter — I wanted my life to have more meaning. That sounds a little ridiculous and dramatic, but that was truly how I felt. And so over the next year I began volunteering in medical clinics and mobile hospitals in underserved neighborhoods. Eventually this culminated in my decision to become a physician and provide care to those who are diagnosed with cancer. My motivation came from a strong desire to reciprocate the heartfelt compassion and support I received during the treatment of my brain tumor.

Six years later and a score of clean MRI scans, I have graduated from medical school and am now in the last year of my residency in the field of radiation oncology. I have found

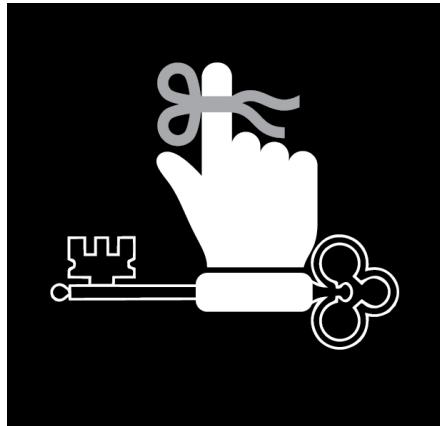
#### Four:Protecting Yourself And Family

fulfillment in life that I would not have had otherwise. The future is always uncertain, for cancer survivors and for everyone else, and I am still learning how to balance living for the moment with planning for the time ahead. Those diagnosed with a brain tumor may tread very different paths, but we are all survivors beginning on Day 1.

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## CHECKLIST OF TOP TEN FIRST THINGS



**Here is the Musella Foundation's most important first things checklist:**

- 1. BEST CARE.** Seek out the most advanced and the most specialized brain tumor care available to you.

**Facility:** Many smaller and local hospital systems may offer neurosurgery and treatment for brain tumors. However, these systems do not usually have the same state-of-the-art facilities, technologies, and doctors specializing in different tumor types that large brain tumor centers have. Even if that means travelling a distance from home, bear in mind that larger brain tumor centers will have (1) more advanced pathology facilities for diagnosis; (2) greater capacity for storing tumor tissue for future testing; (3) better familiarity with the latest surgical and treatment practices; and (4) more clinical trial options to offer.

**Doctors:** You should find the most experienced neurosurgeon and neuro-oncologist you can who specialize in the treatment of your type of brain tumor, and you should ensure your doctors team together to coordinate and administer the different types of treatment your brain tumor will require.

**Treatment Options:** Engaging with our Patient Navigation Program (described below) helps you learn more about your cancer and your treatment options.

- 2. BEFORE SURGERY.** Before surgery occurs, carefully consider various treatment options. There are some clinical trials that require registration before surgery of a

brain tumor occurs. In some trials, such as for certain types of immunotherapies, treatment begins before surgery. There are also treatments, such as Gliadel Wafers or GammaTiles, that can only be received at the time of surgery. For trials related to custom-made vaccines, the tumor sample obtained during surgery needs to be handled in a special way. Discuss your options with your neurosurgeon before surgery.

**3. OPTUNE/TTFIELDS.** Ask whether treatment with the Optune/TTFields' alternating electric-field therapy is available in your case. The Optune device, which treats brain tumors by delivering alternating electric fields called tumor treatment fields (TTFields), is a therapy approved by the US Food and Drug Administration (FDA) for newly diagnosed and recurrent glioblastoma (the most common type of primary brain tumor).

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In addition to being a non-toxic and a non-invasive form of treatment, a recent study conducted by the University of Florida has found that Optune/TTFields dually activates certain pathways (i.e., STING and AIM2) that drive early anti-tumor immune responses.

Not all treatment centers offer the Optune/TTFields and this cap is not appropriate for all patients, but it is worth the discussion with your doctor. A detailed description of this treatment can be found in the section entitled "Optune/TTFields Device" of this Guidebook.

**4. MOLECULAR TESTING.** Make sure your tissue sample, whether obtained by biopsy or surgery, is subjected to comprehensive molecular-marker testing. Ask your doctor if the extent of testing adequately supports treatment decisions now and in the future. If you are treated at a major brain tumor center, the sample of your tumor tissue may be tested for molecular markers that can guide treatment choices.

**5. TUMOR TISSUE PRESERVATION.** Ask your surgeon how your tumor tissue will be preserved. The preservation of your tumor tissue should be discussed with your neurosurgeon before surgery. Brain tumor tissue is commonly preserved by the formalin fixed paraffin-embedded method. A better alternative is for the tumor tissue to be flash-frozen in liquid nitrogen. One advantage of freezing is that the tumor tissue is preserved intact and can be later used to create personalized cancer vaccines.

**6. EDUCATE YOURSELF.** Read this guide and visit the [virtualtrials.org](http://virtualtrials.org) website. In

the “Learn About” section of the website, there is an archive of articles called “Note-worthy Treatments.” In the “Interact” section, there is a video library of talks and presentations on all things brain-tumor related. You can also subscribe to our “Brain Tumor News Blast,” which carries news stories about brain tumors: <https://virtual-trials.org/maillist.cfm>.

**7. JOIN A SUPPORT GROUP.** The Musella Foundation operates online discussion forums covering numerous brain tumor topics. Additionally, Facebook has many brain tumor groups. Some of our favorites are:

Clinical Trials & Noteworthy Treatments For Brain Tumors,  
Novocure, Optune Support For Glioblastoma,  
Glioblastoma - GBM SURVIVORS TO THRIVERS!, and  
Surviving Glioblastoma (GBM).

The website addresses for all these and more can be found in the section of this Guidebook below entitled “Support Groups.”

## **8. THE PAPERWORK.**

**Get organized:** Request, record, organize and keep all brain-tumor-related documents and information. Request all documents related to your diagnoses and treatment, including all pathology reports, and keep these documents organized in a binder. This binder can also contain whatever notes you take along the way. You may also consider making audio recordings (e.g., on your cell phone) of appointments with your doctors for future reference and review. It might also be good to bring a friend or family member with a good memory to all medical appointments.

**Execute the Documents:** Think about and sign such necessary legal documents as an advance directive, a durable medical power of attorney, and a durable financial power of attorney.

**9. DESIGNATE A SUPPORT TEAM.** Receiving a diagnosis of brain tumor is an exceptionally emotional and confusing situation. Unless you are especially skilled and motivated to do your own medical research, it may be best to designate a friend or family member to research treatment options and all things tumor-related on

your behalf. Please give this person this Guidebook to read and direct him or her to the virtualtrials.org website. Another person might be designated to relay news to your larger network of family and friends.

**10. INSURANCE.** Upgrade your insurance and know that some financial support is available. Upgrade to the best medical insurance that you can afford. If you are enrolled in Medicare, seek out the best supplemental policy you can afford but avoid Medicare Advantage Plans because they limit the choice of doctors. The Musella Foundation runs a co-pay assistance program for people with insurance to help with expenses related to the Optune/ TTFields device and several common chemotherapy treatments. For people without insurance, the Musella Foundation offers a Drug Discount Card that gives discounts for prescription and non-prescription medications.



# Brain Tumor Guide for the Newly Diagnosed





## Treatments Overview

### General

Newly diagnosed brain cancer is treated in accordance with a well-established Standard of Care protocol as described below. This protocol was established in 2005 and adopted by the worldwide neuro-oncology discipline following the release of a landmark study headed by Dr. Roger Stupp, a Swiss doctor who currently practices at Northwestern University in Illinois.

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Dr. Stupp's study demonstrated a statistically significant survival advantage to those individuals newly diagnosed with GBM, while affording only minimal additional toxicity. That study employed the use of a chemo drug called Temozolomide (commonly referred to as Temodar) concurrent with radiation of the tumor site.

This protocol applies to adults with a cancerous tumor; it excludes pediatric cases. It is also important to note that there is no set protocol for the treatment of brain cancer in those 70 years old or above. Despite so many elderly people making up the bulk of brain cancer cases, medicine remains fluid about how to best treat them; doctors will examine all factors including such matters as the person's physical frailty and cognitive functioning, as well as the scope of the disease and may decide to tailor the Standard of Care to the person.

It is likely that you have heard of the term "clinical trial" and have recognized that the most advanced treatments are accessible through such a trial. You should be aware that all clinical trials have qualifying requirements and that many, but not all, clinical trials require the completion of the Standard of Care protocol.

There are nearly a dozen cancer treatments approved by the FDA for brain cancer, hundreds of clinical trials at countless locations throughout the US, any number of possible combination therapies, plus more than 150,000 new cancer treatment articles published each year. The neuro-oncologist will present you with selected options he/she believes may work, but there may be other options at other locations.

The latest anti-cancer targeted therapies and immunotherapies are directed at the genetic DNA mutations that underlie the development and progression of brain cancer. Most high-grade patients have 3 or more actionable mutations affecting key cancer regulatory networks including mitogenic signaling pathways, DNA-damage repair pathways and cell cycle checkpoints. Nearly half of GBMs have alterations in DNA-damage repair genes.

Clearly, you need to know the best options for your specific case so that you can make the best treatment decisions possible. You can make these decisions yourself or with your support team, or you can access the Musella Foundation Patient Navigation Program, described below, to help you make these complex decisions at no cost.

## Patient Navigation Program

### **Program Overview**

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The Musella Foundation has joined forces with Cancer Commons and xCures, the Foundation's for-profit spin-off company, to form a world-class cancer learning network and service to patients.

xCures' platform takes all the currently available knowledge about brain cancer treatments to help individuals quickly find promising treatments. This service is provided to individuals at no charge.

When you consent to participate and give access to your medical records, xCures will provide you with a concise, easy to understand graphical summary of your cancer journey and a personalized list of treatment options. These options include the rationale for each suggested treatment option.

Both the summary and the treatment options will be produced using the Artificial Intelligence software called xINFORM. This software uses data from experts, the

medical literature, virtual tumor boards, the Musella Foundation's Virtual Trials registry as well as xCures patient registry.

You can print and share the Cancer Journey, Options Report, and the treatment rationales you will receive. This will allow for more effective and efficient discussions with your neuro-oncologist.

In addition to receiving data to benefit them, patient participation will benefit others. The data patients share with other brain cancer patients on the xCures platform will enable collective learning from each other in real-time. That information then helps others, just as their information helps you.

## **How to Access the Program**

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The Musella Foundation can guide you through the consenting process and submission of your medical records, help you understand your treatment options, and facilitate access to those treatments through clinical trials and expanded access programs.

**To get started, please visit this site, and click on the "Get Report" button:**  
<https://virtualtrials.org/xcelsior.cfm>

## **Privacy Protection**

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When entering the program, you will be asked to register, consent, and submit your medical records. You can submit the records manually, or if it is easier, give the Musella Foundation the login credentials for your medical portal and they can import and organize the records for you. We will do this periodically with no work on your part.

I know we are told never to give your username and password to anyone, but this is different. It is for your benefit, as well as the benefit of all other brain cancer patients accessing this Program.

We promise to treat your records confidentially. No one outside of the Program col-

laborators will be able to see any personally identifiable data. Outsiders may be able to see deidentified aggregate data.

## **Service Levels of the Program**

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There are two levels to the Program. The first level is the collection and analysis of your medical records and generation of your personalized treatment options report. For some patients that is all they need.

For others, there is a second level of service through Cancer Commons, which is available upon your request. In this level of service, a live person will explain the choices on the report, help you decide, and help you get into a trial or get access to a treatment.

There is no charge for either level of service, but Cancer Commons may make a request for an OPTIONAL donation.

For those wishing a higher level of personalized services, Cancer Commons offers such services for a fee.

If you are uncomfortable with any part of the registration process or have any questions contact Deb Christensen MSN, APRN, AOCNS, OCN, Oncology Patient Navigator at Cancer Commons at 650-448-7968 or email her at: deb.christensen@cancercommons.org .

## **Treatment Development Challenges**

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It is recognized that brain cancer needs more treatments and therapeutics. These needs are being addressed in the research labs throughout the world that are working constantly to produce a wave of better treatments and therapeutics.

Among the perplexing challenges faced by researchers is the fact that cell lines and tissue culture plates are not the same environments as the cancer itself, and animal models are not able to adequately mimic the disease in humans. As a result, advances in research technology are increasingly focused on modeling - either in vitro or by computation. These processes require a more profound understanding of the brain's environment such as the tumor-stroma interactions including neural tissue, extra-

cellular matrix, the blood-brain barrier, astrocytes, and microglia.

Just by way of one example, the blood-brain barrier ("BBB") has been the nemesis of many promising cancer drugs. The human brain is encased not only in a boney structure but is protected by the BBB which is a highly selective network of blood vessels and tissue that keeps harmful substances from entering the brain. The BBB will allow certain substances like water, oxygen, carbon dioxide, and general anesthetics, pass into the brain. However, it keeps out bacteria and other substances, such as many drugs intended to treat brain cancer. Researchers are now turning to nano-particle technologies as a way of producing treatments that will be more effective against brain cancer, thus finally defeating the interference of the BBB.

## NCCN Guidelines for Treatment

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The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 31 leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of care so that patients can live better lives. The NCCN issues peer-reviewed and consensus-based guidelines— based on published medical evidence and expert opinion — about what is the best treatment for typical patients with newly diagnosed or recurrent brain tumors.

The standard-of-care treatment for high-grade glioma that is described in this Guidebook is based on the NCCN Guidelines which was issued June 4, 2021. The NCCN Guidelines represent a general standard of care, although there may be some variations in “standard” treatment among the participating cancer centers.

- To access the NCCN Guidelines, please go to this website:  
<https://www.nccn.org/patients/guidelines/content/PDF/brain-gliomas-patient.pdf>
- You may have to register before downloading the guideline.

In the NCCN Guidelines, treatment of newly diagnosed high-grade malignant glioma is determined on the basis of three different characteristics:

- The person's age (70 years old or younger and older than 70 years), and

- The person's Karnofsky Performance Status (KPS) score (See the Section entitled "Karnofsky Performance Status" for details), and
- The tumor's methylated (favorable) versus unmethylated (unfavorable) promoter status. (See the Section entitled "Modification of MGMT Gene and Methylation" for details.)

The recommended NCCN treatments for primary malignant brain tumors can be found in the Journal of the NCCN. This Journal is a peer-reviewed, medical journal read by 25,000 oncologists and cancer care professionals and is the official journal of the NCCN. The Clinical Practice Guidelines can be accessed at this link:

<https://jncnn.org/view/journals/jnccn/18/11/article-p1537.xml>

By way of a summary, for every category of brain cancer patient, the NCCN recommends enrollment in a clinical trial. The next most common treatment recommendation after surgery consists of:

- Standard radiation therapy
- Oral chemotherapy with temozolomide (Temozolamide) during radiation therapy (which is called concomitant therapy) and then after radiation therapy (which is called adjuvant therapy)
- Alternating electric field therapy (the Optune/TTFields device) after radiation therapy (as an adjuvant therapy).

Each of these are described in Sections that follow.

Because patients newly diagnosed with high-grade malignant glioma will be seen by multiple different medical specialists, the NCCN strongly recommends close and regular communication among all medical service providers across the different medical disciplines involved, including physical and occupational therapists, psychologists, and social workers. Bear in mind that this type of interaction is more likely to occur at comprehensive cancer centers and at hospital systems with established brain tumor boards.

The virtualtrials.com website hosts a video library, with up-to-date videos from medical and patient brain tumor conferences that cover all aspects of brain tumor treatment, from radiation therapy to the latest chemotherapeutic drugs. To view a menu of these videos and to start watching them, go to: [www.virtualtrials.com/video.cfm](http://www.virtualtrials.com/video.cfm).

## **Standard Of Care (SOC)**

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Below are the current standards for care. If the applicable standard-of-care treatment is not offered to you, you should ask why not. If cost is the barrier to receiving any part of this standard-of-care treatment, contact us. The Musella Foundation has a co-payment assistance program that may be able to help you in some circumstances with your out-of-pocket expenses.

If the diagnosis comes back as a Grade 2, the doctor will decide what treatment protocol to follow depending on the specific type of tumor, its location, symptoms, and other factors.

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If the diagnosis comes back as a Grade 3 or Grade 4, the Standard of Care (SOC) treatment consists of:

- **Surgery** to the extent possible. (See the Section entitled "Surgery" for detailed information.). Surgery is followed by a period, usually a month, to enable the incision to heal.
- **Radiation with concurrent chemo.** In most cases, radiation will be administered daily (except for weekends) for approximately 6 weeks. Radiation is provided concurrent with a low dose of a systemic chemo called Temozolomide ("Temodar" or "TMZ"). Statistically, through numerous studies, use of Temodar in conjunction with radiation has been shown statistically to be the best initial treatment. For more information about radiation, see the Section entitled "Radiation" and for more information about the chemo Temozolomide, see the Section entitled "Temodar".)
- **Maintenance Chemo.** Following radiation, you may be prescribed a maintenance dose of Temodar which you would take 5 consecutive days out of every 28 days.

- **Optune/TTFields Device.** Certain studies show that use of the Optune/TTFields cap which treats brain tumors by delivering alternating electric fields, enhances the outcome of radiation and chemo. Not every tumor is located where this cap is useful, but where it is and if the person is diligent in use, the Optune/TTFields cap can help fight against the disease.

Although the above standard-of-care protocol has been found in clinical trials to extend survival time after the diagnosis of high-grade malignant glioma — sometimes considerably — nevertheless it only actually “cures” brain tumors in a relatively small number of persons. For that reason, all persons newly diagnosed with high-grade malignant glioma should consider enrollment in a clinical trial of an experimental therapy. Clinical trial enrollment can occur at the very start of your treatment, or it can occur later. Clinical trials and their importance are discussed in the Section entitled "Clinical Trials."

## **Considerations Regarding SOC for High Grade Tumors**

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Many patients upon hearing a high-grade tumor diagnosis want the doctor to order up the strongest, most potent chemo to "blast" the disease away. While the sentiment is understood, there are ramifications that do not make that strategy workable. All treatments have side effects, and a protocol of maximum strength is likely also to be highly toxic and wear the patient's underlying health out. Given that 80% of all previously treated GBMs are expected to regrow and many Grade 3's also regrow, treatment strategies are designed to combat the disease AND protect the health of the patient to the maximum extent.

For that reason, neuro-oncologists prefer to administer a generally tolerable chemo to control the disease immediately after diagnosis. Temozolomide (Temodar) has been used as the standard treatment for newly diagnosed GBMs since 2005. This chemo limits the amount of toxicity from treatment and preserves the patient's health for ongoing and future treatment.

Medicine, however, does apply the research developments for many second line treatments for GBM (subject to other factors like patient age, condition, anticipated responsiveness to treatment, etc.). There is an ongoing emergence of targeted treatments for GBM, and these are reflected in the clinical trials being conducted at the

major brain cancer clinics.

## General Treatment Considerations

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When discussing treatment options with your doctor, you should understand that treatment is evolving. Traditionally, surgery has been the mainstay of treatment for most cancers. More recently, as it relates to benign and low-grade tumors, there has been a movement toward "watch and wait" rather than immediate surgical intervention. In some cases, watching rather than treatment is enough. Some tumors present few, if any, symptoms and cause few problems with little or no pain. They may even remain inactive for long periods of time. Treatment in those cases usually do not enhance your quality of life. Treatment options vary. Learn about your disease and the approaches commonly used to treat it.

Some tumors respond better to radiation, others to chemotherapy or hormonal treatments. Some require one type of therapy, others a combination.

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High grade tumors are aggressive and are assumed to cause major problems. Aggressive medical intervention in those cases is warranted.

Ask what would happen without any treatment and compare the answer with the expected results of treatment.

Not all cancer treatments have disrupting side effects; those that do are often predictable. Your doctor can outline a plan to prevent many side effects and otherwise treat or lessen others. In general, side effects are reversible, and helping you cope with them should be a focus of your doctor.

Take the potential side effects into consideration when choosing a treatment, but also know that most aren't as bad as you've heard. Ask your doctor what you can expect, for example:

- How sick are you going to be?
- How much energy are you going to have during treatment?
- If you work 50 hours a week now, will you be able to work 50 hours a week during treatment? Will you be able to work 20 hours?

Find out the answers to these and other questions you have. Treatment is your decision.

## **Family/Friends Considerations**

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You will have to decide the role your family and friends can play. They may have the best of intentions, but family and friends may overwhelm you with their research efforts. And they can be overly enthusiastic in advocating aggressive treatment when they don't fully understand the side effects and outcomes.

However, friends and family are crucial to supporting the best outcome. Numerous studies have correlated best cancer outcomes with social contacts. But know your limits. It's OK to take a rest and regroup. You set the priorities and your limitations.

## **Work Considerations**

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Many people can work during treatment following surgery and radiation provided that their work schedule allows for their doctor visits and their reaction to the treatment is not so overwhelming that it interferes with their ability to work.

- .....
- Many employers are required by law to change your work schedule to meet your needs during your cancer treatment.
- Talk with your employer about ways to adjust your work during treatment.
- You can learn more about these laws by talking with a social worker that may be part of the staff at your doctor's office.
- .....

Additionally, under the Americans with Disabilities Act (ADA) those diagnosed with cancer have certain rights if they are applying for work, if they wish to keep their cancer diagnosis confidential, and if they need accommodations at work for periodic breaks or a change in schedule. The ADA is administered by the US Equal Employment Opportunity Commission which publishes guidance for dealing with cancer in the workplace. That guidance can be found at this link:

<https://www.eeoc.gov/laws/guidance/cancer-workplace-and-ada>

## **Financial Considerations**

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For help paying for medications that insurance does not cover, two resources are available:

- NeedyMeds, a nonprofit information resource devoted to helping people in need find assistance programs to help them afford their medications and costs related to health care: [www.needymeds.org](http://www.needymeds.org).
  
- The Musella Foundation co-pay assistance program can help patients pay for one or more of the following treatments: bevacizumab (Avastin), Lomustine (Gleostine or CCNU), temozolomide (Temozolamide), and the Optune/TTFields device: [www.braintumorcopays.org](http://www.braintumorcopays.org).

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## **Quality of Life Considerations**

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It is reasonable to consider your quality-of-life goals when considering treatment.

All treatments have side effects and brain tumor treatments have to be as aggressive as the disease itself. Unlike normal, off-the-shelf medications one might buy at a retail store, the side effects for brain tumor treatments can arise more often than not. It is highly recommended that you have a discussion with your doctor about what side effects you can expect and then reach an agreement with the doctor about what you are, and are not, willing to tolerate.

Absent a frank and open conversation with the doctor, the doctor is professionally bound to place the highest priority on managing the disease with a lower priority on quality of life. This does not mean quality of life is unimportant to the doctor. It simply means that given a choice between extending life by even a little bit or avoiding a treatment that may reduce a person's mobility and produce joint pain, the doctor will choose to extend life.

If, however, mobility is as important to you as extending your life, then the doctor needs to know that to see what adjustments, if any, can be made to the treatment protocol.

Understanding what side effects to expect and what benefits the treatment offers will help you avoid wondering why you are getting certain treatments should the side effects become manifest.

The goals of therapy can vary, and only you can decide what side effects you're willing to accept to achieve them. If you're a young person with a curable disease, you may be willing to tolerate very severe, short-term side effects for a chance of eliminating your disease. But if you are 85 and have an incurable disease, you may decide not to accept bad side effects if the goal is to live only an additional month or two.

Ask your doctor what the treatment is expected to accomplish. For example, the doctor's statement that treatment will increase survival by 50 percent sounds great. But if 50 percent means increasing life from eight weeks to 12 weeks, and those remaining weeks are spent vomiting and battling nausea, weakness, and fatigue, maybe you haven't gained much.

## **Making Hard Treatment Decisions**

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From time to time, you may find yourself in the position of having to make some very hard choices. For example, the MRI says that tumor is probably progressing, and the medical team recommends surgery with a certain clinical trial drug administered during surgery. But the trial is not going to open up for a month. Do you wait for the trial or do the surgery now to stop the growth of the tumor?

Here are some pointers for how to make tough treatment decisions:

- **What does your doctor/medical team recommend?** Having enough support and advice to make a choice is important. Do you even want to make the decision? Or do you prefer to leave the decision up to your medical team? If you want to make or contribute to the decision, continue reading...
- **Does your hospital have a health decision aid** you could use? Some top hospitals have a written decision aid you can use to help you to weigh the important factors and make your decision.
- **Gather the facts (even if you have to push your doctor some).** Examples:
  - What are the progression free and overall survival statistics for the treatment options? Were the studies done relevant to someone of your age, your diagnosis and your brain tumor's genetic make-up?
  - Are there any other options you should consider?
  - What are all the eligibility and disqualifying criteria for trial enrollment?
- **Learn the benefits and risks** of each option. Decide which of the benefits matter the most to you.
- **Be prepared for trade-offs.** Example: The good news is that a certain drug has a great progression free status, but the bad news is that it might give you non-stop diarrhea for a month. Be very clear about what you will tolerate and what you won't.
- **Listen to your emotions.** "Gut feels" really have validity. We process a myriad of factors subconsciously. We have to be careful that we are not swayed solely by how we feel, but it is reasonable to consider how we feel instinctively.

## **Long Term Treatment Side Effects**

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In the past, the consequences of long-term side effects were never a big concern because people with newly diagnosed high-grade malignant gliomas did not live

long enough for them to be a concern. Fortunately, there has been a steady rise in the number of long-term survivors of brain tumors, largely due to the success of the standard-of-care treatment described in this section. Now long-term side effects have to be considered when choosing a treatment.

Radiation therapy can cause vascular injury and increase the risk of stroke. Unfortunately, stroke is fairly common among long-term survivors of brain tumors and can be either completely asymptomatic or completely devastating, depending on the location. The possibility of stroke can be reduced by managing risk factors. Please talk to your doctor about stroke risk. Another long-term side effect of radiation therapy is cognitive loss, which varies with the dose of radiation and the volume and location radiated. Cognitive loss is nearly universal with whole brain radiation. These side effects can be minimized by limiting the treatment to only the site of the tumor and a small margin around the tumor.

Chemotherapy is often associated with long-term infertility, but you can offset this side effect by freezing sperm or eggs before chemotherapy begins. Fertility may be the last thing you are worried about now, but what happens if you want kids in a few years and cannot have them? Think about it.

There are also rare cases of myelodysplasia or “preleukemia” conditions related to chemotherapy, particularly in association with alkylating agents like temozolomide (Temodar). So, although the optimal duration of temozolomide treatment remains unknown, staying on the agent forever could increase the associated risk. More research is needed on this question.

## SURVIVOR STORY #4

My brain tumor story began in late 2006, when I suffered a series of debilitating seizures. Such symptoms would typically result in emergency treatment, but my case was complicated by the fact that I had suffered from epilepsy since childhood. It had been kept under control with medication, and by 2006 I had been seizure-free for years. Nonetheless, my physicians attributed these new seizures to my old epilepsy condition. Medication was increased but the convulsions grew progressively worse. One day in early 2007, I awoke to find the right half of my face paralyzed, with generalized stiffness on the right side of my body. My wife took me to the emergency room. I underwent a CT scan, which showed a large tumor in my left frontal lobe along the motor strip.

In February 2007, I had a total resection. Before the operation, the surgeon had requested my permission to be as aggressive as possible (permission I granted) but warned me to be prepared for deficits, including the possibility of paralysis of one side of the body. In reality, my only postoperative deficits were similar to the preoperative ones: facial paralysis, right-side weakness, and minor aphasia. These problems gradually improved in the weeks, months, and years following the operation.

I was sent home to await the pathology report, which arrived within a few days. The diagnosis was glioblastoma, a conclusion confirmed by two other laboratories, which independently analyzed the tumor tissue on paraffin slides. I received the usual prognosis for this disease: almost certain recurrence within 1 year, with slim odds of surviving more than 3 years. Molecular testing reported that the MGMT status of my tumor was unmethylated, meaning that my tumor was less likely to respond to chemotherapy with alkylating agents like temozolomide (Temozolamide).

I sought out therapeutic options. At that time where I lived abroad, what is now the current standard-of-care therapy for glioblastoma was not widely applied. But I found and read the famous paper by Stupp et al entitled "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma," which showed benefit for concurrent administration of daily temozolomide during a 6-week period of radiotherapy followed by adjuvant therapy with temozolomide. I found two radiation oncologists who were willing to offer this therapy to me, and I got started immediately. Even before the radiation phase, I had begun to read everything I could find about brain tumors, searching for ways to improve my survival probabilities. The website PubMed ([www.ncbi.nlm.nih.gov/pmc/](http://www.ncbi.nlm.nih.gov/pmc/)), the

## Brain Tumor Guide for the Newly Diagnosed

US National Library of Medicine index of medical articles published worldwide, was an invaluable resource. At some point I stumbled on the Musella Foundation virtualtrials.org website, which also provided me with substantial information about my illness. I found Ben Williams's story on that website to be particularly interesting and the logic behind his treatment approach compelling. I read Ben's book and his periodic updates, which led to an exchange of email, followed by several telephone conversations. Throughout my ordeal Ben has been an invaluable source of knowledge and support for me, as he has been for many other patients.

I was in the fortunate position of having had a total resection of my brain tumor. However, I was aware that the odds of recurrence within 1 year were extremely high, and that a recurrent tumor is more difficult to control than a newly diagnosed tumor due to its acquired resistance to first-line therapies. My goal, therefore, became that of postponing a recurrence for as long possible and to do so by all means at my disposal. The approach was along the lines of that advocated by Ben Williams: to block multiple tumor growth mechanisms by means of a "cocktail" of agents that have shown some evidence of efficacy against glioblastoma or other types of cancer.



During the 6 weeks of radiation, I had ample time to start planning for the next treatment phase. My oncologist proposed 8 28-day cycles of temozolomide on the standard schedule of drug administration on days 1 to 5 of each cycle followed by 23 days off. I had read that this schedule provided limited benefit for someone like me,

whose tumor MGMT status was unmethylated. But there were some positive reports of experiments using a low dose daily (metronomic) schedule, in which MGMT methylation status had less of an effect on patient outcomes.

Based on this argument, I lobbied my physicians to try the metronomic schedule, and they said that they would consider it. In 2007 the drug bevacizumab (Avastin) was becoming popular as an experimental treatment for recurrent glioblastoma. Bevacizumab is an anti-angiogenesis drug that inhibits the growth of new blood vessels to feed the tumor. Based on positive results from various early studies, I wanted to add bevacizumab to the proposed metronomic therapy for temozolomide. This highly anti-angiogenic approach was attractive to me because it had the potential to forestall recurrence by delaying the growth of blood vessels in the tumor area. I discussed the idea with some prominent neuro-oncologists around the world and received encouragement from many quarters. Physicians at one particular comprehensive cancer center were particularly enthusiastic and generously offered to write letters of support for my plan. With help from a researcher, I drafted a proposal for my bevacizumab/metronomic temozolomide treatment plan, which I presented to my oncologists. They were interested in seeing whether such a treatment plan could work in a case like mine. Provided that I sign a consent form, they were willing to send the proposal through the hospital's internal review board, which approved it as a one-person experiment.

Things were looking good, but I wanted to pursue a more aggressive strategy. I added chloroquine to the therapy, after reading papers that showed that it improved results for chemotherapy. I likewise included verapamil, which could potentially inhibit extrusion of chemotherapy agents from cancer cells and help prevent multidrug resistance. Another addition was aspirin (200 mg/day), mainly as a prophylactic against blood clots from bevacizumab, but it had potential anti-cancer benefits in its own right. The drug celecoxib was also included early on due to promising results from small clinical trials for brain tumors and other cancers. Before going further, I compiled a list of 60-plus agents that could potentially contribute to the therapy, which fell into three categories: (a) they had shown efficacy against some form of cancer, either in clinical or preclinical settings; (b) they had been shown to be synergistic with chemotherapy or other substances already in my therapy; or (c) they had demonstrated positive effects in building up the immune system. The list was eventually refined to 27 substances, many of which were natural supplements, for example, green tea extract, fermented papaya extract, omega-3 fish oils, resveratrol, melatonin, mushroom extracts, selenium, and so on. With minor exceptions, my MRI scans have been clear since the summer of 2007. There were a few scares during

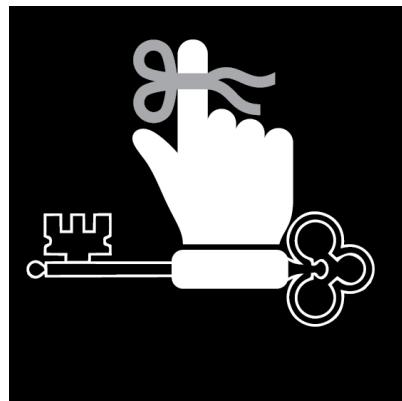
the first 2 years, with images showing small degrees of enhancement in and around the tumor cavity. But these abnormalities, which could indicate recurrence, were likely due to radiation damage. In any case they have disappeared over time. I now get yearly MRI scans, and no changes have been noted for many years.

Note that if I had to go through this again, I would alter many of the details in my treatment plan based on discoveries made in years subsequent to my diagnosis. I would not, however, change my treatment approach — that is, to battle the tumor aggressively using multiple agents simultaneously, thereby inhibiting as many growth pathways as possible.

It has been over 9 years since my diagnosis without any signs of recurrence. After I have passed the 10-year survival point, I will switch from once-per-year to every-other year MRI scans. I still believe that my approach was the most effective way to treat a glioblastoma. For other patients with brain tumors, I thus advise the following:

- Become as educated as possible about this disease and participate in formulating your treatment plan to the best of your ability.
- Make your voice heard.
- Never be afraid to ask questions or offer suggestions, based on what you have learned from other sources (including other patients).
- Finally, if you feel like your input is being ignored, find another physician who will listen to you.

## KEY TAKEAWAYS TO REMEMBER



The current standard-of-care treatment for newly diagnosed high-grade malignant glioma consists of 4 different treatments, depending on patient and tumor characteristics: (1) surgery; (2) radiation therapy; (3) systemic chemotherapy with temozolomide during radiation therapy and then after at a maintenance dose; and (4) alternating electric field therapy (the Optune device) after radiation therapy.

If the standard-of-care treatment is not offered to you, ask why not.

Use the Optune website to find doctors who are trained in administering the device.

Make certain that the members of your medical team are experienced in the treatment of your specific type of brain tumor.

Enroll in the Patient Navigation Program to explore all your treatment options. To get started, please access this link: <https://virtualtrials.org/xcelsior.cfm>

Using the questions in this book as a guide, prepare your own list of questions, being sure to ask the members of your medical team about your treatment options.

Consider entering a clinical trial.

# Brain Tumor Guide for the Newly Diagnosed





## SURGERY

### Overview

Surgery is one of the main treatments for brain tumors. In many cases, brain tumors can be removed by surgery and surgery may actually "cure" some low-grade tumors. For high-grade tumors, surgery alone is not a cure, but it does buy time for other treatments to work and offers a lot of opportunities. For example, a tissue sample from surgery can be analyzed for the molecular contents of the tumor and be tested for resistance to certain drugs. This analysis may point to specific treatments that will best manage the disease. In addition, there are some therapies that require prior surgery and removal of the tumor to make use of the tumor tissue in producing a personalized treatment.

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A well-performed surgery is the #1 contributor to the best outcome when a cancerous tumor is first diagnosed. A 2020 study led by the Johns Hopkins Kimmel Cancer Center found that, among those diagnosed with the most aggressive form of brain cancer, median survival after diagnosis was 8 months for those who had a biopsy but no surgery; 11 months with partial tumor removal; and about 16 months for those whose tumor was completely removed.

Additionally, in high-grade tumors, a good surgery will increase the response to chemo and radiation. This is why one of the single most important decisions you have to make is WHERE and by WHOM you will have brain surgery. A more experienced neurosurgeon may consider relatively easy what another neurosurgeon might consider "inoperable" (see the section below for the definition of "inoperable"). If you have been told your tumor is "inoperable", it is a wise idea to obtain a second opinion from another neurosurgeon.

The use of surgery varies by brain tumor type and location. Some brain tumors are easily separated from the healthy tissue of the brain and are in an accessible area where surgery can be recommended. Other tumors, particularly cancerous ones, may have extensively invaded healthy tissues and would prove to be difficult to safely separate and remove. Additionally, some patients are not candidates for surgical resection because the tumor is located next to critical brain structures, such as those responsible for the senses or for speaking, or because the patient is in poor medical condition. A highly qualified neurosurgeon is able to evaluate all these factors and determine the appropriateness of surgery.

## **Need for Expertise**

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When it is appropriate, surgery is performed by a neurosurgeon. Neurosurgery as a profession runs the entire length of the central nervous system - from head to the bottom of the spine. Certain neurosurgeons are experts at certain forms of surgery to be performed around the head and others perform interventions on the spine. A general neurosurgeon may not have adequate experience in the removal of brain tumors and may be less informed regarding current treatment therapies. Because most neurosurgeons do not see many brain tumors, you need to find one that specializes in brain tumors. The website of your selected treatment facilities should list all the neurosurgeons practicing there; carefully review their expertise to make sure that "brain tumors" is listed as one of the main areas of expertise.

Within the group of neurosurgeons who deal with brain tumors, you want to find an expert. An "expert" neurosurgeon is one who performs a minimum of 25 surgeries per year. Typically, these neurosurgeons are associated with major brain tumor centers. Studies indicate that major brain tumor centers and/or surgical teams that perform 50 or more surgeries a year achieve better survival rates with fewer complications. In brain surgery, experience matters A LOT. Neurosurgeons who have operated on many similar tumors can usually remove more of the tumor, with fewer side effects, than neurosurgeons who have operated on only a few tumors. They are also much more likely to have access to and training on the latest high-tech surgical tools.

While there are over 4500 neurosurgeons in the United States, only 125 (approximately) are considered experts in the removal of brain tumors. Because choosing an experienced neurosurgeon can greatly affect the quality of tumor removal and your recovery, finding an expert and getting a second opinion about which neurosurgeon

to choose is vital.

Only an expert neurosurgeon can assess how much of the tumor is considered operable. Any tumor can theoretically be removed, but a skilled neurosurgeon uses his or her experience to make a judgment on the risks of removal versus the benefits of removal. Each brain tumor is different, and the neurosurgeon can usually predict if — and how much — neurological damage will occur if the brain tumor is removed. Since surgery of high-grade brain tumors is not a cure, sometimes brain tumors are considered inoperable if the expected neurological damage arising from the surgery would create unacceptable problems for the patient.

However, keep in mind that some neurosurgeons may be overly aggressive. Discuss the expected risks of the surgery to make sure your neurosurgeon understands your views on how aggressive you want him or her to be.

If your tumor is considered truly “inoperable,” you may be offered alternatives to surgery, such as stereotactic radiosurgery as described under the Radiation section of this Guidebook. These techniques are generally available at a major brain cancer clinic.

## Selected Definitions

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Some terms unique to brain surgery follow:

**Craniotomy:** The most common type of brain tumor surgery. A craniotomy involves a neurosurgeon making an incision in the scalp, removing a piece of bone from the skull to give the neurosurgeon access to the tumor and then removing as much of the tumor as is deemed safe.

**Debulking:** surgical reduction in the size of the tumor. Debulking may be done in the case of benign tumors to relieve symptoms. Debulking may also be done in the case of high-grade tumors with the goal of increasing the chance that chemo or radiation will kill more cells of the tumor but must be done so with utmost care to avoid bruising the tumor and causing complications. Second opinions are highly recommended prior to debulking a high-grade tumor.

**Eloquent area:** The area of the brain which supports language, motor, sensory or

other important function. Surgery near or within an eloquent area presents a challenge for neurosurgery because of the risk of neurological damage to an important function.

**Inoperable:** an expert neurosurgeon has concluded surgery should not be performed on the tumor for a reason such as one of these:

- the tumor does not have clear borders (sometimes referred to as "margins") and is hard to distinguish from healthy brain tissue;
- the tumor is too close to parts of the brain that control vision, speech, mobility;
- there are multiple tumors;
- the surgery is likely to result in a significant loss of function; or
- the person's underlying health is insufficient for the surgery (e.g., person is quite elderly or has other health problems that make surgery unsafe for them).

Some tumors are labeled "inoperable," but can be removed by neurosurgeons with specialized expertise. If you've been told your tumor is inoperable, consider seeking a second opinion at a large, multidisciplinary brain tumor center. These teams typically offer advanced surgical techniques that allow greater access to hard-to-reach sections of the brain.

**Operable:** a qualified neurosurgeon has concluded surgery may be performed on the tumor and is reasonably (based on the doctor's considerable experience) expected to result in greater benefits than risk to the patient, all factors having been carefully considered.

**Resection:** surgical removal of a tumor. A resection may be partial (also called "subtotal") or total.

**Total or Gross Total Resection:** Surgical removal of every visible portion of a tumor. Surgical removal is not considered "complete" since microscopic portions are left no

matter how precise the surgery has been. This is why there is a need for additional treatment following surgery.

## When Surgery is Necessary

For small, benign (non-cancerous) tumors, like most meningiomas, that do not cause symptoms and are not expected to grow into a critical area, the doctor may suggest a "watch and wait" approach. In those cases, only if the tumor grows enough that it creates symptoms, then the doctor may recommend surgical removal.

If the benign tumor does cause symptoms, a neurosurgeon is likely to recommend removal in order to relieve or reduce your symptoms. Benign tumors can often be removed surgically and do not usually grow back after surgery. In such cases, surgery is considered curative.

For malignant tumors that are located in an area of the brain that is accessible to surgery, the neurosurgeon will thoroughly evaluate the possibility of removing the tumor or as much of the tumor as possible to improve neurological function and obtain an exact diagnosis of the brain tumor. The neurosurgeon's goal will be to completely remove the brain tumor (i.e., perform a total resection) while protecting, to the maximum extent possible, the person's functions and quality of life.

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For high-grade malignant brain tumors, surgery may relieve symptoms caused by too much pressure in the brain and allow time for other treatments to work. Malignant brain tumors can grow so fast that without surgery, other treatments might not have the time to work. Surgery is also an opportunity to try experimental treatments that require direct access to the brain.

A common problem with malignant brain tumors is recurrence (regrowth). Tumors often come back within a short period of time, even if they have been surgically removed and treated with radiation and chemo. When they do recur, they usually grow in or near the same place as the original tumor. Over 80% of recurrences are within 2 centimeters of the original tumor location. Researchers and doctors are hard at work developing ways to discourage tumor regrowth or lengthen the time before the tumor again grows.

The challenge of this disease is sometimes having to experience repeated surgical

procedures, radiation, and chemo. For this reason, the better a person maintains their underlying health with a good diet, exercise (to the extent recommended by their doctor) and good emotional support, the better they are able to withstand the repetitive treatments often needed to manage the disease.

## Pre-Surgery

### Pre-Surgery Health Checks

You should expect to be run through a battery of tests designed to determine your ability to handle the anesthesia that will be given to you during surgery and your ability to recover from the procedure.

Unless you have recently had such tests, your neurosurgeon will likely order some or all of the following:

- Blood tests for general health check
- Urine test for kidney operations
- Electro-Cardiogram to check your heart
- Chest X-ray to check your lungs
- Additional Contrast MRI for the Neurosurgeon's planning
- Vitals: Height, Weight, Temperature, Heartrate

If you have not been admitted to the hospital, these tests can be conducted prior to surgery on an outpatient basis.

### Pre-Surgery Treatments

Before surgery occurs, carefully discuss treatment options with your neurosurgeon. Certain treatments are available only prior to or in conjunction with surgery.

There are certain advanced treatments or clinical trials that require registration prior to surgery.

For example, certain types of immunotherapies need to begin before surgery. For trials related to custom-made vaccines, the tumor sample obtained during surgery

needs to be stored in a special way, so those needs must be known to the neurosurgeon prior to surgery.

There are also treatments that can only be received at the time of surgery, such as implantation of Gliadel Wafers or radioactive GammaTile therapy, as described below. Ask if the Gliadel Wafers or the Gamma Tiles would be appropriate in your case.

## **Pre-Surgery Discussions, Prep and Check-In**

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Prior to your surgery, the neurosurgeon will meet with you to describe the procedure from his or her viewpoint and provide you with any instructions.

If you are on an aspirin routine or if you are taking any herbs or supplements, you should make sure your neurosurgeon knows. Your neurosurgeon is likely to request that you cease the use of all blood thinners including aspirin, ibuprofen, as well as all herbs and supplements at least one week prior to surgery, assuming there is enough time. Aspirin, ibuprofen, and many supplements promote bleeding by slowing your platelets which will discourage healing of your incision after surgery.

You will be told when and where to show up for hospital admission and the surgery. Prior to your surgery, to help you reduce the risks of infection, it is recommended that you take a good, long shower and clean yourself well with soap from head to toe.

Anyone who accompanies you to the hospital for check-in will be shown where they can wait; they will be told when your surgery has been completed and when they can visit you in the recovery room.

## **Post-Surgery Preparations**

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While surgery of a brain cancer is an essential for those tumors deemed operable, even a total resection will not remove all the brain tumor cancer cells. For that reason, other treatments are needed.

So even before surgery, you need to be preparing with your medical team a list of options for postsurgical treatment. Here are some of the things you should request and/or ask about even before surgery occurs:

- Before surgery, verify that the neurosurgeon will order a molecular evaluation of the tumor tissue. As noted in the section of this Guidebook above entitled “Diagnosis Scope/Delays”, there are molecular markers in brain tumors that are essential for diagnosis, may indicate resistance to certain treatments, may determine eligibility for clinical trials or for repurposed drugs that are approved for types of cancer other than brain tumors. Major brain tumor centers routinely perform a diagnostic level genetic evaluation of tumors, but you should ask anyway.
- Before surgery, find out how your brain tumor tissue will be preserved after extraction. If the specimen will not be immediately used either to create a custom-made vaccine or to serve for molecular-marker testing, ask if the specimen can be frozen for future use if needed, and ask about the costs involved.
- Before surgery, ask about personalized vaccine therapy, which requires a tumor sample.
- Before surgery, ask about clinical trials that require registration even before surgery occurs.

## **Pre-Surgery Anxiety**

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The thought of being scheduled for brain surgery can be one of the most anxiety-producing events. “Brain surgery” sounds like a very scary thing. It is. But it is now much safer and easier than ever. Moreover, the goal of a maximally safe resection is now more often reached with the help of intraoperative imaging or by means of fluorescence-guided visualization of tumor tissue, which represents an important advance.

During surgery, it is sometimes extremely difficult to distinguish tumor and infiltrated tissue from surrounding healthy brain. An oral drug called Gleolan is now available for causing tumor cells to become fluorescent — that is, to light up under a microscope with a special blue light — thereby helping neurosurgeons remove as much tumor as possible without harming healthy tissue. (See the paragraph entitled “Fluorescence-guided neurosurgery” below for more information.)

Most long-term survivors of high-grade malignant glioma have had multiple surgeries. Usually, surgery will not be as bad as you expect. The worst part may just be worrying about it the night before. There are risks to surgery anywhere in the body, but surgery today is much safer and easier than it was even 10 years ago. Serious side effects are much less common than they used to be, so don't let horror stories from the past bother you. Problems do still occur but not as frequently as in the past.

There are still some brain tumors that are too dangerous to remove because of their size or location, but the limits to what is possible, safely, are shrinking every year. If you are told that your tumor is inoperable, or that a total resection of the brain tumor is not possible, get another opinion.

You should be aware that the surgical competency available at the top brain cancer clinics today is nothing short of extraordinary. One of the leading neurosurgeons at the University of California at San Francisco is Dr. Mitchel Berger and he has produced with his colleague Dr. Shawn Hervey-Jumper a video describing the outcomes of the current trend in extensive resections (removals) of brain tumors. That video can be accessed at the link in the box below.

.....  
: **WARNING: VIDEO CONTAINS IMAGES THAT MAY BE DISTURBING TO  
SENSITIVE INDIVIDUALS**

.....  
: <https://www.youtube.com/watch?v=RtICiRVcKII>

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There is a long term (20+ year) survivor of GBM who has undergone 6 brain surgeries. Her name is Cheryl Broyles. The advice from this undoubted hero-veteran of brain surgeries can be found at the link in the box below.

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: **WARNING: VIDEO CONTAINS IMAGES THAT MAY BE DISTURBING TO  
SENSITIVE INDIVIDUALS**

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: <https://www.youtube.com/watch?v=r0D2n9e5Lt0>

## Types of Surgery

The techniques and tools available to neurosurgeons are rapidly evolving today. As a result, there are several different types of surgery available to patients. Your neuro-

surgeon will carefully review your MRI images, medical file, and will discuss with you to determine what type is best for your particular situation.

## **Emergency Surgery**

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In some circumstances, emergency surgery at a local hospital might be the only immediate option because of symptoms related to brain swelling caused by the tumor or because of some acute risk of brain injury. Typically, however, the good news is that there is usually sufficient time to locate the doctors who are most experienced in the treatment of brain tumors and to gather information that can assist in your decision-making process.

## **Craniotomy**

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The current trend in neurosurgery is for highly skilled neurosurgeons to attempt to resect tumors to the greatest extent as deemed advisable by means of a craniotomy. In a craniotomy, the neurosurgeon removes a section of the skull (referred to as a flap) to extract as much of the tumor as possible, then replaces the flap.

During the procedure, the neurosurgeon may use a variety of tools including:

**Ultrasonic aspiration (UA).** This is a device that uses vibrating sound waves to break up the tumor and then gently suctions the tumor tissue. A UA device limits damage to adjacent healthy tissue and blood vessels and nerve fibers in the area. Plus, the duration of the surgery and therefore time the person must be under anesthesia is reduced.

**Microsurgery.** This is a special, high-powered microscope to look at the brain tissue to distinguish between tumor tissue and healthy tissue and enable the neurosurgeon to separate between the two with extreme delicacy.

**Fluorescence-guided neurosurgery.** In certain cases, prior to the resection of a high-grade tumor, the neurosurgeon will have you drink a liquid solution of five-aminolevulinic acid (5-ALA) hydrochloride, commonly referred to as “Gleolan”, a few hours prior to surgery. During surgery, the neurosurgeon will then use a fluorescent light with special blue filters to expose the tumor. The Gleolan helps the tumor glow a brilliant blue or hot pink, enabling the neuro-

surgeon to better distinguish between tumor and healthy tissue.

**Interoperative MRI.** In this approach, the neurosurgeon uses an MRI to remove as much tumor material as is deemed safe. The goal may be to remove not just the tumor material that lights up on the MRI image when a contrast dye is used, but also the area around the tumor that does not light up in the image. This form of surgery is used to increase the extent of resection, which has recently been shown to significantly improve the overall survival of high-grade patients. The risk is that an increased resection can cause a new postoperative deficit. For this reason, the neurosurgeon works with great care.

At the conclusion of the procedure, the bony flap may be secured with small metal brackets or staples and the skin of the scalp is pulled back over it. This will leave a scar, but hair hides it in many cases.

## **Awake Surgery/Intraoperative Brain Mapping**

A neurosurgeon may perform an awake surgery, also known as intraoperative brain mapping, when the tumor is very close to an eloquent part of the brain (area of the brain which supports language, motor, sensory or other important function). An awake surgery is designed to allow the neurosurgeon to electrically stimulate part of the brain during the surgery.

This craniotomy procedure is performed while the patient is awake but sedated. Some people are awake and conscious for part of the operation. Other people are awake throughout the whole procedure. Options include:

- Awake throughout the surgery: You would receive an injection of a local anesthesia to numb a small part of your scalp, called a scalp block.



- Sedated (i.e., quiet but not asleep) at the beginning and end of the surgery and awake during tumor removal: You would receive a scalp block and a little anesthesia for sedation (but not enough for you to sleep or become unconscious) at the opening procedure at the commencement of the surgery. The anesthesiologist supporting the neurosurgeon will then stop the sedation when the neurosurgeon signals that he or she is ready to remove the brain tumor, so that you will be awake during the removal. Once the neurosurgeon says that he or she has completed the removal, the anesthesiologist will sedate you again for the closure procedure and you will be allowed to come out of sedation once that process is done.
- Asleep at the beginning and end of the surgery and awake during tumor removal: At the commencement of the surgery, you will receive a nerve block and general anesthesia, which will render you unconscious. When the neurosurgeon signals that he or she is ready to remove the brain tumor, the anesthesiologist will wake you up. Once the neurosurgeon says that he or she has completed the process, the anesthesiologist will again put you to sleep for the closure procedure and you will be awakened for recovery once that process is done.

Your neurosurgeon will have a discussion with you to reach agreement on which approach will work best for your surgery.

Responses during the awake period helps guide the neurosurgeon in removing or substantially reducing tumors that might otherwise be considered inoperable due to their location or size, while at the same time avoiding damaging eloquent areas of the brain. During the surgery, the neurosurgeon will stimulate the area around the tumor with small electrodes and will ask you to perform tasks such as talking, moving a specified part of your body, counting (maybe even doing simple math), and looking at pictures. Some individuals with unique talents, such as singers and musicians, have sung or played their instruments during their surgery.

The neurosurgeon will use computerized maps of the brain taken before and during the procedure (this is why this surgical procedure is also called intraoperative brain mapping). Your responses will create a map of the functional areas of your brain, which will provide the neurosurgeon additional guidance for removing as much of the tumor as possible while avoiding the eloquent areas.

While this sounds like a scary approach, it is actually a common practice and is becoming increasingly common as neurosurgeons attempt to achieve the extent of resection, which, as earlier mentioned, correlates to significant improvements in the overall survival of high-grade patients.

Neurosurgeons and their anesthesiologists are skilled in ensuring patients do not experience pain during the procedure and are able to remain comfortable throughout. Typically, a nurse is dedicated to a patient throughout the surgery with the sole job of helping the person to feel safe and calm.

The only areas of the body involved in this surgery that can feel pain are the scalp and muscles at the site; the brain itself has no pain receptors.

It is recognized that awake surgery is not for everyone. Some of the factors restricting the application include if the person has certain types of sleep disorders (like sleep apnea) or is unlikely to respond calmly to the procedure and the neurosurgeon.

## **Debulking/Partial Resection**

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When an entire tumor cannot be removed, but is causing intolerable functional deficits, a neurosurgeon may perform a surgery to debulk the tumor. Debulking or partial resection refers to reducing the size of a brain tumor.

The following are usually NOT candidates for surgical debulking:

- The tumor is a large, invasive GBM dominating one hemisphere of the brain;
- The tumor is a large butterfly glioma;
- The patient is elderly (65 or over);
- The patient has an infiltrating tumor, is already taking steroids and has a Karnofsky score of less than 70. (See the Section entitled Karnofsky Performance Status for the score chart.) Typically, in this circumstance, the patient's condition is unlikely to be improved with surgery; or
- The tumor is a multicentric glioma. A multicentric glioma produces two or more tumors, all of which are in separate locations of the brain.

It is highly recommended that you obtain a second opinion from a highly qualified

neurosurgeon prior to receiving a debulking of a cancerous tumor. A debulking that expects to leave more than 25-30% of the tumor intact also leaves residual vascular tumor that has the propensity to produce brain edema and intratumoral hemorrhage (a condition referred to as “wounded glioma syndrome”). Several studies have established that patients with malignant gliomas who undergo debulking/partial resection can experience greater neurological morbidity than do patients who undergo gross total resection.

## **LITT Laser Surgery**

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If a tumor is small enough and in accessible locations whether near the surface or even deep inside, it may be possible for the neurosurgeon to use a surgical technique called by several names: "Laser Interstitial Thermal Therapy (LITT) ablation", "stereotactic laser thermoblation", or "MRI guided laser ablation." This Guidebook will just use "LITT".

LITT surgery may be available for tumors previously thought to be inoperable. In this technique, the neurosurgeon makes a small incision (coverable by a small, normal bandage), then makes a small hole through the bone. Through this access point and while the head is secured in place, the neurosurgeon uses an MRI to guide a 1.6 mm thick laser device (about the thickness of a pencil) precisely into the tumor.

The neurosurgeon then uses the MRI to obtain real time thermometry measuring the temperature of the tumor and the normal surrounding tissue. This enables the neurosurgeon to heat up the laser just enough to destroy the tumor (basically by cooking it from the inside out). The neurosurgeon turns off the laser before the heat reaches the normal surrounding tissue, reducing the likelihood of damage to nearby healthy brain tissue.

This procedure has been used with thousands of patients and has been shown to be successful in reducing or removing diseased tissue.

The LITT system used by neurosurgeons consists of a laser system, workstation, and an MRI. There are two FDA-approved LITT systems in the United States: Visualase (Visualase, Inc.) and NeuroBlate (Monteris Medical, Inc.). The main differences between the two systems are the laser wavelength, cooling method, heat production, and distribution pattern. The NeuroBlate system, approved by FDA in 2009, has a

1064-nm diode pulsed laser with a CO<sub>2</sub>-cooled side-firing probe or diffusing tip probe. The Visualase system, approved by the FDA in 2007, has a 980-nm diode continuous laser with a saline cooled diffusing applicator tip.

LITT systems are more likely to be available at a major brain cancer center. Its main advantage over conventional surgery is that it is minimally invasive. Only a small hole is needed; the neurosurgeon does not have to remove a portion of the skull to access the tumor, which reduces recovery time considerably. However, based on decades of experience that tells them about the effectiveness of conventional surgery, most neurosurgeons will still prefer to extract a tumor by a scalpel when they can.

## **Neuroendoscopy/ Key-Hole Surgery/ Neurosurgical Tubular Retractor System**

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Neuroendoscopy, also known as key-hole surgery, is a minimally invasive surgery technique developed in the 1990s and received benefit of rapid developments since. This surgical technique utilizes an endoscope; this form of surgery is used for very limited types of surgical challenges.

An endoscope is a medical instrument, which is a long tube with a camera attached to a monitor and an eyepiece through which the neurosurgeon looks. At the end of the endoscope are tiny forceps and scissors the neurosurgeon can use to perform a microsurgery. An endoscope may be either flexible or rigid and is inserted through a small hole made in the skull or through the mouth or nose.

Neuroendoscopy can be used to remove some or all of a small tumor located in difficult places such as many midline skull base, some parenchymal lesions, and tumors within the fluid filled spaces deep within the brain called ventricles.

The neurosurgeon may also use neuroendoscopy to help relieve hydrocephalus, which is a buildup of excess fluid in the ventricles sometimes caused by a tumor that generates an excess of edema/inflammation. When excess fluid expands the size of the ventricles, this causes the pressure in the brain to increase which in turn can cause a person to experience a variety of intolerable symptoms.

A form of surgery that is a type of neuroendoscopy is the neurosurgical tubular retractor system. In this type of surgery, the neurosurgeon extracts the tumor

through a tube. A retractor which is part of this system pushes or holds delicate brain tissue aside to enable the neurosurgeon to reach the target tumor. This is of important benefit because it is thought to cause less damage than other surgical options since it is moving tissue away rather than cutting through it. This system may be very helpful in situations when a tumor is located deep within the brain. Like neuroendoscopy, it also offers a less invasive option than a traditional craniotomy.

## **Photodynamic Therapy**

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A form of therapy called photodynamic therapy (PDT) was first developed in the 1980's and is now being used in combination with surgery. PDT is a combination of a photosensitizer drug, light, and molecular oxygen. Owing to its low toxicity, this therapy is being tested on both children as well as adults.

PDT takes advantage of the fact that a photosensitizer, a light-activated drug, accumulates more readily in tumors. The patient would be given the photosensitizer a few days prior to surgery. This time allows the drug to collect in the tumor and when later exposed to a specific wavelength of light, the drug produces free radicals that kill the tumor cells. After the tumor that has been treated with PDT is removed, the neurosurgeon would irradiate the cavity with a laser to destroy any residual cancer cells that are beyond the margin of the tumor.

Therefore, PDT, optimizes the removal of the tumor and ablation (cleaning) of the tumor site while minimizing damage to healthy tissue. Unlike surgical resection and radiotherapy, PDT can treat micro-invasive areas, which is a serious benefit in treating the thin outgrowth patterns of GBMs and gliomas.

One photosensitizer is called porfimer sodium ("Photofrin") and is being tested on patients with recurrent GBMs and other high-grade gliomas. Another agent being evaluated is Gleolan. In order to achieve a greater accumulation of a photosensitizer drug in the tumor, nanotechnology is being researched (e.g., Ce6/PTX2-Azo Nanoparticles).

Currently, no device allows the use of PDT without direct, surgical access to the tumor; the light used in PDT is not strong enough to go through more than 1 cm of tissue. Also, PDT is not currently FDA approved, so access to this therapy is through clinical trial, however, it is an emerging technology and is worth discussing with

your neurosurgeon.

## Shunt Implantation

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In some cases, the brain tissue reacts to the presence of the tumor and to treatments such that it produces an excessive amount of fluid. Too much fluid in the enclosed area of the cranium can oversaturate the brain tissue causing symptoms like nausea, headaches, and drowsiness. It can even become life threatening in extreme cases.

Since this fluid cannot be re-absorbed by the body as quickly as it is produced, the situation requires medical intervention. If available medications (such as dexamethasone or Avastin) do not satisfactorily control the situation, the neurosurgeon may recommend the installation of a shunt.

A shunt is a small valve that is installed surgically under the skin right behind an ear. A tube is attached to the shunt internally and drains the extra fluid from the brain into the abdomen where the body can then dispose of it in the normal course.

The surgery for installing a shunt is a true surgery. There will be a few stitches behind the ear, a couple of staples possibly in the torso (to permit the doctor to snake the tube into position in the abdomen) and then a couple of staples where the shunt ends in the abdomen. While there is always a risk of infection with any surgery, the incisions for this surgery are pretty limited, which limits the infection risk.

Shunts come in programmable and non-programmable types. The instructions for either the program or settings (depending on the type of shunt) tell the shunt how much fluid to remove from the brain so that it doesn't remove too much or too little. Shunts do not necessarily come out of surgery adjusted perfectly because it can be a trial-and-error process to get the shunt to drain the right amount. The neurosurgeon is the one who will first set the shunt's meter – usually at a conservative best guess rate - and then make any necessary adjustments afterwards, which is done in the doctor's office by the doctor manipulating the shunt under the skin. (This is typically painless.)

Shunts do malfunction and when they do, a range of symptoms result like headache, vomiting, visual issues, fatigue, irritability, loss of balance, fever, and redness. (This is not a comprehensive list, but you get the idea.) If there is redness along the track of

the shunt, then that could mean there is an infection brewing. If anything like these symptoms show up, then you should call the doctor's office right away and they will probably want to see the patient pretty immediately.

## **Ventricular Access Device Installation**

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The posterior fossa is a small space found near the brainstem and cerebellum. The cerebellum is that part of the brain responsible for controlling balance, coordinated movements and vital body functions, such as breathing. A tumor can grow in this area. Most posterior fossa tumors that appear as a meningioma, schwannoma, epidermoid, cholesteatoma, chordoma, and chondrosarcoma are more common in adults, whereas other rare tumors, such as Ewing's sarcoma, are more common in children. About 70% of posterior fossa tumors are diagnosed in children.

When a brain tumor grows in the posterior fossa area, its critical location leads to brainstem compression and herniation. It can block the flow of spinal fluid and cause increased pressure on the brain and spinal cord, which can produce an array of serious symptoms.

In order to treat this type of tumor, a neurosurgeon may decide to install a ventricular access device if the tumor does not exceed size recommendations. This device, also called an Ommaya reservoir, is placed under the scalp with tubing going to the brain's fluid-filled spaces (ventricles) so the neurosurgeon can sample the fluid, drain it or deliver chemotherapy into the fluid.

## **Treatment Implants During Surgery**

Neurosurgeons can surgically implant chemo into the brain tumor or may place chemo into the tumor site after a tumor has been removed in order to discourage future growth. The neurosurgeon can also imbed radioactive seeds to deliver radiation directly to the site. The options are further described below.

### **Gliadel Wafers (also called Carmustine Wafers)**

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Before surgery, ask about the possibility of implantation of Gliadel Wafers within the brain tumor cavity during surgery.

Gliadel Wafers are dime-sized wafers containing polifeprosan 20 with a chemo called Carmustine. Gliadel Wafers may be appropriate for those with a newly diagnosed, high-grade tumor or those about to undergo surgery for a regrowth of a high-grade tumor.

These Wafers are implanted by the neurosurgeon during surgery at the tumor site. The Wafers are placed onto the walls and floor of the space made available when the tumor was removed. As many as eight (8) Wafers may be used; the number of Wafers will depend on the size of the tumor cavity.

They are left in place and over the following 2 to 3 weeks, the Wafers slowly dissolve, delivering Carmustine to the tumor environment. The goal is to kill tumor cells left behind after surgery.

In the NCCN guidelines, Gliadel Wafers are considered optional for patients who receive a maximally safe resection. Be aware that implantation of Gliadel Wafers during surgery may make you ineligible for some clinical trials further on in your treatment, so plan ahead.

There are risks with this therapy that should be discussed with the neurosurgeon.

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## **GammaTiles (also called Surgically Targeted Radiation Therapy or STaRT)**

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GammaTiles are one-inch square collagen tiles that deliver radiation to the tumor environment. Each GammaTile has four, tiny radioactive seeds that have been shown to delay tumor regrowth and avoid typical side effects of radiation like hair loss. The GammaTile delivers radiation immediately upon placement and is focused right where it is needed.

With GammaTile Therapy, there is no need for patients and their caregivers to travel to and from a radiation treatment center. Patients receive treatment at home while going about their daily life. In a clinical study, GammaTile treatment resulted in nearly twice as many tumor-free months. There are risks with this therapy that should be discussed with the neurosurgeon.

## **Neuroplastic Surgery**

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You may wish to discuss with your neurosurgeon about having a neuroplastic surgeon involved with your surgery. This specialist surgeon can help minimize scar visibility and aid in wound healing. For tumors involving the bone or the scalp, a neuroplastic surgeon can assist with creating personalized implants to help replace removed bone to prevent visible deformity to the head.

## **Length of Brain Tumor Surgery**

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A craniotomy and removal of your tumor typically takes 4 to 6 hours. Remember that brain tumor surgery involves an entire team of people, as well as monitoring of vital signs, positioning of equipment and ensuring you are comfortable before your procedure begins. The time elapsed between your room being cleared of visitors to the actual start of surgery can be up to two hours alone. If you have people waiting for you, they should be aware of this extra time on top of the actual surgical procedure time.

## **Hospital Stays**

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Years ago, patients with brain tumors would stay in the hospital for a week or more after the procedure. Over the last two decades, doctors have been able to steadily decrease the amount of time patients need to remain in the hospital following surgery. Now, the average stay for brain surgery is three (3) days and two (2) nights with the first night in ICU for maximum observation.

## **Risk of Complications**

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Surgery on the brain is serious and complicated surgery. The neurosurgeons performing these types of surgeries in the US today are among the brightest, most competent, and best equipped doctors in the world, thereby reducing the risks associated with this major medical event.

Nonetheless, some post-surgery complications happen as a direct result of surgery and are expected in some cases, but just moving brain tissue around during the surgery can cause other temporary symptoms.

While most people leave surgery in as good a functional state or better than when they

went in, about 18% of the individuals who receive brain surgery develop impairments from the surgery, despite all the best training, planning and efforts by the neurosurgeon. Those most at risk for complications are those who are older and those who have a Karnofsky score of less than 70. (See the Section entitled Karnofsky Performance Status for the score chart.)

Impairments include motor weakness, sensory deficits (e.g., hearing loss or degradation), aphasia/language difficulty, visual deficits, confusion, and ataxia (lack of muscle control or coordination of voluntary movements). It is strongly recommended that the person proceed to rehabilitation as soon as the neurosurgeon approves.

One complication to be mindful of is the risk of infection. Any surgery depletes the immune system, which can give infection a foothold. This is especially true for repeat surgeries because the neurosurgeon is cutting through skin tissues which have been radiated, making those areas more susceptible to post surgery infections. It is important to carefully follow the neurosurgeon's instruction for post-surgery care.

## **Immediate Post Surgery Care**

After your brain tumor surgery, you will most likely spend the night in a neuro-critical or intensive care unit (NCCU or ICU) for observation. You may be connected to an intravenous (IV) line through which you will receive a constant drip of fluid, a heart monitor, a urinary catheter, and an oxygen mask. You will also have a dressing (bandage) on your head for a day or two.

The purpose of your NCCU/ICU stay is to prevent or minimize any complications you may have to the anesthesia and the surgery itself. Anyone emerging from brain surgery is under a significant amount of physiologic stress that can be seen with fluctuations in blood pressure, blood glucose, heart rate and variations in oxygen consumption, so you deserve careful attention and prompt intervention for anything that may arise.

This often translates into a nurse checking your vitals every 15-30 minutes immediately upon recovery from anesthesia for the first 1-2 hours, and then once per hour for the next 6 hours. (Do not plan on getting much sleep in the NCCU/ICU.) Once everything stabilizes, then you are ready to leave the NCCU/ICU for a regular hospital room.

When you leave the NCCU or ICU, you will continue recovery at a neurosurgery nursing unit. You should be able to be out of bed eating and taking short walks the day after surgery. Once you are eating and drinking normally, the IV will be removed from your arm.

You should not experience a lot of pain after surgery. Most people take acetaminophen for minor discomfort, but stronger pain relievers may be appropriate as recommended or approved by your doctor.

## Post-Surgery Home Care and Other Topics

**Post-Surgery Doctor Visit.** After you are released from the hospital, you can continue your recovery at home with home-based or outpatient therapy, as needed. You will need to return for a follow-up visit with your neurosurgeon in about a week or so to assess your health and remove any staples or stitches. In some cases, they will need to stay in for longer.

**Pathology Report.** Be sure to ask your neurosurgeon for a copy of the pathology report from the procedure. Although it may be expensive to do so, you can readily get a second opinion on the reading of the pathology slides. There is a lot of interpretation put into the reading of the pathology slides, and this is the single most important diagnosis you will ever have in your life, so it may be worth the money to double-check it. Best of all, getting a second opinion will not involve any pain — and can be accomplished by mail, so there will be no need for additional travel.

**Steroid.** If you have been prescribed a steroid to help control the swelling, check with the doctor about when you can taper (slowly!) from use. (The most commonly prescribed steroid for brain tumor patients is called dexamethasone.) While a steroid is a great help, it can lead to issues with both short and prolonged use, which are described below in the section entitled “Medications for Swelling.”

For steroid use lasting longer than a few days, it is VERY important to follow your doctor's instructions about decreasing your steroid dosage. Stopping steroids abruptly can lead to numerous withdrawal symptoms including an adrenal crisis which is a rare but fatal reaction to a lack of steroid in your body.

**Healing.** It will take time to return to your usual level of energy. Be patient. Healing requires extra rest, and the surgery probably took more out of you than you might think. The amount of time required to recover after brain surgery is different for each person, and it depends on:

- The procedure used to remove the brain tumor
- The location of the tumor within the brain
- Areas of the brain affected by the surgery
- Your age and your overall health going into the surgery

**Preventing Post-Surgery Constipation.** When they give you anesthesia, they typically also give you a medication like Ondansetron (commonly called Zofran) to help avoid nausea from the anesthesia. Zofran (or similar meds) can cause significant constipation making it very hard for you to relieve yourself for days, can cause you to feel sluggish, and can dampen your appetite at a time when you should eat well. Eating fibrous foods and taking a stool softener approved by the neurosurgeon can help.

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**Hydration.** Keep yourself well hydrated with lots of plain WATER during your recovery. Drinking lots of water helps to flush any medication residues from the body and aids in avoiding the constipation. Fruit juices, sodas, off-the-shelf ice teas and coffees should be limited because of their high sugar content. The best drink always is good old plain water.

**Sleep Position.** Sleep with your head propped slightly upright. The body always sends fluid to the site of a wound, and in this case, the fluid can build up pressure, so you want the fluid to be able to drain downward.

## SURVIVOR STORY #5: BEN WILLIAMS

At the age of 50, I had surgery for glioblastoma on March 31, 1995, after an MRI scan in the emergency room the preceding day. The tumor was located in my right parietal cortex and was very large (it was approximately 180 cc and described as the "size of a large orange"). My neurosurgeon later told me that I would have been dead within two weeks had I not had the surgery when I did.

During the first two months after my diagnosis, I spent many hours on the Internet and in our medical school library, learning all that I could about possible treatment options. While I initially entertained boron neutron capture therapy, gene therapy, and radiation-loaded monoclonal antibodies as much more promising than conventional treatment, I finally rejected all of these based on likely problems of various sorts. I therefore opted for conventional chemotherapy but in combination with other agents that seemed likely to improve the effectiveness of chemotherapy over that which typically occurs.

All of my MRI scans since chemotherapy have been free of any sign of tumor. Throughout my first year of treatment, I added various nutritional supplements that can be obtained at most health food stores. The inspiration for the various treatments and health food commodities I opted for has come from many different sources. Much of it came from my own research on Medline, sometimes after hearing about a treatment in passing from participants in an online support group. I also found the webpage of the Musella Foundation as a source of leads to follow up on.

My treatment philosophy has been very similar to the treatment approach that has developed for AIDS. Both HIV and cancer involve biological entities that mutate at high rates, so unless a treatment is almost instantaneously effective, the dynamics of evolution will create new forms that are resistant to whatever the treatment may be. However, if several different treatments are used simultaneously (instead of sequentially, which is typically the case), any given mutation has a much smaller chance of being successful.

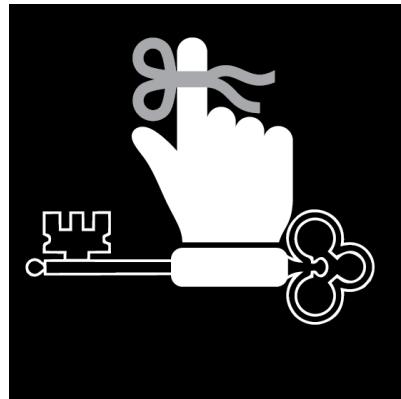
A second feature of my treatment philosophy is that any successful treatment will need to be systemic in nature since it is impossible to identify all of the extensions of the tumor into normal tissue.

Ben Williams, a 24-year survivor of glioblastoma, is the author of the 2002 book *Surviving Terminal Cancer: Clinical Trials, Drug Cocktails, and Other Treatments Your Oncologist Won't Tell You About*. At the [virtualtrials.org](https://virtualtrials.org) website, he has posted various updates of this book as well as a 2017 update of the long report entitled "Treatment options for malignant gliomas." To access these important sources, go to:

<https://virtualtrials.org/williams.cfm>



## KEY TAKEAWAYS TO REMEMBER



Find an expert neurosurgeon specializing in brain tumors – someone who performs a minimum of 25 surgeries per year. Typically, expert neurosurgeons are associated with major brain tumor centers..

If you are told that your brain tumor cannot be maximally resected or is inoperable, seek a second opinion.

**Before surgery takes place**, ask about molecular-marker testing, enrollment in clinical trials, custom-made vaccines, and implantation of Gliadel Wafers.

Note that if you are interested in treatment with a personalized vaccine, you must make arrangements **before surgery** to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.



## Radiation

### Overview

Many decades ago, upon the diagnosis of a GBM, neurosurgeons would try a few times to remove the entire half of the brain in which the GBM was located. It was determined that even with such a radical surgical approach, the disease would return, infect the remaining half brain and lead to the patient's demise. Doctors realized that removal of the visible part of the disease was not enough. It was essential to treat also the non-visible, microscopic cancer cells that continued to be present. Radiation therapy was then employed.

At the right dosage, radiation will kill brain cancer cells almost as effectively as surgery but will kill the invisible cells. The radiation does so by damaging the DNA within the cancer cell, which then stops them from growing and dividing. The injured cell perishes leaving no descendant cells to continue the growth of the tumor.

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Depending on the kind of tumor, a person may only get radiation therapy. In the case of high-grade tumors, patients will receive radiation, unless some health problem precludes them from getting radiation (e.g., extreme old age.)

Radiation treatment must be tailored for each person based on the type, status (e.g., resected or not) and location of the tumor or tumor cavity.

Radiation therapy is typically performed under the care of a radiation oncologist at a radiation facility or by a neurosurgeon either during surgery when radioactive materials are implanted or during radiosurgery when conventional surgery is not an option.

The tumor and a small margin around the tumor are usually targeted by a powerful beam of radiation.

Because tumor cells reproduce more rapidly than normal brain cells, they are more affected by radiation than normal cells. The radiation disrupts the DNA of the cells that are reproducing. Compared to tumor cells, normal cells are also better able to repair damage caused by radiation.

## Radiation Approaches

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There are three main approaches used in radiation treatment:

**Radiosurgery.** As the name implies, this is the use of selected radiation technologies to perform surgery-like treatment on a lesion or tumor. It is nonsurgical in the sense that no incision is made, but the tumor is so damaged that the treatment goal is removal. Radiation is often delivered at a single high dose in a one-day session, but can be delivered in several sessions (e.g., 3 to 5) of smaller dosages, called fractionated stereotactic radiotherapy, for larger tumors. Radiosurgery is appropriate for only tumors such as those one and one-half inches in diameter or smaller.

**Whole-Brain Radiation Therapy (WBRT)** administers radiation to the entire brain. This approach is used when there is widespread cancer in the brain (e.g., numerous tumors or metastatic lesions) or when a cancer in another part of the body is metastasizing to the brain. Recent studies have demonstrated that WBRT may have more disadvantages owing to its tendency to produce cognitive neurotoxicity, which is an overall decline in brain function, and WBRT may not necessarily offer corresponding improvements in the control of the cancer when compared to the next approach, which focuses radiation on the tumor. However, studies have also found that in the case of brain metastasis, if a person has just one metastatic lesion which is removed surgically, and then is treated with WBRT, they are likely to have increased survival. In addition, safer ways to administer WBRT have been developed. By blocking out the memory structures from the radiation fields (sometimes referred to as Hippocampal Avoidance) and the use of certain medications during therapy, a person's memory can be protected.

**Localized Radiation Therapy** is the other approach. In the late 1990s through early

2000s, the use of localized radiation became more prevalent than WBRT. In this approach, the objective is to deliver radiation only to the tumor. There are numerous technologies, with increasing precision, available that offer this approach, which is applicable when there is a single tumor or just a few tumors. Side effects from this form of therapy are reduced.

The radiation oncologist, and possibly also a neurosurgeon, will decide which approach is best based on all factors of the particular case given the twin goals of improving longevity by increasing the effectiveness of the treatment against the disease while at the same time preserving to the maximum extent possible quality of life by decreasing treatment toxicity.

### Radiation Technologies

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The field of radiation has become the beneficiary of rapid and amazing enhancements in its technology over the last 30 years. As a result, there are a variety of types of technologies employed today. Not all brain cancer centers will have every technology, but a major brain cancer center is likely to have excellent, state of the art radiation technology.

Prior to the start of your therapy, you should find out exactly what type of technology will be used. (This is one of the many questions suggested below under the section “Pre-Radiation Questions to Ask.”)

These are the types of technologies you may encounter. The equipment used by each are described below.

- Stereotactic Radiosurgery (SRS)
- External beam radiation therapy (EBRT)
- Internal radiation therapy (Brachytherapy)

### Stereotactic Radiosurgery (SRS)

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#### Overview

Although no “knife” or incision is used to expose the brain during stereotactic radiosurgery (SRS) but rather a precise high-dose beam of radiation, SRS is considered “surgical” because of the degree of change that takes place after the procedure. Although not part of the standard-of-care treatment, it is good to know about SRS.

SRS is a noninvasive approach to treat brain tumors using pencil-thin beams of radiation directed only at the tumor. SRS is a standard treatment for selected primary and metastatic brain tumors and may be delivered as:

- An addition to conventional EBRT (described below), called local “boost” radiation, when the patient has already received the maximum safe dose of conventional radiation therapy, or
- The only technique used to deliver radiation therapy to some brain tumors, or
- A substitute for surgery for a metastatic brain tumor or a benign tumor (such as a pituitary, pineal region, or acoustic tumor).

This focused technique allows radiation to be delivered in an area of the brain or spinal cord that might be considered inoperable and can be delivered to tumors that are small (generally 2 centimeters or less).

SRS can involve one treatment session or several (fractionated) sessions over a period of several days or weeks, assisted by computer-aided planning. SRS delivers a much higher dose of radiation to the target than conventional radiation therapy. For some low-grade tumors, SRS can be curative. SRS is also sometimes used for small tumor recurrences.

Prior to SRS, the patient is fitted with a head frame, although some forms of SRS are frameless. CT and/or MRI scans are performed with the head frame in place to locate the tumor and obtain information necessary for computerized treatment planning. Treatment is totally non-invasive and painless, although the headframe may be somewhat uncomfortable for some people.

Patients maintain their normal function and are completely awake and alert throughout the entire procedure.

## Types of SRS Devices

Many different manufacturers have developed devices for administering SRS. Some of the notable brands are Gamma Knife, CyberKnife and ZAP-X. Other systems which may be used for both SRS as well as External Beam Radiation Therapy (EBRT) are Novalis Tx, LINAC and TrueBeam. These are not the only SRS devices available; the information below is solely to provide some representative information to understand the state of the advances in radiation technology.

Each SRS device has its own advantages and disadvantages. Just know that if you are told your tumor is too large or the wrong shape for SRS, get another opinion from a doctor who uses a different type of SRS device.

### GammaKnife

Gamma Knife: The Gamma Knife is an instrument that was developed by researchers in Sweden nearly three decades ago. It delivers 201 beams of radiation using radioactive cobalt that are focused by a computer so that they intersect at the precise location of the cancer. The patient is placed on a couch and then a large helmet is attached to the head frame. Holes in the helmet allow the beams to match the calculated shape of the tumor.

The most frequent use of the Gamma Knife has been for small, benign tumors, particularly acoustic neuromas, meningiomas, and pituitary tumors. For larger tumors, partial surgical removal might be required first. The Gamma Knife is also used to treat solitary metastases and small malignant tumors with well-defined borders.

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### CyberKnife

Like Gamma Knife, CyberKnife delivers sub-millimeter accuracy, but is enabled by an enhanced tumor tracking technology and real-time imaging so that a person does not have to be immobilized during treatment. CyberKnife, which was first used in the US in 2001, offers flexible treatment options. A person can have a single high dose treatment, or two to five lower dose treatments, generally completed within a week. CyberKnife uses electrically generated photon beams.

### ZAP-X

The ZAP-X system is a new addition to radiosurgery. It is based on state-of-the-art linear accelerator (LINAC) technology and has a novel, fully integrated dosimetry

validation system that monitors and verifies delivered radiation in real time. It uses a gyroscopic motion to direct high dose beams from a multitude of unique angles to precisely aim at the tumor, resulting in less healthy brain tissue exposure. The system has unique self-shielding technology (like a bank vault) so that radiology departments do not need to build a special room and bunkers for it. ZAP-X does not use Cobalt-60, avoiding the costs involved in licensing, storing, and replacing radioactive isotopes, so it may be a less costly alternative for some.

### Novalis Tx

Novalis Tx is a highly sophisticated SRS/EBRT device developed by NASA engineers. It is equipped with “Novalis Body” software for image-guided radiotherapy delivery. Its X-ray-based localization technology allows the doctor to treat the tumor with sub-millimeter accuracy. The system includes a 6-dimensional robotic couch that positions patients automatically and with the highest degree of precision. It has high dose conformity within a shorter period of time making treatment times shorter.

### LINAC

Also used for SRS and EBRT, an adapted linear accelerator can deliver a single, high-energy beam that is computer-shaped to the tumor. The patient is positioned on a sliding bed around which the linear accelerator circles. The linear accelerator directs arcs of radioactive photon beams at the tumor. The pattern of the arc is computer-matched to the tumor’s shape. This reduces the dose delivered to surrounding normal tissue.

LINAC radiation therapy may be used in the treatment of metastatic cancer or some benign brain tumors.

### TrueBeam

TrueBeam is a system with a sophisticated architecture that was engineered with motion management technologies, advanced 3D imaging and patient comforts in mind. It is able to provide pinpoint accuracy with less time on the treatment couch; treatments that may take another system 15 minutes or more may take the TrueBeam two minutes. TrueBeam uses a cone-beam computer tomography (CT) that uses 25 percent less of an X-ray dose than other image-guided technologies. It is a quiet machine and has built-in music to provide a more relaxing therapy experience. TrueBeam can be used for both SRS and EBRT.

## Side Effects of SRS

Possible side effects of SRS include edema (swelling), occasional neurological problems, and radiation necrosis (an accumulation of dead cells). A second surgery to remove the build-up of dead tumor cells may be required.

## **EBRT Radiation (Proton, 3D-CRT, IMRT)**

### Overview

EBRT (which may also be referred to as Stereotactic Radiation Therapy or SRT) involves directing radiation beams from outside the body into the tumor. Machines called linear accelerators produce the high-energy radiation beams that penetrate the tissues and deliver the radiation dose directly to the cancer.

EBRT divides treatment into multiple sessions. This approach is best for large tumors or tumors within or close to critical brain structures that cannot tolerate a large radiation dose. This form of radiation technology significantly reduces side effects while improving the ability to deliver a high total amount of radiation directly to the tumor.

EBRT is typically delivered as an outpatient procedure a few minutes per day, every day (often weekends are excepted) or approximately six weeks. EBRT begins with a planning session, or simulation, during which the radiation oncologist takes measurements in order to line up the radiation beam in the correct position for each treatment. During treatment, you would lie on a table and the radiation will be delivered from multiple directions. The actual area receiving radiation treatment may be large or small, depending on the features of the brain tumor.

### Proton Beam

Proton beam therapy is a form of EBRT. It offers excellent dose localization that permits treatment of brain cancer by administration of a high dose to the tumor while minimizing damage to surrounding normal tissues. A proton beam has a sharp energy peak called the Bragg peak, which spreads out to cover the tumor volume. The energy behind the peak is nearly zero, unlike some other forms of EBRT. This means that the dose to normal tissue around the tumor can be less than that experienced in other forms of radiation therapy.

Note that proton beam radiation is more expensive than conventional photon beam used in most of the other technologies and as a result, not all insurance companies will approve use of proton beam therapy. Some insurance companies have approved use after appeals.

Proton radiation therapy may have a role in the treatment of unusually shaped tumors and small tumors that are located deep in the skull, such as skull base tumors or pituitary tumors. Proton radiation therapy has been evaluated in the treatment of meningiomas and appears to be effective in a high percentage of cases.

### **Proton or Photon?**

In several of the top brain cancer centers, the radiology department has both proton beam as well as photon beam technology and patients may be perplexed about which is best for them. The best answer can only come from the radiation oncologist, who will evaluate the location, type, and shape of the tumor, as well as your age and underlying health and other factors. However, here are some considerations you may wish to discuss with your radiation oncologist.

Proton radiation has the physical advantage of better spatial selectivity (i.e., this form of radiation can offer a more condensed “hit”). Plus, proton beam radiation seems to also have better radiobiological efficacy than photon type radiation, meaning that it is better suited for the treatment of radioresistant tumors (e.g., a tumor that might be hard or dense compared to one that might be soft and jelly like or a tumor which is located near the eloquent (sensitive) parts of the brain.)

Though protons may release a larger mean energy per unit length, the radiobiologic properties of protons and photons are not all that different.

In proton beam radiation, there is less radiation “spillage” into neighboring areas because the treatment is highly localized. This is a desirable feature if the tumor’s margins are well defined.

However, photon therapy may be more helpful in the case of a diffuse tumor; that is, one which has finger-like tentacles extending some distance from the main tumor mass and invading healthy areas. Since the particles emitted by photon beam radia-

tion “bounce around” a little more than proton radiation, photon beam may present an advantage for those dealing with a diffuse tumor because the radiation will have a greater opportunity to deliver destruction to those invasive, tentacles of the tumor.

### **3D-CRT**

Three-dimensional conformal radiation therapy (3D-CRT) is another form of EBRT. This technology conforms a specific arrangement of x-ray beams to the tumor’s shape to maximize tumor dose and minimize exposure to normal tissue. This treatment is tailored to your specific anatomy and tumor location. Your doctor may use CT and/or MRI scanning to plan your treatment. The use of 3D-CRT is believed to reduce the chance of injury to nearby normal tissues.

### **IMRT**

Intensity-modulated radiation therapy (IMRT) is another form of EBRT. This is an advanced mode of high-precision radiotherapy that uses computer-controlled x-ray accelerators. The accelerators conform and deliver a precise radiation dose, sometimes referred to as “beamlets”, to the three-dimensional (3-D) shape of the tumor. The machines control the intensity of the radiation beam to focus a higher dose on the tumor and minimize radiation exposure to healthy cells.

At Brigham’s and Women’s Hospital, researchers conducted randomized controlled trials comparing IMRT to 3D-CRT. They found that IMRT results in significantly less changes to the salivary glands in patients with head and neck cancers.

## **Brachytherapy**

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Brachytherapy is internal radiation treatment. The most common form of brachytherapy places radioactive material directly into or near the tumor. In those cases, the radioactive material is often referred to as “implants” or “seeds.” A new, alternate radiation technique involves the insertion of a balloon at the tumor site during site and administering radiation through a catheter into the balloon.

Brachytherapy is used in the treatment of newly diagnosed or recurrent brain tumors. It may be administered as the primary radiation therapy or as a “boost” of additional radiation delivered before or following standard ERBT.

For boost therapy to be effective, the tumor must be no more than 2 inches in diameter and accessible by surgery. Larger tumors may require surgery to reduce the size of the tumor before the Brachytherapy is applied. Brachytherapy is a local therapy; it is not commonly used for widely spread or multiple tumors.

While standard radiation aims rays at the tumor from outside the body, brachytherapy attacks the tumor from the inside. The advantages to this internal delivery of radiation are:

- Reduced damage to normal tissue, and therefore, reduced side effects. This technique limits radiation exposure to a localized area around the radiation sources, minimizing exposure of healthy tissues away from the tumor,
- More concentrated delivery of radiation to the area where the cancer is most-ly likely to recur, and
- Reduced risk of damage to normal brain tissue makes brachytherapy an option for patients with recurrent tumors who have undergone radiation treatment for recurrent brain tumors and may not be able to tolerate additional EBRT.

Brachytherapy may be permanent or temporary. In permanent brachytherapy, the radioactive seeds are left in place permanently. Some radiation oncologists may advise patients to avoid close contact with young children or pregnant women for the initial several weeks, but after that time the radioactivity diminishes to such a low level that it would not be harmful.

In temporary brachytherapy, the radioactive materials are inserted for a specified period of time and then removed before you would go home. Temporary brachytherapy may be administered at a lower dose over a longer period of time or a higher dose over a shorter period of time.

### Radiation Seeds

To implant radiation “seeds” in the tumor, catheters (tubes) are placed into the tumor bed using surgical techniques that are directed by CT and MRI. The radiation “seeds” are placed in the catheters. Depending on the isotopes used, the implant is removed either after a few days, after several months or is left in place perma-

nently. Steroids are commonly used with this therapy to decrease brain swelling. In rare instances, implantation might be repeated. Brachytherapy implants are typically temporary and are removed once treatment is completed. In some cases, an implant may be permanent.

### GliaSite Radiation (RTS)

An emerging form of Brachytherapy is the GliaSite® radiation therapy system (RTS). The GliaSite RTS involves placing an inflatable balloon in the area of the brain tumor at the time of surgery. Low-dose-rate radiation is delivered through a catheter (tube) into the balloon.

The GliaSite RTS offers the advantage of a shorter stay in the hospital; most patients who undergo traditional external beam radiation therapy remain hospitalized for six weeks, whereas patients who receive their radiation treatment with GliaSite may return home within a week. GliaSite is approved by the FDA for the treatment of malignant brain tumors.

Three published clinical trials indicate that GliaSite is a safe treatment for high-grade gliomas and brain metastases and may increase survival in the treatment of recurrent gliomas compared to surgery alone or surgery plus internal chemotherapy.

### Treatment Schedule

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The NCCN recommendations mention two different types of radiation therapy — standard and hypofractionated.

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When you receive standard radiation, the total radiation dose is fractionated, which means the dose is often split into many smaller portions or fractions delivered over several weeks. This is done in order to maximize damage to the cancer cells while minimizing damage to healthy brain tissue.

In hypofractionation, the total radiation dose is divided into fewer, larger fractions given in less time.

Standard, fractionated radiation therapy usually starts a few weeks after surgery, normally as soon as the surgical wound heals. Normal EBRT is usually given in 30–40 sessions over a 6-week period, 5 days a week (usually Monday through Fri-

day). The actual treatment may take only a few minutes, but you should expect to spend 30 to 45 minutes preparing before each treatment session.

You would also take a low dose of the chemo Temodar each day throughout the 6 weeks. After the completion of the 6 weeks, you will often be given a 4-week break for recovery.

Brachytherapy may be administered for only a few days, followed by removal of the radioactive “seed”.

Stereotactic radiosurgery is typically conducted in one single session that may last an hour or more.

## What to Expect During Treatment

The first step in radiation treatment is a consultation with the radiation oncologist. In this important visit, you and your radiation oncologist will meet each other and discuss your situation. During the consultation, the radiation oncologist will review your medical history and perform a physical examination. If your radiation oncologist is not associated with the treatment facility where you had your diagnosis and surgery, you should bring any images, records, referral forms, list of medications you are taking and your insurance information.

The radiation oncologist is likely to impact a great deal of information to you in your consultation, so it would be helpful to take someone with you to help you remember all the details. Also, this is when you bring out any questions you may have. Below you will find some sample questions you may wish to ask.

The radiation oncologist may order additional images or tests before radiation begins. Your sessions will be scheduled once these additional results are in, and the doctor has had a chance to review them. The radiation oncologist most likely will make his treatment recommendations to your neurosurgeon and/or neuro-oncologist to ensure a multi-disciplinary consensus. Once this is achieved, the radiation oncologist will communicate the plan with you and seek your consent to commence radiation treatment.

## Planning Session

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At this point, you can expect to be asked to come in for a planning session. During this session, you will become acquainted with the treatment facility, equipment and you may undergo a radiation simulation. You will not receive any radiation during this planning simulation, but you may be fitted with a mask that will help hold your head steady during treatments.

The skin of your head may also be marked (temporarily) as the radiation oncologists maps out the alignment and delivery plan for the radiation beams. You may have some low energy red laser lights appear on your head when they completely darken the room, but these will not be emitting any radiation and you will probably not even feel them; they are just for alignment and planning purposes.

You should expect to spend quite a bit of time at the planning session as the radiation oncologist and staff prepare a highly precise, highly sophisticated computerized program for your radiation sessions. It may take a few days for that program to be prepared and double checked. Once that is done, then your sessions can begin.

## Radiation Sessions

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To prepare, you'll be positioned on a table. Cushions and restraints will be used to hold your head and body still. Then you'll undergo an imaging test, such as an X-ray or CT scan, to make sure you are in the same precise position before each treatment.

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During radiation treatment, you must lie very still on the treatment table while the radiation beam is targeted to the exact area of the tumor. Depending on the equipment used, the machine and treatment table may rotate on a gantry up to 360 degrees so that the radiation hits the tumor from all angles.

The radiation oncologist and technologists will not be in the room during the treatment, but they will be watching you via a video camera and can hear you through an audio connection with the treatment room so if you have an issue, you will be able to communicate with them.

You'll probably hear the machine when it's turned on and delivering your radiation, but you will not feel the radiation as it is being delivered.

Once your treatment session is complete, you can go about your day. You won't be radioactive or give off radiation or glow green.

## **Weekly Checks**

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You may undergo weekly CT scans to see if the dose you receive needs to be recalculated based on any changes in weight, or tumor size and shape. You probably will meet with your radiation oncologist weekly for a quick check to see if you are having any issues that need discussing.

## **Post-Radiation MRIs**

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Expect that any MRI taken within a month or even two after radiation treatment may contain a significant amount of swelling (edema) that could cause the image to be very cloudy. In terms of understanding if the tumor is active, this (or these) MRI images could be inconclusive and not worth the anxiety. However, the imaging is important for the future comparison purposes.

## **Pre-Radiation Therapy Questions to Ask**

### **Questions About Treatment Equipment & Techniques**

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- Do you treat many patients with this type and size of tumor, and in a similar location often?
- What type of equipment do you plan to use for my radiation?
- How do you ensure my safety and the accuracy/ consistency of daily treatment?
- Will treatment be tailored with different doses, margins, depending on proximity of tumor to adjacent Organs at Risk (OAR)?
- How will OAR be protected? e.g., Optic nerve, hippocampus, temporal lobe, frontal lobe, cavernous sinus, carotid artery, pituitary gland, cognitive abilities, etc.?
- How will tumor target volume be determined? Who interprets and reviews the clinical target volume (CTV) prior to treatment?
- How will the tumor boundaries be determined for bone and dural tails to

- ensure nothing is missed? Will MRI, CT, PET/CT, PET/MRI be used? (A dural tail is a thickening of the membranes next to the tumor.)
- Will the “radiation plan” be explained? (Including how much radiation exposure does healthy brain tissue and OAR receive?)
  - Are there any medications that will maximize the effectiveness of the radiation and will they be used?

## Questions About Side Effects Of Treatment & Management Of Side Effects

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- What healthy areas are most at risk from the radiation plan? (Identify areas of hair loss, skin irritation, muscles, ears, nose, eyes, lacrimal gland, pituitary gland, etc.)
- What potential neurological deficits risks/side effects/complications are associated with the treatment?
- Can I develop seizures as a result of radiation treatment? (Answer should be yes but perhaps as a rare occurrence because the brain is likely to swell some and swelling may trigger a seizure.)
- What functions/ parts of my brain may be injured temporarily or permanently by this treatment? Odds?
- What about the development of necrotic tissue as a result of treatment? Odds? (Answer should be between 20 and 30%)
- What emotional side effects can I expect to have from this treatment? How soon, how far into the future?
- How will these issues be managed, near term, long term?
- What side effects from treatment can I expect to have?
- How much medical care & assistance might I need during the worst side effects of his treatment?
- Are there medications/supplements that will help prevent or minimize expected side effects before, during, after treatment? For how long?
- What are the side effects of these medications?
- What vitamins/supplements can be taken during treatment? (Expect that the answer is “None whatsoever” because vitamins/supplements can interfere with or un-do the beneficial effects of the radiation treatment.)
- (If applicable:) What effect will radiation have on any other medical problems I have and medications I take?
- Can I continue to work and drive during treatment? (Neither is a good

- idea because a person receiving radiation will likely be fatigued from the treatment, but you should be guided by what the doctor says.)
- What will be my follow-up care after all radiation sessions are complete and who does that?

## Side Effects to Expect From Radiation Treatment

The most common side effects of radiation follow.

**Scalp problems.** Your scalp may be red, irritated, or sensitive where the radiation beam goes through the scalp. If the tumor site is closer to the outside of the brain, the beam may be more intense.

**Hair loss.** Where the radiation beam goes through the scalp hair may be lost, most likely temporarily. You might want to find a very gentle shampoo to use during radiation. Avoid all shampoos that are harsh and have alcohol, salicylic acid, grapefruit juice, or strong fragrances in them. (Check the ingredients of any shampoo). Go for organic, natural shampoos, and don't waste money on products like Nioxin and Rogaine to restore hair after radiation. Those products don't work for radiation hair loss.

**Swelling (edema).** Swelling in the brain at or near the treatment site can cause signs and symptoms such as headaches, nausea, maybe even some weakness.

If you are having to travel any distance in the car to get to the daily radiation appointments, you should consider having supplies ready in case of nausea. The movement of the car, plus intracranial swelling stimulated by radiation, can sometimes (but not always) result in spontaneous vomiting.

Symptoms from swelling are likely to increase across the period radiation is given as the irritation to the brain increases across time. In short, the last 3 weeks of radiation (in a 6-week schedule) and a few weeks afterwards are probably going to be the most sensitive time. Be aware that the swelling in the brain may cause a seizure during this period, especially if the patient overexerts themselves. Not everyone experiences serious symptoms like that, but it is a good idea to be aware and watching.

The radiation oncologist may prescribe an anti-inflammatory medication (such

as the steroid dexamethasone commonly referred to as “dex”) to treat symptoms caused by too much swelling if they appear. Ideally, you should only take the least amount of dex for the least amount of time necessary to manage symptoms.

**Fatigue.** Tiredness and fatigue may occur during radiation and/or for the first few weeks afterwards. The way the brain heals from any injury is to rest, particularly within deep sleep. So, you should not be worried about tiredness; it is a sign that the brain is doing what it should to respond to the radiation and heal.

**Necrosis.** A possible complication associated with radiation is the build-up of dead tissue called necrosis. The radiation therapy being administered kills the cancer cells, and in some cases, this may cause dead cells to build up faster than the body can remove them. Large amounts of necrosis can cause complications. Some patients may require follow-up surgery to remove the necrosis. Necrosis happens in around 25% of cases and can show up on an MRI at any time after radiation.

The typical time to first see radiation-induced necrosis is about three (3) months after radiation has finished, but it can appear as late as 18 months or even longer. Radiation necrosis has been reported to occur between 3% and 24% of patients and there are no known predictive factors for radiation necrosis.

**Radiation Injury.** Over time, it becomes apparent that the tissue irradiated is damaged, hence the drive to radiation technologies that minimize effects to healthy brain tissue. Radiation damaged tissue will generally lose blood supply and becomes oxygen deprived. There can be chronic radiation complications result from scarring and narrowing of the blood vessels within the area which has received the treatment.

## Post-Radiation Self Care Tips

Here are some simple things that you can do to help your brain heal after radiation:

- Sleep at least 8 hours every night, at the same time, preferably starting early (like at 8PM).
- Sleep with your head slightly elevated. That will help with any swelling.

- Take a good, 2-hour power nap in the afternoon starting not later than 4:30PM (or else you may not sleep that well at night).
- Eat healthy. Include lots of fruits and veggies. The brain likes fish and dark berries (dark cherries, blackberries, blueberries, strawberries)
- Meditating about 15-20 minutes a day helps calm down any built-up stress (which inhibits healing) and....it can help boost the immune system.
- Do some physical exercise/activity every day. Follow the guidance of the doctor for physical activity and do what is safe but avoid (to the extent possible) taking root in a recliner. Sensible physical activity will help the brain recover after radiation.
- Do some mental exercise/activity. You need to do something every day that you think is fun and stimulating such as painting/drawing, putting puzzles together, making scrap books, building model cars, anything that makes you think. The brain likes to have its neurons stimulated, which helps with recovery and if you enjoy what you are doing, it is likely a good, restorative activity.

## Radiation Limits

There are limits on the amount of radiation that a person can safely have. These limits are both annual and lifetime.

When a person goes through the standard-of-care radiation therapy for a high-grade brain tumor, they receive all of their annual (rolling 12-month) limit and half of their lifetime limit. This is calculated as follows:

Average radiation treatment amount for brain cancer is 60 GY (Grey which is a method for measuring radiation). Dosages vary from 50GYs to 66GYs depending on the cancer; brain cancer's normal dosage is 60GYs.

The typical length of treatment for brain cancer is 33 sessions, making the total

amount of radiation received 1,980 GYs.

Most guidelines recommend an annual radiation limit of 2000GYs and a lifetime limit of 4000 GYs.

If a person received standard radiation of 1980GYs in Year 1, they can theoretically be re-radiated at least 12 months after the conclusion of their prior radiation but will have a limit of roughly 2000GYs at which point, they will have exhausted their lifetime limit and no further radiation can be provided.

Concerning Gamma Knife, dosages for GBM are typically 10 to 22GYs given in a single session. To be eligible for Gamma Knife, the tumor has to be quite small, normally measuring less than 3 centimeters (1 inch).

## SURVIVOR STORY #6

On September 19, 2012, I had a grand mal seizure. It was during my lunch break at work, and I was talking with a coworker when I started feeling strange. It felt as if my eyes were crossing each other. It seemed like just a minute, but the next thing I knew was that I was lying on the floor, with an emergency technician asking me whether I could see him. My co-worker was also looking down at me, and he seemed scared. I was 35 years old, the mother of two young girls, and in good health. I rarely even had headaches, let alone a seizure.

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I spent several days at the local hospital. More seizures followed. A biopsy revealed that I had a grade IV glioblastoma in my left parietal lobe. Family and friends researched our options, and we selected a comprehensive cancer center as the best place for my treatment. My doctor there told me that with a tumor the size of the one I had, I should have undergone immediate surgical resection rather than first having a biopsy.

At the comprehensive cancer center, I did undergo surgery to remove as much of the tumor as possible. During surgery, the neurosurgeon placed Gliadel Wafers in the tumor cavity. After surgery, I completed 4-weeks of radiation treatment with concomitant temozolomide (Temozolamide). After radiation, I continued with adjuvant temozolomide at home and had an MRI scan every 2 months.

Seven months after my first diagnosis, I had recovered well enough to run a 5K race with my family. But the adjuvant therapy with temozolomide left me feeling weak, and the MRI scans indicated that my tumor had recurred at the original site. When I was initially diagnosed, the molecular profile of my tumor indicated that it might not be as responsive as possible to alkylating agents like temozolomide because my MGMT status was unmethylated.

By fall 2013, my family and I began an intensive search for a clinical trial for me. We felt that the type of clinical trial that would offer the most hope would be one that enhanced my own immune system to combat cancer cells. We searched websites, especially the listing of clinical trials on the clinicaltrials.gov website of the US National Library of Medicine, and eventually narrowed down a list of potential clinical trials.

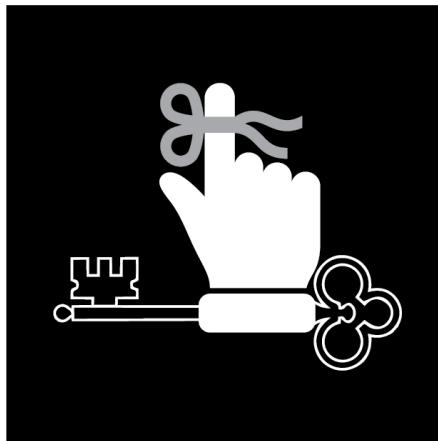
To find a clinical trial, I needed to consider my eligibility as well as the nature of the study itself. I applied to several clinical trials and came close to entering two of them before I was accepted for a clinical trial at a comprehensive cancer center in Los Angeles that seemed the best fit for me. My husband and I flew out there, and I underwent surgery again to remove the recurrent tumor and to have a port inserted. After cells were collected from my tumor, killer T immune cells taken from my body as well as from donors were "trained" to attack the tumor. The concept was that these modified T immune cells could be inserted every two months through the implanted port to help my body fight any residual cancer cells.

After the second resection, I returned home to await my flight back to Los Angeles for the first treatment session. I had lost vision in my right eye as a result of the second surgery, and I also had a low-grade fever, but nonetheless I was ready to proceed. I flew to California and received the first injection through the port. Unfortunately, my fever became worse, and it was discovered that meningitis had developed because my body was rejecting the implanted port. I thus had another surgery to remove the port, and the decision was made to place the modified T immune cells directly on the site of the tumor.

It took a stay in intensive care, time, and antibiotics. Luckily, after several weeks I recovered from the meningitis. I was disappointed to learn that I could not continue in the clinical trial. But my MRI scans showed no sign of tumor. The decision was made for me to go home to wait and see. I have been waiting and seeing for four and a half years. So far, my MRI scans show no sign of recurrent tumor.

The cancer and the surgeries have taken a toll. Although I am on antiepileptic drugs, I still have seizures. I have no vision in my right eye, and I have not been able to return to my former career as a mechanical engineer. But I am lucky. I am a stay-at home mom to two wonderful girls. I can sew and work in my garden. I spend time with my friends and family and enjoy my life. I hope that sometime soon we will all have treatments that are more effective than chemotherapy.

### KEY TAKEAWAYS TO REMEMBER



If at all possible, have your radiation administered at a top brain cancer clinic because they are most likely to have the latest, most advanced radiation equipment which can best treat your tumor and preserve the healthy parts of your brain.

Find out exactly what type of radiation technology will be used.

Talk to your radiation oncologist about what side effects that you may expect.

If you have not been prescribed the chemo Temozolomide (Temodar) to take concurrently with your radiation, ask why. This chemo has been shown to sensitize cancer cells to the radiation leading to a better outcome.

# Brain Tumor Guide for the Newly Diagnosed





## Chemotherapy

### Overview

Chemotherapy (often referred to as “chemo”) is the use of a drug or combination of drugs to kill tumor cells. In the case of malignant high-grade tumors, the chemo lessens the chances the tumor will return or grow. In other cases, chemo may stop the growth of the tumor entirely.

Chemo is considered a “systemic” therapy because the drugs will go throughout the body, which is a benefit if any cancer cells have moved away from the original tumor (a process called metastasis).

Not all chemo drugs work the same way. Depending on the particular type of chemo, the drug may damage the cancer by (1) destroying the tumor’s DNA directly; (2) restricting the tumor cell’s ability to divide, grow, and invade healthy tissue; or (3) blocking the blood supply to the tumor itself and inhibiting the growth of new blood vessels that would otherwise feed the tumor.

When a brain tumor requires treatment with chemo, doctors will be reluctant to use the word “cure”, although their objective has a curative intent. The realistic goal of chemo treatment with brain cancer is to control and manage the disease by discouraging further growth and spread.

Chemo for brain cancer is given in different ways. Many chemos are administered at home orally in pill or capsule form. Other chemos are delivered in an infusion room at the clinic or hospital intravenously through a thin needle placed directly into a vein. In very rare cases, the chemo may be delivered intra-arterially, that is, inject-

ed directly into an artery that travels to the tumor. How you receive your chemo depends on what specific chemo you have been prescribed.

## Is My Chemo Working?

The only way you and the doctor will be able to determine if the chemo you are taking is working is by observing the reaction of the disease. If your regular MRIs are returning absent evidence of disease, or showing signs of stability/no growth, then it is understood your chemo is working.

The side effects you may experience to the chemo are not indicative of its effect on the cancer. Some people have no/few side effects, but the chemo is slamming the cancer. The effects of the treatments on you are independent from the effects of the treatments on the disease.

The most common prescribed chemotherapies for brain tumors follow.

### Temozolomide (Temozar or Temodal)

#### Overview of Temozar

Temozolomide (typically referred to as "Temozar" or "Temodal") is the standard, most prescribed first chemo for brain cancer. It is a derivative of a class of drugs called imidazotetrazines. Temozar entered critical trials in 1985 and was released to the market by Schering-Plough in 1999. Since then, it has been widely used in combination with radiation as the standard first-line treatment for brain cancer.

Temozar has excellent characteristics. It has 100% oral bioavailability which means that it can be administered in pill form. Also, Temozar usually produces only moderate side effects relative to other chemos.

Absorption is rapid; the peak concentration in the blood happens between 30 minutes and 2 hours after the Temozar is taken, and then its by-products are quickly excreted in the urine. When Temozar is at its peak and as it circulates through the body, it immediately kills any rapidly dividing cells, most notably cancerous cells. However, Temozar will kill other rapidly dividing cells like hair follicles, cells

in the gut, and blood cells. This is why hair loss should be expected with Temo-  
dar treatment and also why blood tests are needed during Temodar treatment.

Temodar is an alkylating agent. It kills the cancer cells by disrupting the DNA repli-  
cation happening in the cancer cell, thus causing programmed cell death (apoptosis).

For a tumor to be most responsive to Temodar treatment, the tumor should be deficient in MGMT (O6-methylguanine-DNA methyltransferase) but proficient in MMR (DNA mismatch repair proteins). For alkylating agents like Temodar and like Carmustine (the chemotherapeutic agent used in the Gliadel wafer), methylation of the promoter of MGMT is a major favorable prognostic factor, and it is found in approximately 35% to 45% of patients with Grade 3 and 4 gliomas. That is, if you have an MGMT-methylated tumor, Temodar (or Carmustine) is more likely to pro-  
vide a greater magnitude of progression-free and overall survival than if you have an MGMT unmethylated tumor. Consequently, if you are among the majority of patients with an MGMT-unmethylated tumor, you should seriously consider enrollment in a clinical trial because it is likely that you will derive less benefit from stan-  
dard of- care treatment.

Temodar rapidly crosses the blood-brain barrier (BBB) and has been shown to induce tumor regression in patients with high-grade astrocytomas and GBM.

### **Dosage and Frequency**

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The dose for Temodar is dependent on the phase. There are two phases for Temodar administration during SOC: an initial phase and a maintenance phase.

In the initial phase, a low dose of Temodar is usually prescribed to be taken daily concurrently with radiation, which generally consists of 42 sessions and runs about 6 weeks. Treatment with the combination of radiation plus Temodar has been found to improve survival in all patient groups, even elderly patients, because it has been found to be a sensitizer that makes the radiation more effective. As an adjuvant to radiation, Temodar is administered daily (even on weekends when radiation might not be administered).

Unless otherwise directed by the neuro-oncologist, the maintenance phase of Temo-  
dar begins after a 4-week break commencing at the end of radiation. In the mainte-

nance phase, a higher dose of Temodar is prescribed and is taken for 5 consecutive days out of every 28 days.

The exact quantity of Temodar to be taken during each phase is calculated based on Body Surface Area, taking into consideration your bone marrow toxicity (as determined by blood tests) and your tolerance (e.g., absence of abnormal or intolerable side effects).

Body Surface Area (BSA) is determined by weight and surface area in square meters. The BSA for the average adult male is 1.9 and for the average female is 1.6.

For the initial phase, the daily dose of Temodar in milligrams is calculated using this formula:

- 75 mg/m<sup>2</sup>/day (where m<sup>2</sup> is your BSA).
- For instance, for a person with a BSA of 1.84, the dosage would be calculated as follows:  $1.84m^2 \times 75 \text{ mg}/m^2 = 138\text{mg}$ . This would be rounded up to 140 mg/day.

For the maintenance phase, Temodar dosage is higher, but the chemo is not taken daily as it was during radiation. It is taken for 5 consecutive days every 28 days, which is called a cycle. The dosage for the first maintenance cycle will be lower than the other maintenance cycles to enable the doctor to judge your tolerance level for Temodar. The formula for the maintenance phases of Temodar are as follows:

- First maintenance cycle: 150 mg/m<sup>2</sup>/day (where m<sup>2</sup> is your BSA.)
- Subsequent cycles: Assuming you show acceptable levels of tolerance, the Temodar is increased to 200 mg/m<sup>2</sup>/day for each of the remaining cycles (where m<sup>2</sup> is your BSA. This is considered the maximum amount.

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For a reality check on your Temodar dosage, please see the dosage calculator on the Musella Foundation website at this link:

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<https://virtualtrials.org/temodar/dose.cfm>

## **Length Of Maintenance Phase**

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Your doctor will decide how many cycles of Temozolamide you will receive in the maintenance phase, depending on how you respond to and tolerate treatment. The standard number of cycles is six (6) but may be increased to twelve (12) cycles.

Evidence from studies suggests that there may be an improvement in progression-free survival for those who take more than 6 cycles, but there could also be a higher risk of significant hematological toxicity with no increase in overall survival. For that reason, the doctor has to carefully assess your tolerance to the chemo and the tumor's responsiveness and decide if you should continue Temozolamide for some other period such as 12 or 18 months. In other cases, the doctor may prescribe Temozolamide until it stops working or causes side effects or until the tumor is either completely gone or sufficiently stable.

## **Side Effects and Toxicity**

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Temozolamide is considered somewhat less toxic and better tolerated than many other chemotherapies but does have the common side effects of weakness and fatigue, nausea and vomiting, constipation, gastrointestinal upset, alopecia, and low blood cell counts caused by bone marrow suppression.

Temozolamide may increase the risk of infection by lowering the number of white blood cells you have in your blood. Symptoms mimic those of a cold or flu: a change in your temperature, general muscle aches, headaches, feeling cold, shivering. Your doctor may prescribe a mild, generic anti-microbial like Bactrim to help guard against infection.

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Contact your doctor or physician's assistant/nurse immediately if you develop signs of an infection which includes a temperature of 100.4 degrees Fahrenheit or 37.5 Celsius, or an alternate temperature advised by your doctor.  
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Temozolamide may cause your gums or nose to bleed. This is caused by a drop in the number of platelets in your blood. Platelets help form clots when we cut ourselves. You may notice bloody gums when you brush your teeth, or you may see small bruises or spots on your arms and legs.

Because a simple cavity or early gum infection (gingivitis) can quickly escalate into an acute infection, you should obtain a thorough dental examination prior to beginning Temodar treatment and follow up regularly with your dental care team.

You may also lose your appetite when on Temodar. The fatigue or feeling sick can decrease one's appetite.

You may also have headaches. You should tell your doctor's office if you keep getting headaches so that the doctor can recommend treatment.

Less common but potentially severe adverse events included severe myelosuppression, myelodysplastic syndromes, pneumocystis pneumonia, hepatotoxicity, and embryo-fetal toxicity.

## **How To Take Temodar (Sample Protocols for Information Only)**

Your doctor is going to give you specific instructions for how and when to take the Temodar you are prescribed, and those instructions must be carefully followed. To give you an idea of what you might expect, sample protocols are provided below solely for informational purposes,

### **Low Dose**

During radiation, Temodar is taken daily throughout the period of radiation treatment. A low dose of Temodar is usually taken every morning in order to sensitize the tumor to the radiation.

### **High Dose**

#### **General Notes**

- Temodar should be taken on an empty stomach in the evening. This means you shouldn't eat anything for two hours before and an hour after you take it. You can drink water during this time but should not have any solid food.
- It is important not to open or split the capsules. Temodar should be swal-

lowed whole with water. Never chew the capsules.

- If you miss a dose, contact your doctor or nurse. Do not make up the missed dose by taking a double dose.

A sample, time-ordered schedule based on going to sleep at 9 PM follows. This schedule would need to be adjusted based on your specific time to go to sleep.

- 6PM: Only if your doctor so instructs you, you would first take your Nexium/Pepcid or whatever the doctor recommends to coat the stomach. Some leading doctors do not consider this step necessary for those without stomach problems.
- 6:30PM: dinner. Must be only light and white, easy to digest foods. No heavy dinners. No red meats (e.g., no burgers, no steak), no red sauces.
- 7PM (or 30 mins after finishing dinner): take one (1) Zofran pill. Zofran is the anti-nausea pill prescribed by the doctor.
- 7:30PM (or 30 mins after Zofran): Only if your doctor so instructs you, take the sleep aide your doctor may have suggested to help you sleep through any breakthrough nausea. This pill may be a mild herbal sleep aide. Many people do not need this pill. If you can handle the high dose Temodar without this sleep aide, it is good to avoid it, but if nausea wakes you up, this is the solution.
- 8PM (or 30 mins after taking your sleep aide): take your prescribed daily dosage of Temodar with a full (8 ounce) glass of water. (No other liquid; just water.)
- Only if your doctor so instructs you, sit upright for one (1) hour after taking Temodar. Your doctor may consider this step important if the doctor thinks that by laying down right away after taking the Temodar, you might cause the Temodar to splash back and damage your upper gastro-intestinal system. People who suffer from gastroesophageal reflux disease (GERD) may need to do this step.

- 9pm (or after one hour of sitting upright). Go to bed for sleep.
- Next morning: Because Zofran constipates with a vengeance, drink a glass of MiraLAX or some other anti-constipation aide, as recommended by the doctor. Many also use a stool softener like docusate or Senna. (For Senna a typical schedule for taking it is at 8am and 8pm.)

As mentioned, the doctor will go through the process he or she wants you to follow in detail. Since the above schedule has a few practical concepts woven into it based on practical experience, it might be helpful to copy this, take it to the doctor's office when you have your discussion, and then find out from the doctor what changes the doctor wants. The doctor's word, of course, is the final authority on how you should take the Temodar.

## FDA Data Sheet

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The official FDA approved Data Sheet on Temodar is available online at this link:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021029s031lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021029s031lbl.pdf)

## Lomustine/CCNU/Gleostine

Lomustine, also referred to as CCNU or Gleostine, is another chemo that, like Temodar, is an alkylating agent (i.e., it interferes with the DNA of cancer cells, thereby inhibiting their growth). Whereas Temodar acts by alkylation of guanine, Lomustine also introduces interstrand crosslinks and leads to carbamoylation of amino acids, which interferes with certain processes necessary for the replication of cancer cells.

Lomustine is probably the most prescribed chemo for brain cancer second only to Temodar, and it is usually prescribed in the following situations:

- For those diagnosed with a newly diagnosed high-grade tumor, some doctors, notably those in the UK or Europe, may prescribe a combination of Lomustine with Temodar. In small studies, the overall survival has been superior in those receiving the combination therapy, however, toxicity is

## Eight: Chemotherapy

higher compared to those taking Temozolamide as a monotherapy, so further study comparing these treatments is needed.

- For those diagnosed with a recurrent high-grade tumor and previously treated with Temozolamide, many doctors will prescribe Lomustine, absent other treatments (e.g., clinical trial).
- For those newly diagnosed with Oligodendrogloma, doctors may prescribe a combination of Procarbazine hydrochloride, Lomustine (CCNU), and Vin-cristine sulfate, a combination known as PCV. PCV may also be prescribed for those with a recurrent high-grade glioma which is not an Oligodendrogloma. Lomustine is considered the most active ingredient of the three (3) chemos.

Lomustine is a moderately emetogenic chemo, that is, it can cause vomiting that requires a standard anti-emetic medication, which is usually sufficient. The most relevant adverse effect is thrombocytopenia (lower than normal number of platelets, which may result in easy bruising and bleeding). Neutropenia, which is a lower-than-normal number of a certain type of white blood cell, can be seen, often in a delayed time frame, that can make a patient at a higher risk for infection.

Certain studies have shown that the combination of Lomustine and Avastin may effectively increase overall survival (OS), progression-free (PFS), and 6-month PFS in patients with GBM.

The official FDA approved Data Sheet on Lomustine/CCNU/Gleostine is available online at this link:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/017588s042lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017588s042lbl.pdf)



## Carmustine/BCNU

Carmustine is another common alkylating-type chemo for high-grade brain cancers. Its brand name is BCNU.

It has been given to brain cancer patients by IV, but that approach produces what some doctors consider an unacceptable level of toxicity. For that treason, Carmustine is most often used by wafer implantation in the resection cavity in conjunction with surgery, whether at the time of initial diagnosis or recurrence.

Biodegradable wafers impregnated with Carmustine (referred to as Gliadel® wafers) is thought to provide a therapeutic bridge during the healing period between surgical resection and the onset of radiation.

For more information, please refer to the discussion of Gliadel Wafers in the section above entitled "Surgery".





## Immunotherapy

### Overview

In the past few decades, there has been rapid development in tumor immunotherapy, which is recognized as a key strategy to treating malignant tumors. Normally, the immune system recognizes and eliminates foreign or abnormal cells, like bacteria, viruses, and even cancer cells before they can harm us. However, once a brain tumor reaches a certain point in its development, chemical signals from the tumor prohibit the immune system from recognizing tumor cells. Some tumor cells are able to escape detection by the immune system and continue growing and invading. (For more information about tumor cells' ability to escape the immune system, please see Appendix C entitled "Causes of Brain Tumors" at the back of this Guidebook.)

Knowing this, researchers and doctors have led efforts in the specialty of immunotherapy to stimulate and activate the patient's immune system in a manner to "wake up" the immune system to kill tumor cells. Other cancers have used immunotherapies with success, which encouraged work to direct this line of therapies toward brain cancers.

However, treating the brain with immunotherapy presents problems not found with other organs. The brain is protected by a blood-brain barrier (BBB) which can prevent certain drugs from entering the brain and it has a unique immune environment. There is a strong presence of cells in the tumor environment that are immunosuppressive (resistant to the beneficial actions of the immune system), plus there are few T cells (critical immune cells that react against foreign antigens). In addition, gliomas are composed of glioma cells with a high degree of microheterogeneity (i.e., differences in structure) even within the same tumor, making some cells responsive to a certain treatment and others less so.

As a result, researchers constructing immunotherapies for the brain must use the maximum of skill. Some approaches they are now using to overcome these various problems are improved grooming of the native immune system cells (i.e., natural killer cells, macrophages) and the adaptive immune system (i.e., cytotoxic T lymphocytes, B lymphocytes) to basically wake them up to do their jobs and “marking” of epitopes (that part of an antigen that the immune system is able to detect) so that the immune system recognize the cell with that antigen as being foreign. To accomplish these tasks, researchers are pursuing novel approaches, including combination therapies which are likely to show improved results against brain cancer.

Some studies have suggested that the use of the steroid called dexamethasone which is used to reduce the swelling caused by brain tumors and procedures like surgery and radiation may decrease the effectiveness of immune checkpoint inhibitors. Dexamethasone has potent immunosuppressive properties and inhibits the beneficial actions of T cells. As a result, many doctors are now recommending patients about to start immunotherapy to reduce their dexamethasone dosages to the lowest possible necessary to handle symptoms.

The various types of immunotherapies being developed against GBMs are described below.

## Personalized Vaccines

### **Selected Definitions**

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**Antigen:** Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances from outside the body. Cancer cells also have antigens on them that can cause an immune response.

**Autologous:** cells obtained from the patient themselves.

**Dendritic cell:** A special type of immune cell that is found in body tissues and that enhances an immune response by showing antigens on its surface to other cells of the immune system. A dendritic cell is a type of phagocyte and a type of antigen-presenting cell (APC).

**Primary endpoint:** means the result of a trial measured at the end to see if the treatment being tested worked, i.e., that there was a positive and clinically significant difference in survival between the group of patients getting the treatment and a control group of patients who did not.

## Overview

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Emerging as a potential addition to the Standard of Care in the treatment of GBM is a form of immunotherapy that involves personalized vaccines that use the patient's own dendritic cells. The antigens these dendritic cells collect are designed to stimulate an immune response, thereby activating the powerful killer T immune cells to destroy the tumor. Results from vaccine trials suggest that patients with GBM receiving such a personalized vaccine may survive significantly longer than patients receiving the current Standard of Care treatment.

Please note: If you are interested in treatment with a personalized vaccine, you must make arrangements before surgery to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.

Dendritic cells were first discovered in the late 1800's but were thought to be a type of nerve cell. Later it was understood that dendritic cells, which are made in the bone marrow, are the most potent type of cells in the immune system that carry an antigen.

Due to the way these cells are shaped, they have a very large surface area which enable them to contact many other immune system cells such as T- cells, natural killer cells, neutrophils, epithelial cells. In the lab, one fully grown dendritic cell was able to stimulate up to 3000 T-cells.

## DCVax-L Vaccine

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It made sense to researchers to capitalize on these sentinels of the immune system and manipulate them into stimulating the immune system against brain tumors. Research on this approach has been well underway for many years, and one of the research products is DCVax-L, an autologous dendritic cell vaccine.

At the time this Guidebook was being issued, results of an extensive Phase III trial on the DCVax-L had just been released. This data is just interim and may get either better or worse as the data continues to be analyzed. For the latest information about the DCVax-L vaccine and to view the presentation slides of the interim Phase III results, please go to this link:

<https://virtualtrials.org/dcvax.cfm>

## **Other Personalized Vaccines**

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Other products using personalized vaccines include vaccine pulsed with lysate or peptides, again showing how researchers are working creatively to combine approaches and technologies. Exploiting the potency of dendritic cells holds promise for brain cancer treatment, so those looking for novel, advanced therapy should watch for developments in this technology.

## **Monoclonal Antibodies/Immune Checkpoint Inhibitors**

A vital capability of the immune system is to be able to tell the difference between a normal cell and a cancerous one. Doing so enables the immune system to destroy the cancerous ones while leaving the normal cells alone. One of the ways in which the body does this is by targeting a particular checkpoint protein, which acts as a type of switch turning the immune system on and off. The class of medicine that does this is called a monoclonal antibody.

In cancer treatment, monoclonal antibodies are used to remove the “brakes” and turn on the immune system so that the system can perform its function of destroying the cancer. By blocking particular checkpoint proteins, the body’s natural, pre-existing anti-cancer immune responses are unleashed.

There are several monoclonal antibodies being used in brain cancer treatment and they are known by the specific checkpoint protein they target.

## PDL/PD-L1 Checkpoint Inhibitors

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If a GBM is found to be positive for PD-1 (programmed cell death protein 1) or /PDL-1, then the doctor may recommend a PDL/PD-L1 checkpoint inhibitors. These proteins are found on T cells, a potent immune cell that can become activated and eliminate the cancer cells.

Pembrolizumab (Keytruda) or Nivolumab (Opdivo) are common types of PD-1 immune checkpoint inhibitors. Another one called Cemiplimab (Libtayo) is used for treating certain brain metastasis.

Atezolizumab (Tecentriq) or Avelumab (Bavencio) or Durvalumab (Imfinzi) are common types of PD-L1 checkpoint inhibitors. Durvalumab is being tested against primary brain tumors; the others are being used to treat certain brain metastasis.

## CTLA-4 Inhibitors

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Another checkpoint protein that is found on T cells is the CTLA-4 (cytotoxic T-lymphocyte protein 4) protein. A checkpoint inhibitor that targets this protein to take the brakes off the immune system is Ipilimumab (Yervoy). As an example of the attempts being made to combine approaches, researchers are testing a combination of Ipilimumab and Nivolumab (described above) in conjunction with surgery for recurrent GBMs.

## LAG-3 Inhibitors

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A recent avenue of study for ways to defeat GBM involve targeting the LAG-3 (lymphocyte activation gene 3) checkpoint protein. LAG-3 is currently thought to be a promising checkpoint protein along with PD-1 and CTLA-4. About 10% of GBMs are thought to express for LAG-3. Where a GBM does show LAG-3, then the doctor may recommend Relatlimab. Sometimes, Relatlimab may be combined with Nivolumab.

## Chimeric Antigen Receptor T-Cell Therapy/ CAR T Therapy

Each brain cancer cell has antigens on its surface that identify the cell as foreign to the body and, therefore, a potential target for destruction by the immune system. Each T-cell, which is an immune system cell, has a receptor that hunts for the antigens carried by the cancer cells. When a T-cell identifies a foreign antigen, it attaches to that cell and signals other parts of the immune system to attack the foreign cell.

In brain cancer, the tumor sends out chemical signals that confuse the T-cells so that they no longer can recognize the foreign antigens, leaving the cancerous cells to flourish unimpeded. In CAR T-cell therapies, T cells are taken from the patient's blood and are changed in a lab by adding a receptor called a chimeric antigen receptor or CARs. The CAR enhanced T cells are then given back to the patient. This process effectively re-educates the person's T cells, which is designed to restore their original function of attaching to the cancerous cell and triggering their disposal.

CAR-T therapy is a process which can take several weeks.

Trials have been underway to utilize this technology against GBM. One trial has involved the use of IL13Ralpha2, which is overexpressed in about 75% of GBMs, and another trial has involved GBMs that express for EGFR Variant III.

Despite early successes with CAR-T cell therapies, the effectiveness of the treatment tends to diminish over time, and this has launched a search for ways to boost the function of T cells. Scientists are working to identify a way to supercharge T cells, which will not only improve the effectiveness of this type of therapy, but also expand the number of cancers it can treat.

The results from the trials so far show that more work is needed to make this a viable immunotherapy for brain cancer, but this technology has only recently been attempted. CAR-T research is continuing to address the unique challenges posed by brain cancer.

For example, a novel CAR T-cell treatment is being tested at Stanford University which targets GD2 (disialylganglioside), a glycolipid found on nerve cells and highly expressed in H3 K27M mutated gliomas like DIPGs and DMGs (dif-

fuse intrinsic pontine gliomas and diffuse midline gliomas) is showing some progress. A few patients are showing significant reductions in their tumor volume from this treatment.

There are currently no approved CAR-T cell therapies to treat brain tumors, but work is ongoing to ripen this therapeutic approach. It is still worth asking about.

## Oncolytic Viral Therapy

Oncolytic virus therapy uses a modified virus that can cause tumor cells to self-destruct and stimulates the body's natural, pre-existing immune response against the cancer.

Oncolytic viruses - viruses that are able to infect and break down cancer cells but not healthy cells - are able to selectively replicate within and cause the death of cancer cells. Brain cancer cells have defects in them that allow for invasion by viral proteins. It is believed that oncolytic viruses will infect tumor cells and block the replication of those tumor cells. Through a process called lyses, the presence of the oncolytic virus may then cause the infected cancer cell to break down.

Several viruses, including adenovirus, measles virus, polio virus, parvovirus, HSV, and retroviral replicating vectors (RRVs) have been engineered to treat GBM. Below are described a few of these efforts.

### **Polio-Rhinovirus Chimera (PVSRIPO)**

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A vaccine under serious investigation is PVSRIPO. This treatment is composed of the live attenuated (Sabin) type 1 poliovirus vaccine with a foreign internal ribosomal entry site (IRES) of human rhinovirus type 2.

The PVSRIPO is called a chimera, which is an organism with two or more genetically different sets of DNA.

This vaccine has been shown to be safe in recurrent GBM patients and preliminary data suggests this vaccine offers extended survival.

The PVSRIPO chimera is able to attach to and infect malignant glioma cells; it recognizes CD155, which is a poliovirus receptor often expressed on GBM cells. Once inside the GBM cells, research suggests that the PVSRIPO causes an immune response so that the tumor cells can be recognized and destroyed by the body's own immune system. The FDA has granted PVSRIPO a breakthrough therapy designation as a potential treatment for patients with recurrent glioblastoma, citing evidence from an ongoing phase I trial.

## **Adenovirus**

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Trials using the oncolytic adenovirus are also underway. This virus has also been shown to cause glioma cell death and enhanced antitumor immunity in preclinical models.

## **Retroviral Replicating Vectors (RRVs)**

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Another approach, combining virotherapy and gene therapy, uses an RRV. The theory in this approach is that the virus will integrate into the host genome and spread through rapidly proliferating cells. Early phases of clinical trials evaluating the RRV called Toca 511 in recurrent high-grade glioma patients showed the virus was safe and persistent in the tumor, but the trial failed to meet its goals for effectiveness, so the developers have returned to the lab with this one.

Nonetheless, the survival data in the application of oncolytic viruses suggest that certain individuals will benefit from this technology. The key will be finding the genetic traits in the tumors that can predict which patients are more likely to respond to this form of therapy.

## **Vaccines**

### **Survivin-Targeting Vaccines**

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Survivin is a protein that is expressed in a variety of human cancers, including brain cancers. In GBMs, survivin is present in about 95% of them.

## Nine: Immunotherapy

The presence of the Survivin protein prevents cells from dying, so it is expressed highly during embryonic development (when we do not want cells to die off), but it is absent in most normal adult cells.

Investigators have created a synthetic Survivin vaccine, called SurVaxM, that stimulates the immune system to target this cancer molecule. In a phase II trial of patients with newly diagnosed glioblastoma, the addition of the Survivin vaccine to standard-of-care treatment provided a survival benefit even in patients with an MGMT unmethylated promoter status. Other trials with SurVaxM used as an adjunctive therapy for high-grade glioma are underway.

Another viral vaccine approach involving the Survivin protein, which also shows how researchers are combining technologies, is an oncolytic adenoviral virotherapy that contains the tumor specific Survivin promoter and a fiber protein polylysine modification (pk7), that is believed to have antitumor potential. Like the other oncolytic virus studies, this one enters and destroys glioma tumor cells. For detailed information please see ClinicalTrial.gov web site: NCT03072134.

For more information about Immunotherapy including a listing of clinical trials, please go to this website:

[https://virtualtrials.org/Immunotherapy\\_treatments.cfm](https://virtualtrials.org/Immunotherapy_treatments.cfm)



Image by Ryan McGuire, Pixabay

## SURVIVOR STORY #7

In September 2008 I had dizzy spells and a heightened sensitivity to bright lights. Upon visiting my family doctor, he ordered blood work and asked me to wear a Holter monitor, thinking that I might have a heart problem. I was 43 years old, and other than having low blood pressure I was in good health.

On October 2, 2008, I woke up at my usual time, 6:30 AM, went about my routine, got the kids up, made breakfasts, lunches, etc., feeling fine to this point. Around 8:00 AM, I felt dizzy again and began banging into door frames and tripping as I walked from the carpet onto the hardwood floors. My daughter, 11 years old, was talking to me and I couldn't understand what she was saying. I started to panic and I was sweating. I had to get my daughter to the bus stop and figure out what was going on. I came home from the bus stop shaking and afraid. My left side went all tingly. I thought I was having a stroke.

I called my husband at work and told him I needed to go to the emergency room. He rushed home and took me to the hospital, where I was taken for an electrocardiogram right away. They told me that I had not had a stroke and that there was nothing wrong with my heart, and they were getting ready to send me home, thinking I may have had just a fainting spell. With pressure from my husband and my family doctor, I was sent for a CT scan. Soon after came the news: a 3-cm brain tumor. The tumor was located close to the surface in the left parietal region, just above my ear. We were told to go directly and immediately to the regional neurological center.

Shocked and dazed, we first picked up our children at high school and elementary school, told them what was happening, had a group cry, dropped them off at home, and then went to the center. I had surgery 5 days later. The surgeon was able to remove only about 25% of the growth as the tumor mimicked the appearance of the brain and in places he was unable to differentiate between the tumor and healthy brain tissue. While we were obviously distressed by this, the surgeon told us to take heart because in these types of cases, surgery is not the primary determinant of the final outcome. After a week in hospital, I was sent home to recover and await the results of the biopsy. I was diagnosed with a grade III anaplastic astrocytoma and was referred to a cancer center for further treatment.

## Nine: Immunotherapy

In the early days, we were sometimes disheartened, especially as we learned more about this disease. In particular, while the Internet can be a tremendous source of information, it can also contain information that may be misleading. One of the scarier things to read about was the statistics, which can seem very grim. I made a conscious decision not to even think about statistics, and I encourage anyone going through the experience of a brain tumor to do the same, because we are not statistics.

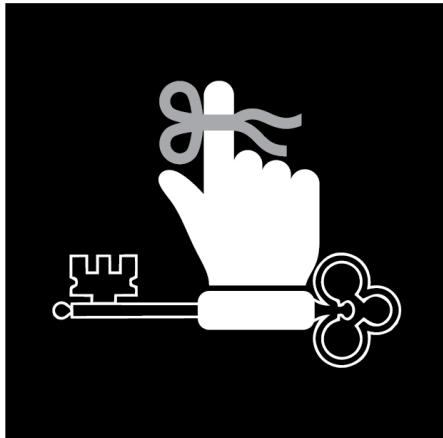
My initial assessment at the cancer center was on October 30. My radiation oncologist and the medical oncologist felt that because I was young and strong I could handle the most aggressive treatment. On November 17, I began a treatment regimen of radiation and chemotherapy together. I had radiation treatments Monday to Friday and took a low dose of temozolomide (Temodar) 7 days a week. I had a short break from radiation over Christmas and finished this phase of treatment on January 5. Overall, I tolerated it very well. Other than losing my hair, the biggest adverse effect I felt was increased fatigue. Also, the steroids I was taking to relieve headaches and pressure in my brain caused bloating and affected my sleep patterns.

After a four-week recovery period, I had an MRI that showed that the tumor had shrunk. That day I began the next phase of my treatment, which consisted of a higher dose of temozolomide for 12 months on the cycle of 5 days on and 23 days off. There was a target dose of chemotherapy toward which my doctors gradually brought me. At the lower doses, I tolerated the chemotherapy except for nausea and vomiting, but as I was brought to the target dose, my entire body became itchy, I became tired, and my level of blood platelets was greatly reduced. After a break to recover, I received again a lower dose of chemotherapy, which I remained on until my treatment finished. I have had no further treatments since then.

I am now a 10-year survivor of grade III anaplastic astrocytoma. I have difficulty dealing with multiple things at the same time, and I have problems with short-term memory, which means I have to make notes for everything. This has been my "new normal," but I am not complaining.

One thing I did not mention, which I think is very important, is having a positive attitude, and for me personally, the power of faith. I was surrounded by people who kept my spirits up and always encouraged me. I thank God each day for the miracle of healing that I have received.

## KEY TAKEAWAYS TO REMEMBER



To date, only a few drugs and devices have been approved by the Food and Drug Administration specifically for the treatment of brain tumors, but research is ongoing, including in the area of immunotherapy.

Immunotherapy works by enhancing the body's own immune system response against cancer cells, and there are many immunotherapy trials for brain tumors underway.

If you are interested in treatment with a personalized vaccine, you must make arrangements **before surgery** to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.



## Optune/TTFields Device

### Overview

Optune is a wearable battery-operated device that has been approved by the Food and Drug Administration (FDA) for the treatment of newly diagnosed glioblastoma. The device is approved for use in combination with the chemo, temozolomide (Temodar), after concurrent radiation therapy and temozolomide treatments are completed. The Optune device has also been approved by the FDA for treatment of recurrent glioblastoma.

### How it Works

The Optune device delivers alternating electric fields (called Tumor Treating Fields or “TTFields”) through four insulated transducer arrays. These arrays are worn on a shaved scalp and are connected with a battery-operated electrical-field-generating device, which can be carried as a travel case or backpack. The transducer arrays can be worn continuously for 3 to 4 days before they need to be removed for hygienic care of the scalp, re-shaving of hair, and reapplication with a new set of arrays. Loose-knit wigs, hats, or other head coverings can all be worn over the arrays. The photograph at the end of this chapter shows a man wearing the Optune array and carrying case.

The electric fields of the Optune device alternates 100,000 to 300,000 times per second. Once the electric fields enter the cancer cell, they attract and repel charged proteins during cancer cell division selectively disrupting that division by delivering low-intensity, intermediate-frequency alternating current. These alternating electric fields affect only dividing cells; non-dividing cells are spared. Since alter-

nating electric fields do not enter the bloodstream like drugs, they do not affect cells in other parts of the body. The most common side-effects Optune device users experience are mild-to-moderate scalp irritation, headaches, and logistical difficulties.

## Initial Testing Results

A large randomized controlled trial was conducted to compare the use of the Optune device plus adjuvant temozolomide (Temodar) versus the use of Temodar alone in patients with newly diagnosed glioblastoma who had received radiation therapy along with concurrent Temodar. The FDA actually stopped this trial early because there were clearly evident increases in progression-free and overall survival in the group treated with Optune device plus Temodar compared with the Temodar-only group. The FDA stated that all of the patients in the trial should be allowed to benefit from Optune treatment. This FDA action might be the first time ever that a brain tumor trial was stopped early because a treatment was found to be so clearly effective.

## Latest Results and Trials

Based on the EF-14 Phase 3 pivotal study in those with newly diagnosed GBMs, Optune is proven to extend survival.

Overall Survival	Temodar Only	Temodar plus Optune
24 months/ 2 years	31%	43%
60 months/5 years	4.5%	13%

The 5-year probability of survival when Optune was used with 90% compliance is 29.3% versus 4.5% when using Temodar alone.

There is also a Phase 2 trial underway studying a combination of Optune, Temodar and Keytruda for newly diagnosed GBMs. Early results from that study, which is still ongoing, a median of at least 11.2 months progression free survival has been achieved and 24% of those patients have achieved a partial to complete response.

Another Phase 2 study is testing a new high intensity array concept in recurrent GBMs, given recent in vitro data that suggests an increase in effectiveness may be possible with higher intensity.

## Optune Availability and Use

Doctors must be trained and certified to prescribe the Optune device, however, its use has been expanding over the last decade so that it is now available for prescription from most major brain tumor centers as well as some smaller hospitals in the US and in over 260 centers outside the USA.

The device is intended to be worn continuously for at least 18 hours per day, and a shaved scalp must be maintained for the duration of therapy. If that seems burdensome, recent studies clearly indicate a dose-response curve with alternating electric-field therapy: patients who have the highest compliance (greater than 90%) in wearing the device for 18 or more hours per day have the best outcomes, including,

as mentioned above, in one sub analysis, a 5-year survival rate approaching 30%. Because the Optune device has to be worn practically continuously, it is for some patients a disturbingly constant reminder of the disease. Patients who choose not to use the Optune device should therefore not feel guilty about seeking other treatments. However, the best time to start Optune is right after radiation ends (or possibly during radiation), when it has the best chance of helping.



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*The Optune array and carry case / backpack.  
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# Brain Tumor Guide for the Newly Diagnosed





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## Bevacizumab (AVASTIN AND BIOSIMILARS)

### How it Works

Bevacizumab, more commonly referred to as Avastin, is a very powerful drug that was approved for use in high grade brain cancer treatment in May 2009. Avastin is also used in certain cases of pediatric low-grade tumors.

With the expiration of the patents for Avastin, more than a dozen companies have begun development on products biosimilar to Avastin. A biosimilar product is a product that is approved on the basis of it demonstrating substantial similarity to the product previously approved, have the same mechanism of action, type of administration, dosage form and strength, and no meaningful differences in terms of safety and effectiveness. Biosimilar products are often less expensive and, therefore, insurance companies are more inclined to approve their use.



## Brain Tumor Guide for the Newly Diagnosed

At the present time, Avastin biosimilars are:

DRUG NAME	MANUFACTURER	STATUS
Alymsys/Oyavas (MB02)	Amneal Pharmaceuticals/mAbxience	Approved by EC (European Commission) March 2021, and by FDA April 2022
Mvasi (ABP 215)	Amgen/Allergan, USA	Approved by FDA in September 2017 and by EC in January 2018
Zirabev (PF-06439535)	Pfizer, USA	Approved by EC in February 2019, FDA in March 2019, Japan's MHLW in June 2019, Australia's TGA in November 2019.

For simplicity sake, the term “Avastin” as used below includes both Avastin and its biosimilars.

Avastin is not a chemo. Instead, it discourages the growth of new blood vessels that bring nourishment to tumors. Tumor tissue requires about five (5) times more blood than normal tissue, so suspending the growth of blood vessels to tumors can readily be seen as a potent strategy.

Some cancer cells like those found in many GBMs make a large amount of a protein called vascular endothelial growth factor (VEGF). It is this VEGF that enables the development of the tumor-supporting blood vessels. By adding Avastin to therapy, VEGF is blocked and with it, the growth of those new blood vessels, thereby starving the tumor.

In addition, Avastin tends to “dry out” the tumor environment. This is especially helpful for individuals whose production of intracranial fluids exceeds the ability of their bodies, with or without steroid treatment, to control. An excess of such fluids

can lead to a variety of distressful side effects including severe headaches, memory, and cognitive problems and even loss of mobility.

## **Avastin Administration**

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Avastin is administered intravenously (IV) about once every two (2) weeks. About 40% do quite well on Avastin and some may go as long as 22 IV cycles (about 66 weeks). In rare cases, some will go even longer. But about 60% who get Avastin will either have no noticeable change to the disease or will have side effects ranging from tolerable to serious. In some cases, Avastin can cause irreversible cognitive and/or physical deficits. There unfortunately is no way yet to know who is going to benefit or be adversely impacted from Avastin.

While the potential benefits from Avastin are great, Avastin is a powerful drug that, like any drug, may cause some serious side effects.

Please be aware that Avastin use may disqualify a person from certain clinical trials, or its use must be stopped for a certain period of time before joining a clinical trial.

## **When Best to Use Avastin**

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For the reasons given above, it is best used in one of the following situations:

- When everything else has been tried and the disease keeps growing. In such cases, Avastin has been shown to improve progression free survival, but it has not demonstrated an improvement in overall survival.
- In very carefully selected newly diagnosed patients with bulky inoperable tumors or multi-focal tumors. In these cases, Avastin has been shown to prolong neurologic preservation and reduce the need for steroid use (which can be a problem if used long term).
- When the tumor regrows and the intracranial swelling is so great that unwanted symptoms (like immobility) occur but can no longer be controlled by use of safe dosages of a corticosteroid like dexamethasone.

- To treat the formation of necrosis for a limited period.
- In conjunction with a clinical trial which requires use of Avastin.
- Because of some unique situation where the doctor believes the Avastin is the best treatment option, such as using Avastin as a “super steroid” to prevent or treat swelling from immunotherapies.

## Side Effects

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Like any powerful drug, Avastin can produce a variety side effects. Most are tolerable.

Some people may experience joint pain serious enough to require treatment. Often, this joint pain is controllable by an over-the-counter antihistamine recommended by the doctor.

About 33 to 82% of patients will experience fatigue as a result of Avastin treatment.

In certain rare cases, Avastin can produce a high-risk side effect. There are 4 to watch out for. They are:

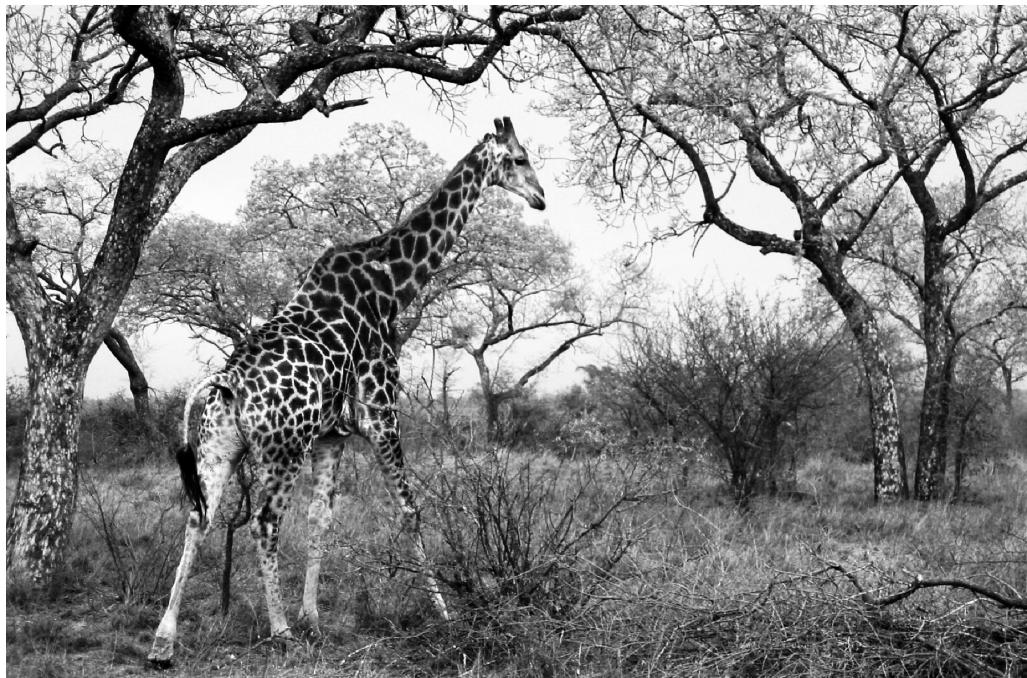
- GI perforation. In rare cases, a hole might develop in the stomach or intestine. Symptoms include pain in the abdomen, nausea, vomiting, constipation, or fever. This is a rare development; it tends to happen to older people and those who have had GI issues before.
- Wounds that don't heal. A cut can be slow to heal or may not fully heal when someone is on Avastin. Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed (or for whatever period the doctor says).
- Serious bleeding. This includes vomiting or coughing up blood; bleeding in the stomach, brain, or spinal cord; and nosebleeds.
- Circulatory issue. The most frequent toxicity reported from Avastin was hypertension (high blood pressure), and Avastin is also associated with an increased

risk of arterial and venous thromboembolic events, like deep vein clots. The symptoms of a deep vein clot, which may be worse when lying down, are:

- Swelling in a leg. In rare cases, both legs may be swollen.
- Pain in the leg. The pain often starts in the calf and may feel like a pulled muscle or some cramping or soreness.
- Red or discolored skin, like a bruise, on the leg.
- The area with the swelling is warm or even hot to the touch.

Please call the doctor's office right away (even after hours) if you suspect any GI perforation or deep vein clot, especially if your symptoms appear suddenly.

Call 911 if you experience any coughing up of blood, shortness of breath, pain when breathing, sharp pain in the chest, fast heart rate, serious lightheadedness.



# Brain Tumor Guide for the Newly Diagnosed





## High Intensity Focused Ultrasound (HIFU)

High intensity focused ultrasound (HIFU) is a developing, minimal invasive cancer treatment that aims to kill cancer cells with high frequency sound waves. HIFU was first used in the treatment of brain tumors during the late 1960s and early 1970s, but it was not until the advancement of adjacent technologies (e.g., MRI guidance systems and robotic manipulators) did researchers return to HIFU to further explore its clinical applications, including as a treatment for GBMs (as further described below) and as an alternative to stereotactic radiosurgery (SRS) for brain metastasis.

Recently, HIFU is being practiced on other cancers and the results to date are encouraging. When HIFU is turned on a solid tumor within the body, the cancer cells die and turn to foam, but the healthy cells are not impacted.

In the case of brain cancer, researchers are attempting to use HIFU in a few new ways such as to open the blood-brain barrier (BBB) temporarily and reversibly in GBM patients who are undergoing standard chemo treatment to see if doing so will improve the effectiveness of the chemo treatment. The BBB is a protective layer of tightly joined cells that lines the blood vessels of the brain to prevent harmful substances from getting into brain tissues. However, this barrier can also prevent therapeutic agents like chemos from getting into the brain. Currently, HIFU is available only by clinical trial.

# Brain Tumor Guide for the Newly Diagnosed





## Medications For Symptom Management

In the treatment of brain tumors, not unlike the treatment of any other acute or chronic illness, a variety of medications are used to combat symptoms, such as pain, fatigue, swelling, and seizures. The medications may include antibiotics, steroids, analgesics or narcotics, and anticonvulsants. It is necessary to take responsibility for your medications to ensure your safety. As your medical team will be made up of physicians from various specialties, all of whom may prescribe different medications or alter dosages in the context of your care, it is vital that you keep ongoing and accurate (up to date) records in your treatment binder and on your phone regarding your medications, including:

- Medications you are currently taking (including dosages) and who is responsible for monitoring you (prescribing physician) or providing refills. This information can be very helpful to any caregiver seeking information or assistance on your behalf.
- Medications you have taken in the past, noting their value (e.g., “was most helpful for sleep”).
- Medications discontinued due to negative side effects.
- Any allergic or adverse reactions, mild or otherwise, noted in RED.

You should always:

- Ask your doctors to review your list of current medications prior to prescribing something new.
- Check to ensure that the recommended drug is covered on your insurance plan's drug formulary, or if you'll need a prior authorization.
- To avoid receiving the wrong medication at the pharmacy (a growing concern), write down the specific medication and dosage as stated on your prescription before submitting it to a pharmacist and compare this information to the label on the bottle you receive to ensure it is the same drug as stated on the prescription.
- Your prescription might be filled with a generic substitution if your doctor did not prescribe it to be "dispensed as written." If the medication you receive is different from what was written on the original prescription by your physician, ask the pharmacist. Also ask the pharmacist for his/her thoughts on the generic. Most generic drugs are okay to use, but for some drugs that have a very narrow effectiveness range, such as anti-seizure drugs, it may be worthwhile to pay the extra for the brand name or insist on the same brand of generic each time.

Whenever possible, having all your prescriptions filled through a single pharmacy source can be an additional safeguard against medical errors, preventing adverse drug interactions, as most pharmacies now use computer systems that automatically flag dangerous interactions based upon your previous medications. Should your physician fail to recall a particular medication that might present a problem, chances are your pharmacist will catch it. Still, asking your physician(s) to review your medication sheet in your treatment binder — each and every time a new drug is prescribed — is an important, life-saving step.

It is important that you understand the side effects and drug interactions of all the medications you are prescribed. Most of the drugs we use have very scary package inserts and list every side effect ever reported to happen in people who were taking the drugs — whether the drug caused it or not. Our point is to be aware of the most common side effects and watch for them, not to be scared away from using the drugs.

Additional information regarding your medications and drug interactions can be found at websites like Drugs.com ([www.drugs.com](http://www.drugs.com)).

## Common Medications

The following is a general description of medications commonly used to treat symptoms and/or conditions caused by a brain tumor itself or resulting from surgery and/or other standardized treatments of brain tumors. Many of the significant/ common side effects associated with a particular medication are noted, but the list may be incomplete. Your physician may recommend medications not covered within this general guide. You are advised to thoroughly discuss and understand all the benefits and side effects with your physician before a prescription is issued. Physicians are often creatures of habit — ask about alternative medications and why your physician would choose the recommended medication over another. This is a general overview.

Always ask your doctor before taking anything, even over-the-counter pain medications.

### Medications for Heartburn/Acid Reflux

A good example demonstrating why your doctor must be consulted before taking ANY medication is the situation with over-the-counter medications for treating heartburn or acid reflux, which are referred to as a Proton Pump Inhibitor (PPI). The best-known PPIs are Prilosec,Prevacid,Protonix,Dexilant,Nexium and Acid-phex, but there are others.

Researchers have been surprised recently to find that PPIs (particularly omeprazole and pantoprazole) significantly increase the production of a certain enzyme called ALDH1A1. A vast number of reports from other studies demonstrates that ALDH1A1 is a contributor to cancer therapy resistance and is associated with poor prognosis across a variety of human cancers.

When this surprising finding appeared, some researchers recommended an immediate change in the clinical practice of routinely prescribing PPI's for neuro-oncology patients. It turns out that among other activities both good and bad, when it

comes to brain cancer treatment, some of the data suggests that PPIs contribute to supporting tumor regrowth and recurrences of GBM.

However, most major brain cancer centers continue to prescribe PPIs when needed (e.g., for patients needing long term GI prophylaxis). Because scientific studies on PPIs and many other medications are not always perfectly conclusive and because your doctor is particularly skilled to sift through the scientific data and determine what is best in your particular case, it is essential that you first discuss with your doctor the appropriateness of you taking PPIs, as well as ANY over the counter medication, vitamin, herb, or supplement.

## **Medications For Pain Relief**

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Because the brain itself does not feel pain, studies show that physicians treating patients for brain tumors often overlook pain. However, pain as a by-product of disease or due to complications from surgery or other forms of treatment is very real and deserves real attention. Headaches from brain inflammation or tension, scalp sutures, muscular pain, and hairline fractures due to steroid therapy, and pressure points on arms and hips from extended bed rest require medication. Pain left untreated can slow healing, deplete emotional reserves, exacerbate depression, and sleep deprivation, and detract from your quality of life.

**Mild pain.** The lowest level of pain can usually be managed with Tylenol (acetaminophen), Advil (ibuprofen), or Aleve (naproxen). Note that aspirin can affect how fast your blood clots, which may be bad or good. Always ask your doctor about it first.

**Moderate pain.** More powerful prescription medication, such as Percocet (the combination of oxycodone and acetaminophen) and Percodan (the combination of oxycodone and aspirin), can be taken as directed by a physician.

**Severe pain.** Codeine, Vicodin (the combination of hydrocodone and acetaminophen), oxycodone, and stronger, morphine-type medications are typically long acting and are taken less frequently. Many also come in “patch” form for slow absorption and continuous relief. Ritalin (methylphenidate) is used to treat attention-deficit hyperactivity disorder (ADHD). If taken in small doses with pain medication, Ritalin can increase the narcotic effect (enhancing pain relief) while

reducing the drowsiness commonly associated with these drugs. Ritalin has also been shown to benefit patients who suffer from fatigue. According to package inserts for drugs that contain morphine, such drugs should not be used in patients with brain tumors. The reason is that they can hide symptoms. However, they are still commonly used, and the benefits may outweigh the risks when you are in severe pain. Discuss any concerns you might have with your physician.

## Medications For Swelling

Steroids are powerful anti-inflammatory drugs typically prescribed to reduce swelling in the brain (cerebral edema) before and/or after surgery, during radiation treatments, or to relieve symptoms such as memory loss and limb (arm/leg) weakness caused by brain swelling. While common, swelling can be harmful if excessive and must be controlled.

Synthetic steroids such as Decadron and Hexadrol (dexamethasone) are man-made hormones similar to cortisol, which is produced naturally by your body. Taken orally, these steroids create higher levels in the body than what is normally secreted, reducing inflammation but also causing the body to temporarily stop natural production on its own. For this reason, it is very important to “wean” yourself (cut back slowly) when stopping oral steroid therapy. Always follow your physician’s recommended schedule for reducing dosages. During this reduction period, your body will slowly come back “online” and begin to produce normal cortisol levels again.

It is VERY important to follow your doctor’s instructions about decreasing your steroid dosage. Stopping steroids abruptly can lead to numerous withdrawal symptoms including adrenal crisis which is a rare but fatal reaction to a lack of steroid in your body.

While the benefits of steroids are undeniable, often unmatched by any other medication, they are not without short and long-term side effects.

Long-term side effects can include (but are not limited to) diabetes, muscle pain/weakness, osteoporosis (bone loss) leading to fractures, and susceptibility to infections. Short-term effects can include (but are not limited to) increased appetite,

weight gain, and indigestion; swollen or “moon-faced” appearance; stretch marks, rash/flushing of skin, and acne; increase in blood sugar; brittle bones; depression and/or behavioral changes; anxiety and/or paranoia; and suppressed immune system.

Other oral steroid therapies include prednisone or prednisolone. While not as strong as Decadron or Hexadrol, side effects are generally the same, although perhaps not as severe in most cases. There are nonsteroidal medications that can help with swelling, such as Avastin (bevacizumab) and Diamox (acetazolamide).

## **Medications For Reducing Seizures**

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Roughly 30 to 40 percent of patients will experience some level of seizure activity and require medication to reduce electrical responses in the brain. Due to the location and/or size of some tumors, many neurosurgeons will prescribe anti-seizure medication as a matter of routine before, during, and/or after surgery when the risk of seizure is considered high. In the past, all brain tumor patients were put on anti-seizure medications routinely for life, but since they can have a lot of side effects, many doctors now try to do without these drugs until seizures occur.

Most anticonvulsants share common side effects, such as fatigue and dizziness, so for obvious reasons you may be restricted from driving a car or operating dangerous equipment while taking anti-seizure medications, even when seizures have not been documented or have subsided. Other medications and certain foods can prevent proper absorption, so frequent blood draws for proper dosage and serum levels are necessary.

Among the most often prescribed anti-seizure drugs are:

**Keppra/ Levetiracetam.** Probably the most prescribed anti-seizure. The reasons this drug is often prescribed is because it inhibits malignant glioma cell proliferation and increases glioma cell sensitivity to the chemo Temodar and does not interfere with chemos. This benefit is maximized in patients whose tumors are methylated. (For a full discussion of methylation, please see the section entitled “ Key Genetic Markers That Enable and Stimulate Tumor Growth” above.) However, Keppra can cause fatigue, moodiness,

even heightened crankiness/irritability in some people.

**Vimpat/ Lacosamide.** Like most anti-seizures, it may cause dizziness, double vision, nausea when first starting, but after a while, these symptoms should lift. Often used in combination with Lamictal.

**Topiramate/ Topamax.** Those that experience too much moodiness on Keppra often turn to this drug.

**Valproic Acid/ Depakote/ Depakene.** Works well for many. Depakote and Depakene (Valproic acid or valproate) are commonly prescribed for focal seizures and require periodic blood levels to ensure adequate dosage and guard against liver damage. Because Depakote interacts with many medications, make sure your physician reviews your current medication list, including over the counter and herbal supplements, at the time of recommendation.

**Zonisamide/ Zonegran.** May cause dizziness, insomnia, lack of coordination, double vision, diarrhea, but many people who take this drug don't report any side effects at all.

**Trileptal.** Sometimes the doctor will add Trileptal to another drug, like Keppra.

**Lamotrigine/ Lamictal.** Works well for many. This is the antiseizure drug that pregnant women will take; however, can cause rashes in some people.

**Carbamazepine/Tegretol.** Some with repetitive seizures use this one with reasonable success. Tegretol (carbamazepine) is an anticonvulsant that is also prescribed in the treatment of manic depression and other psychiatric disorders. Effective in its ability to control grand mal seizures, Tegretol must be monitored closely with frequent blood-level measurements, since in rare cases it may suppress bone marrow production. You should report any onset of a rash to your physician immediately. Tegretol also reduces or increases the effects of many medications. Double vision, pounding or slow heart rate, and nausea are noted side effects with this drug.

**Gabapentin/ Neurontin.** Particularly popular with those who also suffer from nerve pain/neuropathy. Neurontin (gabapentin) has similar side effects as Dilantin, as well as the side effects of double vision, tremors, and involuntary eye movements. While Neurontin has fewer drug interactions than Dilantin, it does interact with certain antacids, such as Maalox.

**Phenobarbital** (a barbiturate and strong depressant) and primidone are less frequently prescribed, as the effectiveness of other anticonvulsants can be more easily achieved without the potentially addictive qualities of these drugs.

**Phenytoin/ Dilantin.** This is one of the longest used standard drugs for those with epilepsy/seizures. Phenytoin, often prescribed under the brand name Dilantin, is a commonly used medication to prevent full-body seizures in high-risk patients. People metabolize Dilantin differently, so periodic blood levels are taken to ensure that dosages are adequate and stable. Side effects of Dilantin include muscle fatigue, dizziness, and loss of coordination, as well as tooth decay and gum problems. Regular dental checkups and extra attention to oral hygiene are advised. Long-term use of Dilantin can cause a decrease in certain nutrients, such as folic acid and calcium. Ask your physician about supplements if necessary. Dilantin can also interact with other medications, including over-the-counter drugs, birth control pills, and herbal supplements. Dilantin can also make some chemotherapy drugs less effective.

For more information about seizures, please see the section in this Guidebook entitled “Seizures” under “Side Effects.”

## **Medications For Reducing Nausea**

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Nausea is common with brain tumors, as both a part of the disease process itself and as a by-product of radiation and chemotherapy treatment. The most commonly prescribed medications for reducing nausea are:

**Zofran (Ondansetron)** is used to control nausea caused by chemotherapy or radiation. It is usually administered intravenously prior to treatment and can be taken orally after treatment, if necessary. Effective for only a few

hours, Zofran is limited to nausea caused by chemotherapy and radiation only and is not to be taken for motion sickness or other generalized conditions related to nausea. While mild in nature, side effects of Zofran include headache, fatigue, diarrhea, and constipation, and the drug may exacerbate pre-existing liver disease.

**Kytril (Granisetron)** is similar to Zofran in both treatment administration and side effects, although it may also cause abdominal pain. It lasts up to 12 hours. Granisetron is also available in a patch (called Sancuso). Using a patch formulation of nausea medication may be a good option if you cannot swallow due to nausea or vomiting.

13

**Compazine (prochlorperazine)** is a commonly prescribed medication for the treatment of generalized nausea and is given orally, intravenously, or as a suppository. Compazine belongs to a family of antipsychotic agents called “phenothiazines” and may cause drowsiness, low blood pressure, dizziness, constipation, dry mouth, blurred vision, and sensitivity to light. While effective in the management of nausea, Compazine should not be used in conjunction with alcohol, may interact with other medications, and could potentially cause an irreversible condition called tardive dyskinesia — involuntary movements or twitches of the face, tongue, or arm muscles.

**Haldol (Haloperidol)** is another antipsychotic medication that is used to control nausea and has risks and side effects similar to those of Compazine. Haldol and Compazine should not be taken without a detailed discussion with your physician.

**Transderm Scop** contains the seasickness drug scopolamine, which can sometimes be used for nausea. Transderm Scop is a patch formulation of the drug that is applied to the skin and works for 3 days per patch. A main side effect is dry mouth, which can be a benefit when there is difficulty swallowing and too much saliva is being produced.

There are also many alternative treatments. Some patients report that acupuncture, biofeedback, and hypnosis provide nausea relief with no side effects and are much cheaper than most commonly used drugs.

## **Medications For Improving Mood**

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Being diagnosed with a brain tumor alone is enough to create overwhelming anxiety and stress. It is important to understand that during the course of treatment, intense and seemingly “over-emotional” reactions — such as acute depression, sexual dysfunction, sudden outbursts, and visual or audio hallucination — may be the result of medication or a condition stemming from the tumor itself, not necessarily an emotional response. It is also important to communicate about these emotional changes with your medical team in order to seek proper assistance and guidance to help you distinguish the many moods of treatment and recovery, and to help you cope.

A psychiatrist is a medical doctor who can assist with the mood-related conditions directly caused by the tumor or its treatment. Psychologists can also provide help with coping difficulties and with mild depression due to issues of long-term care, financial strain, or the stress placed upon family and other important relationships. Ask your medical team to refer you to a psychiatrist or psychologist experienced in treating brain tumor patients.

Herbal remedies may be of some benefit. However, herbal mixtures can adversely interact with other prescription medications and should always be discussed with your medical team for safety and adequate dosing information. If you are thinking of taking hypericin, one of the principal active compounds of St. John’s wort, make sure to ask your medical team first, for hypericin can interfere with other drugs.

## **Medications For Reducing The Formation Of Blood Clots**

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Brain tumor patients are at a higher-than-normal risk for developing dangerous blood clots. Blood clots commonly start in the legs as deep vein thrombosis (DVT). Symptoms of DVT may include pain, tenderness, swelling, discoloration of the affected leg, and skin that is warm to the touch. If you develop these symptoms, you must call your doctor and get it checked quickly. Left untreated, blood clots can break away and travel to the lungs where they may cause a pulmonary embolism, which can be rapidly fatal. Symptoms of a pulmonary embolism include sudden shortness of breath, chest pain (worse with breathing), and rapid heart and respiratory rates. If you develop any of these symptoms, you must go to the emergency room immediately.

Medications called anticoagulants help to thin the blood and reduce clotting, the body's normal response to help stop bleeding. Heparin is an anticoagulant that is given by injection, usually for a short period of time to prevent or treat blood clots. Warfarin (commonly referred to as coumadin) is an oral medication that can be taken over a long period of time to prevent blood clots. Warfarin can have many drug interactions and requires monitoring of blood levels. Another class of oral anticoagulant that may be used are called DOACs (Direct Acting Oral Anticoagulant.) Medications in this class include: Apixaban, Rivaroxaban and several others. Aspirin is a milder blood thinner, which some doctors recommend to prevent blood clots.

When you are taking anticoagulants, normal cuts and scrapes may take longer to stop bleeding or heal, and there is an increased risk of the tumor bleeding into the brain — so these drugs are double-edged swords and should be taken exactly as prescribed. Warfarin interacts with many medications and should be discussed thoroughly with your medical team before treatment. Your doctor will also order periodic blood tests to ensure that appropriate medication levels are maintained. Plavix is another commonly used drug that prevents clotting.

It is important to note that changes to your diet can have a negative effect on the blood-thinning measures of anticoagulant medication. Suddenly increasing foods such as spinach in your diet can adversely affect bleeding times. The sudden introduction of fish-oil capsules as a dietary supplement, which are full of omega-3 fatty acids, can also alter bleeding times. While there is no need to eliminate spinach and other healthy items (including supplements) from your daily routine, you are advised to maintain your normal diet and not increase or decrease items significantly or add new supplements without discussing them with your physician. This is not the time to begin a new diet for weight loss without consulting your physician.

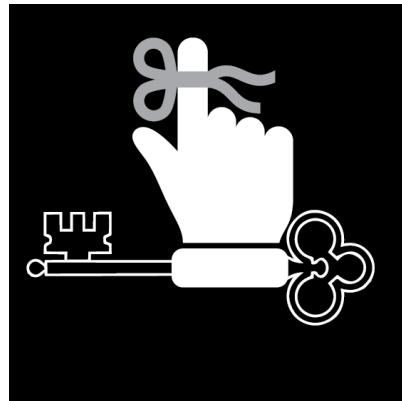
It is always a good idea to wear a medical alert bracelet informing medical personnel that you are taking anticoagulants in the case of an emergency. They are widely available in most retail pharmacies and on the Internet, inexpensive, and an important safeguard for your health.

Of course, you should take your medicines as directed, not changing the frequency or dosage without talking to your doctor. If you need help with co-payments for drugs, please go to [needymeds.org](http://needymeds.org) and look up each drug you take. If you cannot afford a drug, don't stop taking it. Instead, speak to your doctor about a less expensive alternative.

- .....
- To get additional information about any medication, go to the drug information site **Medline Plus**: <https://medlineplus.gov/druginformation.html>.
- Medline Plus is provided as a service of the US National Library of Medicine.
- On this website, drugs can be looked up by their brand or generic names.
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## KEY TAKEAWAYS TO REMEMBER



13

Always follow your doctor's instructions when decreasing your dosage of any medication, especially steroids.

Always check with your doctor before taking any over-the-counter medications.

Because your medical team will be made up of doctors of different specialties, it is vital that you take responsibility for keeping an ongoing and accurate record of the medications you are taking, including their dosage and the names of the physicians who prescribed them.

Always ask your medical team to review your complete list of medications before they prescribe anything new.

If possible, always fill your prescriptions at the same pharmacy to safeguard against medical errors and adverse drug interactions.

Make yourself knowledgeable about the most common possible side effects and drug interactions of the medications you are taking.

# Brain Tumor Guide for the Newly Diagnosed





## Clinical Trials

### Importance of Clinical Trials

Clinical trials offer experimental treatments that may provide new inroads for extending life expectancy and improving quality of life. Understanding the current availability of clinical trials requires time and due diligence. Each brain cancer center will have its own clinical trial offerings; what is available at center may not be available at another. We hate to say this, but some doctors are reluctant to refer you to other treatment centers. You must search out for yourself the appropriate clinical trials available for your specific tumor type, always advocating in your own best interests toward a cure. A clinical trial is the best way of trying experimental therapies because the doctors will watch you very carefully for signs of side effects.

14

There are other ways to gain access to an experimental treatment in the United States. That is the Right to Try law and expanded access program, which allows terminally ill patients access to experimental drugs and devices. The Right to Try law and expanded access program are discussed below.

People in clinical trials seem to do better than people who choose not to participate. And once a cure is actually found, the first people to get it will be those in the clinical trial for it. Cures have been found for other types of cancer, and we all hope it will happen for brain tumors, someday soon.

### Understanding Clinical Trials

Clinical trials have a designation — phase I, phase II, or phase III — that is based upon the specific types of questions that are being asked about the treatments in question. These clinical trial phase designations are defined by the US Federal Drug Administration (FDA) and published in the Code of Federal Regulations. A sum-

mary of the definitions follows. For the most current, full definitions, please go to this site:

<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.21>

**In a phase 0 trial, also referred to as Early Phase I.** This phase differs significantly from other phases of clinical trials as it is not a required part of testing for a new drug. However, the purpose of this phase is to expedite the drug approval process. Phase 0 studies use only a small dose of the new drug in fewer than 15 patients over a short period of time. The goal is to determine if the new drug or agent behaves in human subjects as is expected based on preclinical studies.

**In a phase I trial,** a new drug or treatment is studied in a small group of people (20 to 80 patients or volunteers) for the first time to evaluate its safety, determine a safe dosage range and identify potential side effects.

**In a phase II trial,** the study drug or treatment is given to a larger group of people (100 to 300 patients) and further assessed for effectiveness and safety. The dosage of medication may be increased to determine toxicity levels.

**In a phase III trial,** the study drug or treatment is given to large groups of people (300 to 3000 patients) to confirm its effectiveness within a sizable population, monitor side effects and toxicity levels, compare it with standard treatments, and further determine safety.

Statistics are used to try to make sense of the trial results. A number is calculated called the significance level. The number usually chosen as the benchmark is 0.05, which means that there is a 95% chance that the effect seen in the trial was caused by the treatment and not by chance alone. Conversely, this means that if you run 100 trials of a worthless drug, about 5 of those trials may report success even though there is none. This is why multiple trials are needed, and it is best if they are conducted by different centers.

The FDA will approve a drug that is better than standard treatment, or is at least as

good as standard treatment, if it has fewer side effects. Once a treatment is approved by the FDA, everyone can get access to it, not just those in clinical trials.

## Why Should You Consider Participating In A Clinical Trial?

Clinical trials provide access to some of the newest and most promising treatments for diseases that have no cure. In many cases, these trials, guided by experts, may represent your best possible chance for survival or for a better quality of life. By participating in a clinical trial, you help researchers take one small step, or even a giant leap, closer to a cure. Aside from helping yourself, your experiences can support advances in the state of the art in the field, leading to improved treatments for others in the future.

Earlier (under the “Treatment Overview” section), this Guidebook discussed the brain cancer guidelines developed by the National Comprehensive Cancer Network (NCCN), the not-for-profit alliance of 31 leading cancer centers. For every patient category in the NCCN guidelines, enrollment in a clinical trial is recommended for those who are eligible.

Another advantage to enrolling in a clinical trial is the cost. Brain tumor treatments are very expensive. In general, the experimental treatment used in a clinical trial is free to you. There may, however, be charges for associated costs of treatment — such as surgery, doctor’s consultations and visits, MRI scans, and blood tests — so, ask about costs and what your insurance will pay and what your out-of-pocket expenses will be. If you have no insurance, there may be clinical trials available that cover all the costs.

## When Should You Consider A Clinical Trial?

The decision of when to participate in a clinical trial should be discussed with your medical team. Some patients and physicians feel more comfortable exhausting possibilities with the standard-of-care treatment first. Others choose right away to participate in trials from the onset of diagnosis. You may wish to discuss certain points of progress (or lack of progress) with your medical team as a guideline to help you with your decision. Obviously, if you have a low-grade tumor for which good treatments are available, you will be less likely to try something experimental. If you have a high-grade malignant tumor and the expected outcome of the standard-of-care

treatment is not acceptable to you, it is easier to make the decision to try something experimental.

Some clinical trials are conducted specifically for treatment of recurrent tumors rather than treatment of newly diagnosed tumors. Whether or not you decide to wait or move forward, it is important to research available trials early for your specific type of tumor and to know in advance if, or when, you might qualify. Be especially careful not to miss trial-entry deadlines. Some trials require that you sign up for them before surgery. Others require that you sign up before radiation therapy ends. One thing to keep in mind is to plan ahead and think through a large range of contingencies. Among those contingencies are the trial eligibility requirements and disqualifiers.

Each clinical trial has their own set of eligibility requirements that might include the age range of participants, location of the tumor, grade and/or type of tumor, the presence of specific molecular markers, or the requirement of a specific degree of stabilization as a trial enrollment criterion.

Clinical trials also have their own sets of disqualifiers which may include another form of treatment. In some cases, the trial coordinator may agree to a "washout period" - a period of time during which you do not take that certain other treatment before being enrolled in the trial. Both the eligibility requirements and the disqualifiers are included in the description of the clinical trial on the National Cancer Institute's website (see below for how to find trials).

It is possible that you will not have enough real data to make an informed decision. In the old days, it was an easy decision. The standard-of-care treatment provided so little hope that you had nothing to lose by joining a trial. But the current standard-of-care treatment has progressed to the point where you now have a difficult decision to make about when to enter a clinical trial, since the standard-of-care treatment does help some people for a long time and new trials with advanced treatments are opening up continuously.

## How Do You Assess A Clinical Trial?

The best way to evaluate if a clinical trial is right for you is to speak with your primary physician, your neuro-oncologist or neurosurgeon, and other members of your

medical team, including those to whom you have turned for second opinions. You might also contact one of the major brain tumor centers for additional insight into a specific clinical trial. You should also consult with the physician in charge of the trial. It is always helpful to know how earlier trials of the proposed treatment came out. Lastly, it is important to ask any physicians not in favor of your participation: Why not? What would they recommend instead, and why?

Although individual case results are meaningless statistically, the experiences of others may help give you enough information to choose between two treatments that are otherwise a toss-up. You can find these individual experiences in the online support groups, in real-world support groups, and in the results of the Brain Tumor Virtual Trial, a study run by the Musella Foundation (see below).

## How Do You Find Clinical Trials?

You can find listings for clinical trials at the resources described below.

14

### **Musella Foundation Resources**

At the [virtualtrials.org](https://virtualtrials.org) website of the Musella Foundation, clinical trials can be located in two ways online. To access either method, go to: <https://virtualtrials.org>, then click on the box on the middle right that says, "Find Treatments!".

Patient Navigation Program is the first option. As earlier described in detail in this Guidebook, this program uses the xCures platform which is loaded with all the currently available knowledge about brain cancer treatments and matches it to the details about your tumor to help you quickly find promising treatments. This service is provided at no charge.

Clinwiki is another option. Using a few details about your tumor that you key in to this online system, treatment options can be found.

The Musella Foundation can also be directly called at 1-888-295-4740.

## National Cancer Institute

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The National Cancer Institute is not specific to brain tumors, but it does maintain a powerful clinical-trials search engine. In addition to allowing you to search by cancer type, location, and other variables, it also allows you to search by the type of trial (that is, whether it is a phase I, phase II, or phase III trial). To access the National Cancer Institute clinical-trial search engine, go to: <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search>.

## Clinicaltrials.gov

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Clinicaltrials.gov is the world's largest clinical trials database, currently holding registrations from over 410,300 trials from more than 220 countries. You can search for trials by condition, intervention, sponsor, location, and type of trial. To access this resource, go to: <https://www.clinicaltrials.gov>.

## DIPG/DMG Trials

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For parents whose child has received a diagnosis of DIPG (Diffuse Intrinsic Pontine Glioma) or DMG (Diffuse Midline Glioma), a resource for comprehensive information about the latest clinical trials can be found at this link: <https://dipg.org/dipg-treatment/active-clinical-trials/>.

## The Brain Tumor Virtual Trial

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The Brain Tumor Virtual Trial is a registry managed and run by the Musella Foundation. The virtual trial consists of a database of brain tumor patients, the treatments they are using, and their outcomes. Participants record the treatments that they and their medical teams decide to pursue. The Musella Foundation does not tell participants what treatments to receive; we just record the outcomes. There is no cost to participate in the virtual trial. The patient or caregiver records information on simple forms right on the virtualtrials.org website and posts an update each month. We send email reminders on the first of each month. The patient or caregiver also sends in copies of MRI reports (not the MRI films) and pathology reports so that information can be verified. Participants are able to view the ongoing results of the project.

The concept behind the Brain Tumor Virtual Trial is to identify which treatments,

or which combinations of treatments, are working the best. In addition to providing greater insight for researchers about beneficial therapies in the real world, the virtual trial also supports participants in learning how to become expert managers of their own conditions. For example, participants can generate reports on the information they have entered, such as a graph of their status over time. For more information on the Brain Tumor Virtual Trial, please go to: <https://virtualtrials.org/brain/index.cfm>.

## Treatments, Trials and the Food and Drug Administration

When considering clinical trials, it is useful to understand the difference between approved and experimental treatments. In general, there are two general classes of treatment: (1) those approved by the US Food and Drug Administration (FDA) specifically for brain tumors on the basis of evidence from clinical trials; and (2) experimental treatments, sometimes with drugs approved by the FDA for other types of cancers or other diseases, and sometimes with drugs not yet approved at all by the FDA.

- The virtualtrials.org website of the Musella Foundation has separate sections, each with extensive information, about several of the key brain tumor treatments. Be sure to visit each of the following sections for the latest updates about these treatments:
  - Immunotherapy: [https://virtualtrials.org/Immunotherapy\\_treatments.cfm](https://virtualtrials.org/Immunotherapy_treatments.cfm)
  - Optune device: <https://virtualtrials.org/optune>
  - Temodar (temozolomide): <https://virtualtrials.org/temodar>
  - DCVax: <https://virtualtrials.org/dcvax>

### FDA Approved Treatments for Brain Tumors

At the time of the issuance of this edition of the Guidebook, these are the FDA approved treatments for brain tumors. Treatments not on this list are repurposed/"off label" drugs (as described in the following) or treatments found in clinical trials.

## Brain Tumor Guide for the Newly Diagnosed

Name(s) of Drug/Treatment Approved	What it is Approved For	FDA Approval Date	Comments
Afinitor/Everolimus	Subependymal giant cell astrocytoma	Aug.30, 2012	Approved for adults and children aged 1 year or older who have tuberous sclerosis and are not able to have surgery.
Belzutifan/Welireg	Brain/spinal cancers linked to Von-Hippel-Lindau disease including hemangioblastoma	Aug. 13,2021	
Bevacizumab/Avastin	Recurrent GBM	May 5, 2009	For use in adults. This use is approved for the Avastin, Zirabev, and Mvasi brands of Bevacizumab
BiCNU/BCNU/Carmustine (Non wafer form)	Approved for glioma patients, and most often used in low-grade gliomas and in recurrent GBM patients	March 1977	Carmustine is used in the treatment of certain types of brain tumors, including glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors
Carmustine Implants/Gliadel Wafers (Wafer form)	Recurrent GBM and untreated malignant high-grade glioma	Sept.1996 for rGBM and 2003 for newly diagnosed high-grade gliomas	rGBM: Used with surgery; glioma: used with surgery and radiation therapy
Gleostine/Lo-mustine/CCNU (Originally marketed as CeeNu but rebranded Gleostine in 2014)	Recurrent (non-specified) brain tumors	Aug. 5, 1976	For those who have already been treated with surgery or radiation; this is an orally active nitrosourea chemotherapeutic agent

## Fourteen: Clinical Trials

Optune (formerly NovoTTF-100A System)/ Tumor Treatment Fields	Recurrent and newly diagnosed GBM	April 8, 2011 for rGBM; in 2015 approved for newly diagnosed GBM	For treatment for adult patients (22 years of age or older) with histologically confirmed GBM. The device is intended to be used as a monotherapy and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.
PCV (P=Procarbazine Hydrochloride, C=Lomustine/CCNU, V= Vincristine Sulfate)	Certain types of brain tumors	Combo approved in 2015	Often used with radiation therapy
Pembrolizumab/ Keytruda	For unresectable or metastatic solid tumors with high tumor mutational burden. (GBMs are generally low mutational burden when initially diagnosed but may change over time.)	Jun.16, 2020	For adult and pediatric patients
Temozolomide/ Temodar	Anaplastic astrocytoma and GBM	Mar.15, 2005	For Astrocytomas, approved for patients with refractory disease that got worse during therapy that included a nitrosourea and procarbazine hydrochloride. For GBMs, used with radiotherapy in patients with newly diagnosed disease and then alone as maintenance therapy.

## **Repurposed / Off Label Drugs**

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Even if an FDA-approved drug is not approved specifically for “brain tumors,” your medical team is still able to prescribe it for your brain tumor. When doctors prescribe a drug for a therapeutic purpose other than the one approved by the FDA, it is called “off-label” prescribing. Many drugs commonly used for brain tumors are prescribed off label. Although the use of these drugs by your medical team is legal, and the drugs are easily available, you might nonetheless have trouble getting your insurance company to pay for off-label usage of a drug because it will argue that such off-label treatment is experimental. In such cases, know that you can fight the insurance company’s denial. You should enlist your neuro-oncologist to help get the drug approved by your insurance company.

## **The Right to Try law and Expanded Access Program**

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In 2018, the US Congress passed the Right to Try law, allowing terminally ill patients to try experimental therapies (drugs and devices) that have completed phase I FDA testing but have not yet been approved by the FDA. Before the federal law was approved, 41 states had passed Right to Try laws.

To be eligible for a right to try a drug that is not approved for any use, a patient must meet the following conditions: (1) be diagnosed with a life-threatening disease or condition; (2) have exhausted approved treatment options; (3) be unable to participate in a clinical trial involving the eligible investigational drug, as certified by a doctor; and (4) give written informed consent regarding the risks associated with taking the investigational treatment. To request a drug or device under the Right to Try law, the patient, the patient’s representative, or the patient’s physician has to send a letter to the director of compassionate use or to some other designated representative at the drug or device manufacturer to discuss options for access to the drug or device.

Please note that drug and device companies are not required to provide treatments to patients under Right to Try laws. Each company is responsible for developing its own processes and procedures for approving Right to Try requests. It is reasonable that companies should not be forced to provide treatments when they do not think the treatments are appropriate or when they have limited supplies of the treatments

apart from their use in clinical trials. In addition, doctors who do not think that a treatment will be helpful have no obligation to request a Right to Try treatment for a patient.

The Expanded Access Program is another pathway that may permit a patient to obtain investigational drugs or devices outside of a clinical trial. The same drugs or devices that would be available under the Right to Try law may be available under the Expanded Access Program and the conditions for use are generally the same as described above for the Right to Try. As with Right to Try, the investigational drugs or devices under this Program have not yet been approved by the FDA and have not yet been determined to be safe or effective. However, if you and your doctor believe the emerging drug or device may help in your case, you should consider contacting the Expanded Access Program. Contact information follows below:

- Oncology drugs: 240-402-0004 or ONCProjectFacilitate@fda.hhs.gov
- Investigation drugs: 301-796-3400 or druginfo@fda.hhs.gov
- General/Patient Affairs Staff: 301-796-8460 or patientaffairs@fda.hhs.gov

## Alternative And Complementary Treatments

Discussing alternative and complementary treatments is a little like discussing religion and politics. These topics are hard and emotional, there is often a lot of fear associated with them, and there can be many points of view.

This Guidebook will give you an understanding of alternative and complementary treatments, but as with anything else, the final decision to use them must be yours.

**Alternative treatments** are treatments that have not yet been proven to work based on scientific testing and are used INSTEAD of mainstream treatments.

**Complementary treatments** have also not yet been proven to work but are used IN ADDITION to mainstream treatments. Once a treatment has been shown to work, it crosses over from “alternative”/“complementary” to “mainstream.”

### The Mainstream Path Of Treatment Development

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When someone invents or discovers a therapy that he or she thinks might effectively treat a brain tumor, the path to the treatment’s becoming part of mainstream medicine begins with laboratory testing on cell cultures and/or on animals. If the treatment still seems promising, human trials are started. We discussed clinical trials in an earlier section, but basically the treatment is tested on people with a brain tumor and is compared with either historical controls or with a control group.

The early stages of a trial, when only a few people are tested, cannot really show how well the treatment actually works. All phase III trials have had successful phase I and phase II trials leading up to them. However, most phase III brain tumor trials have failed to show significant benefit compared to standard treatment even though a new tested treatment looked very good in early trials. The reason for this is that the course of a brain tumor is variable. A small percentage of patients will do well no matter what treatment you give them, and the natural history is a roller coaster —you have wild ups and downs. If you happen by chance to select a handful of brain tumor patients who happen to have the right subtype, genetics, age, resection extent, Karnofsky Performance Status score, and other prognostic factors, and are on the right track of the roller coaster at the time, they may do well in a small trial even if the treatment is not as good as the standard treatment.

The next step is to test the treatment in a large group. This is when you conduct a randomized clinical trial, in which patients are assigned by chance to receive treatment with either the new therapy or placebo (an inactive substance that looks just like the new therapy) or standard treatment. Then, when the two groups are compared, you get a much better feel for how the new therapy works, since all the other variables are controlled. The trials need to be repeated a few times on large numbers of patients treated before you will know if the effect is treatment related or chance related.

Statistics are used to try to make sense of the trial results. A number is calculated called the significance level. The number usually chosen as the benchmark is 0.05, which means that there is a 95% chance that the effect seen in the trial was caused by the treatment and not by chance alone. Conversely, this means that if you run 100 trials of a worthless drug, about 5 of those trials may report success even though there is none. This is why multiple trials are needed, and it is best if they are conducted by different centers.

The Food and Drug Administration (FDA) will approve a drug that is better than standard treatment, or is at least as good as standard treatment, if it has fewer side effects. Once a treatment is approved by the FDA, everyone can get access to it, not just those in clinical trials.

## How Alternative Treatments Are Developed

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An alternative treatment is developed when someone has an idea that a certain therapy may help a brain tumor, or the researchers notice that a brain tumor survivor has tried a certain therapy. They then try the treatment on a few more brain tumor patients and see that some of them get better. (As mentioned before, some brain tumor patients are on the upswing of the roller coaster and would have been doing better even without the treatment.)

At that point, the researchers are convinced the treatment works, and they try to promote it so that more people can benefit from it. In many cases, these are the most well-meaning people with the best of motives. They saw something work in a few patients and want others to do well also. However, the difference is in the science. At this point, it would be good to follow the mainstream path and do rigorous trials

of a new treatment, and if it passes the tests, the novel treatment will become mainstream and help everyone. However, that is often not the path taken. Instead, many promoters of alternative and complementary therapies skip the proof and go on to marketing. They use individual case reports or small trials to justify the treatment.

On the Internet we read about many of these types of treatments, but these stories introduce a huge new problem: selection bias. This means that you hear from and see the people who do well with a treatment, but you do not see the ones who died. For example, if the standard treatment for a brain tumor has an average survival period of 5 years (and some of the experimental treatments exceeds that), an alternative treatment needs to reach that point to just say it is as good as standard treatment.

Put another way: If you take 1000 patients and put them on standard treatment, you expect 500 of them to be alive in 5 years. If you take the same 1000 patients and give them a treatment that is half as effective as standard treatment, you expect to see 250 alive at 5 years. If you see 250 people telling you that this miracle alternative treatment worked for them, you may tend to believe them. But you are not seeing the 750 who died — they can't tell you that it didn't work for them. So, at that point, what question should you ask? If they tell you they have 250 5-year brain tumor survivors, ask out of how many started? If it is 250 out of 250, it is a miracle. If it is 250 out of 1000, it is only half as good as standard treatment.

Frequently, those who recommend alternative treatments for serious illness will say “It doesn’t hurt to try since the standard treatment does not result in a cure.” This statement is erroneous, because even if the treatment itself is not toxic or dangerous, the use of such treatment often works against the science-based treatment, or sometimes is even used as a sole approach (stopping the scientific treatment that, while not curative, may extend their life and temporarily bring some relief to patients).

Also, the high cost of alternative treatment, usually not covered by health insurance, can cause serious financial pain to families and patients who desperately cling to straws of a “cure” offered by those who sell these nonscientific treatments.

There are “red lights” to watch out for when dealing with non-scientifically based treatments. The following are some of the most common “red lights” associated with alternative treatments:

- They are proprietary (available from one source or a limited number of sources) and are not available on the standard pharmaceutical market (which is subject to government supervision and regulation).
- They are expensive, and patients and their families must usually “pay up” in advance before the treatment can be started or continued. Most true clinical trials are licensed and supervised by government entities and are backed with public or private grants so that patients pay little or nothing for the treatment. Most legitimate studies are run in or by major universities or other institutions of higher learning, whereas the majority of alternative schemes are run by for-profit entities.
- The results of the alternative programs have not stood the test of review by a **peer-reviewed scientific journal** (in most cases, the data have not even been submitted to peer-reviewed scientific journals for publication). The alternative programs rely on “testimonials” by patients or former patients, and these are highly unreliable, especially when the diagnosis (of cancer) has not been based on scientific diagnostic techniques, such as pathological examination of tissue.
- There is often a tendency for the providers of alternative treatment to speak ill of traditional scientific medicine, frequently asserting that organized medicine is involved in a conspiracy to force patients to get orthodox treatment for the economic gain of the medical profession.

Brain tumor patients contact us frequently at the Musella Foundation. Many of them have tried just about every alternative treatment ever proposed for brain tumors. Some of them do well. Most do not. We track them with our Brain Tumor Virtual Trial project. Analyzing our data for this project, we found that not one of the alternative treatments reported had any positive effect on the outcome of the cases.

We still keep an eye on the patients who do not join the project. The ones that use mainstream treatments do better than the ones who use alternative treatments alone. We have seen many people decline and die rapidly when refusing standard treatments. They usually change their minds near the end and start standard treatments, but of course it is too late. Unfortunately, they then blame the standard treatments for the death.

However, when it comes to complementary treatments, when you use mainstream treatments but add to them, you may see some positive results. There may be some complementary treatments that do help with treatment side effects and possibly may make treatments more effective. However, keep in mind that if you feel a complementary treatment is powerful enough to change the course of your tumor in a positive way, it is just as likely — or more so — to be able to change it in a negative way. The body is very complicated. You cannot predict what would happen if you change one thing, because one small change can upset the delicate balance of the body and have unseen consequences. The only way to tell is by trying it in a well-designed trial. Proponents may say there is no money in it so no one would fund the trial. That is not true. The Musella Foundation, as well as most of the over 100 other brain tumor foundations, fund research projects like this.

Conspiracy theories may be put to rest by these two simple thoughts: (1) there is no way the medical industry is organized enough to keep away from the public a cure that would be the biggest money maker in the world; and (2) there are many researchers who dedicate their lives to finding the cure.

Patients need to learn to ask the right critical questions. These are some to consider:

- What exactly is this treatment?
- Who has received it?
- How many brain tumor patients have had documented responses, and how many patients have tried it?
- How are responses assessed?
- Why is it not given as part of mainstream practice in the United States?
- How was the diagnosis of brain tumor made? In some countries, MRI scans are not routine for brain tumor patients, and even if there is an MRI, there are some diseases that look similar to a brain tumor. A biopsy is the best way to tell if the diagnosis is a brain tumor and which type it is.
- Have the treatment results been published in a peer-reviewed scientific journal? If not, why not?

### **Natural Treatments/ Supplements**

High grade brain tumors do not materialize overnight. They could have been devel-

oping for as long as 7 years and gaining more DNA mutations to become more aggressive across time. Not only that, but the brain tumor is the product of many factors including immune system dysfunction, exposures to toxic substances, diet, level of inflammation, other genetics, stress, and other things all coming together.

Despite that, after a diagnosis almost everyone rushes to find the natural supplements that will undo all those years of complex, interlocked factors. You may decide to do the same and there is much to be said about being an empowered patient or caregiver, which may include the use of supplements to aid in dealing with the side effects of treatment. However, just be aware that some supplements can interfere with medical treatment.

For example: Most radiation oncologists do not allow patients to take any supplements of any kind during radiation treatment because it can inadvertently reverse the beneficial effects of treatment.

Researchers have found that patients using probiotic supplements were 70 percent less likely to respond to anti-PD-1 checkpoint inhibitors - a type of immunotherapy. It was discovered that the greater the bacterial diversity in the gut, the more the person responds to immunotherapy. Most probiotic pills add billions of only certain selected bacteria into the system, decreasing that diversity. So, the immunotherapy does not work as well. (On the other hand, patients who ate a high-fiber diet were five times more likely to respond to immunotherapy treatment with anti-PD-1 checkpoint inhibitors.)

Researchers have found that cannabis use has been associated with shorter time to progression and shorter overall survival among patients with advanced cancer who received anti-PD-1 checkpoint inhibitors (like Keytruda). This is according to an observational study reported at the European Society of Medical Oncology (ESMO) Virtual Congress in 2020.

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It is important that you check with the doctor on the appropriateness of using any natural treatment or supplement, and if it is permissible, what dosage the doctor views as appropriate before buying or using any such products.

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## SURVIVOR STORY #8

In April 1989, asked by the girls' softball coach to demonstrate a slide (I had played softball in high school and college), I spent an afternoon practicing and banged my head on the gym floor. I was 27 years old at the time, living at home with my parents, recently engaged to the love of my life. My family physician told me to rest, but I was suffering migraines and was very tired.

The following Thursday I drove home from work with a friend. During the drive, I had another migraine, but this time the left side of my body was going numb. We went straight to the emergency room. In the meantime, my mother described my signs and symptoms to a neurologist, and he told her to have me carry over my CT scans to him. When he looked at them, he told me that I had a tumor that needed to be removed.

On May 2 the neurosurgeon did a craniotomy and removed a cystic astrocytoma from my right frontal lobe. I opted to not receive radiation therapy for there was no guarantee that the tumor would not reoccur. My husband to be and I wanted to start having children; our physicians felt that the tumor had been sufficiently well contained within the cyst. Wasting no time, we began trying right away to conceive a child.

In January when I went for an MRI scan, my pregnancy test was positive. Two more children followed. My neurologist retired. When I met my new neurologist, he shockingly asked whether my husband was ready to raise our children without me. He stated that no one survives the type of brain tumor I had. My husband and I were then contemplating having a fourth child, and I had mentioned that to the new neurologist. He felt we were being foolish.

That's when I discovered the virtualtrials.org website of the Musella Foundation. I went on a rampage to learn more about brain tumors than I ever cared to know. I read many articles and emails. Some made me laugh, some made me cry. It is all such real-life stuff.

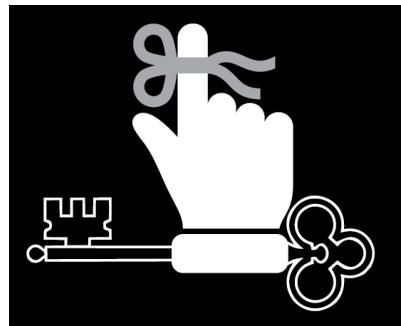
I fired the neurologist and spoke with my former neurologist, telling him that I needed a physician that knew that I was going to survive. We had a fourth child.

## Fourteen: Clinical Trials

Since the removal of the tumor 27 years ago, I am alive and well. I have added survival of a hurricane to my life's story, when Hurricane Sandy flooded my home and my four boys, and I were not able to evacuate. But the fact that I had already survived a brain tumor made even that horrific storm just another day that God has blessed me with. I continue to have clear MRI scans, and my newest neuro-oncologist has called me an outlier, a designation with which I am perfectly content. I am blessed with good health and an interesting life. Indeed, overcoming a glioma has become the measure by which I readily estimate everything else that God has sent my way.



## KEY TAKEAWAYS TO REMEMBER



Clinical trials may provide your best possible survival or for a better quality of life. At the [virtualtrials.org](http://virtualtrials.org) website of the Musella Foundation, you can have access to important resources for locating clinical trials, including:

Patient Navigation Program, which uses the xCures platform loaded with all the currently available treatments and matches it to the details about your tumor to help you quickly find promising treatments, and

Clinwiki which uses details about your tumor that help you find treatment options.

Alternative treatments have not yet been proved to work based on scientific testing and are used instead of mainstream treatments.

Complementary treatments have not yet been proved to work based on scientific testing, but they are used in addition to mainstream treatments.

There are several “red lights” to watch out for if you look at using non-scientifically based treatments — few sources for the products; an expensive cost; reliance on patient “testimonials” rather than publication of data in peer-reviewed scientific journals; and conspiracy talk.

Learn to ask the right critical questions about alternative and complementary treatments. What is it? Who and how many have received it? How were responses assessed? Why is it not part of mainstream practice? How was the diagnosis of brain tumor confirmed? And have the treatment data been published in a peer-reviewed scientific journal?



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## Diet

The effect of diet on brain tumors is not completely understood yet. Much more needs to be done. The interactions between changes in diet cannot be predicted. It may help in some way and hurt in others. The following ideas are generally healthy recommendations but keep in mind that recommendations change frequently. Subscribe to our Brain Tumor News Blast to keep up to date!

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## Overview

If you have been diagnosed with brain cancer, you are probably searching for anything you can do to keep the disease managed so that you can go about living your life. One thing you can do is consider possible adjustments to your diet. There are two important reasons relevant to any brain cancer patient:

**Gut-Brain Immune Relationship.** While adjusting the diet might be interesting for other cancers, in the case of brain cancer the situation might be more urgent. Recent research conducted by the National Institutes of Health and Cambridge University have shown that some of the immune cells that are dispatched to protect the brain first spend time in the gut getting “trained” for their brain protection mission. This study found that gut-educated antibody-producing immune cells inhabit and defend regions that surround the brain as well as the rest of the central nervous system.

Several studies have found that particular microbiota in the gut were closely associated with treatment effect. Other data show that adjustment of the microbiota in the gut could enhance the effectiveness and relieve resistance during immunotherapy treatment. One of the major factors enabling these benefits is diet. As a result, steps to enhance the health of the gut and subsequent immune response with dietary

changes can be an important part of a brain cancer patient's overall management of the disease.

**Sustaining Underlying Health.** What also matters is recognizing that the brain cancer is less than 1% of the body and the remaining 99% of the body needs, more than ever when a brain cancer fight is on, as good a nourishment as you can give it (and tolerate). Another important benefit of a good diet is maintaining one's underlying health during what can be a vigorous fight. A good diet can help stave off some treatment side effects.

Many clinics and hospitals have classes for cancer patients on how to eat better. It is a good idea to see if your clinic or hospital has such classes and attend one. Another option is locating a clinical nutritionist for individualized assistance.

If you are a caregiver of a person who has no interest in changing their diet, understand that cleaning up your loved one's diet, while important, is a bonus. So, if your loved one refuses, it is better not to fight over it. Keep the bigger picture in mind.

## The Inflammation Factor

In those studies that seem to produce the best evidence of effect between diet and brain cancer, the top issue is reducing inflammation. Why is that?

Inflammation in the brain, being encased in a boney container, has nowhere to go. Plus, if there is too much of it, the pressure it puts on the brain can create an array of unwelcome symptoms. Plus, when inflammation happens there is a release of substances that promote cell division, which can trigger the cancer's growth.

How can a person best reduce their inflammation? Turn to mostly plant-based foods. It won't eliminate your risk, but it will reduce it.

## First Fix

SOME nutrition experts believe that the first thing any cancer patient needs to do is cut out all ultra-processed foods from their diet. To know what an ultra-processed food is, this is a quick definition: If it comes in a box or a can, and the ingredient label is long and filled with chemical names you can't easily pronounce, and don't

recognize as healthy — it's probably ultra-processed.

## Diet Mix

The ideal diet for an adult should be about 25% of calories from protein, 50% from high fiber fruits and veggies, and 25% of calories from whole grain carbs or starches like peas, corn, potatoes.

## Calories/ What To Do About Lack Of Appetite

Cancer can cause a person's metabolic processes to affect how the person's body uses proteins, fats, and carbs. (The condition is called hypermetabolism. It is important to get the required amount of food each day.)

A rough estimate of caloric needs would be between 11.5 and 16 calories for every pound of weight (25 to 35 calories per kilogram of weight). For determining what should be your personal caloric target, a discussion with your doctor or nutritionist/dietician is best.

Calorie restrictive diets should be avoided, unless the doctor says otherwise, because that could lead to an unhealthy decrease in weight and muscle mass during treatment. Statistically, those who do better in the long run are those who maintain a healthy weight.

Sometimes a person just does not feel like eating, for example, when nauseated from treatment. But they still need the calories. In those times, it is advisable to try having smaller more frequent meals, avoid filling up on liquids at your meals, and consider supplementing a meal with one of those meal replacement milk shakes sold in pharmacies. Look for those with the lowest sugar content. A person should not exceed one of these shakes per day and only for the purposes of ensuring an adequate caloric intake.

## Proteins

The current recommended daily allowance for protein is 45 to 60 grams per day (or whatever it takes to get your intake to be about 25% of your calories). More than what you need makes your body have to process all that extra protein; less than that

may make it hard for your body to protect itself from infection and heal (e.g., lowered blood cell counts may result because your body cannot make blood cells.) This is another area where your personal target should be set with your doctor or nutritionist.

The ideal in protein consumption is to look for low fat/ high protein foods such as skinless chicken, fish, turkey, low fat dairy, nuts, and seeds.

## **Red Meat**

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Red meat contains hormones which can stimulate cancer growth. It also contains endocrine disrupting chemicals and iron which is a potentially gene-damaging oxidant. Then, if the meat is cooked on a grill, it develops heterocyclic amines, which in lab studies has been shown to increase the cancer risk.

## **Fish**

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In addition to being a good non-meat source of protein, fish has anti-inflammatory properties in the form of polyunsaturated fatty acids (PUFAs). Best fish for PUFAs are the cold-water fatty fish such as tuna (the light ‘skipjack’ tuna, but not the albacore tuna, since the bigger the fish, the more possibility it will have mercury), sockeye salmon, sardines, herring, and mackerel.

## **Eggs**

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Eggs are a good source of non-meat protein and are rich in choline, lutein, and zeaxanthin, which are all micronutrients believed to have disease-fighting properties. A couple of eggs per week is generally recommended.

## **Yogurt**

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While even a small amount of normal dairy milk may increase the risk of triggering cancer growth due to the hormones in the milk, once that milk is fermented into yogurt, the risk is reduced or removed. Yogurt, which is a good source of calcium and protein, contains beneficial bacteria (probiotics). Yogurt may help reduce inflammation and aid against the cancer.

## A Word About Soy

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Some people turn to soy as a protein source. Be careful of unfermented soy products like tofu, soymilk, soybeans, soy-burgers, soy-based cheese, soy shakes, supplements, or soy protein. Unfermented soy contains a phytoestrogen – an estrogen from a plant source. Some doctors believe that the phytoestrogen in the soy may trigger growth, including tumor growth, particularly in postmenopausal women.

Fermented soy products (like miso and tempeh) are thought to be fine. Natural tofu is not fermented, but a tofu product called Chao is fermented, which removes some of the antinutrients and is thought to be healthier.

## Carbohydrates

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Carbohydrates (“carbs”) should be about 75% of your diet consisting of 50% fruits and veggies and 25% whole grains and legumes.

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Fruits and veggies are loaded with healthy carbs, as well as vital fiber, vitamins, minerals (including important trace minerals) and phytonutrients that reduce inflammation and promote brain resilience.

### Vegetables

Veggies should make up half of your plate at meals. Studies show that people who consume 1-2 servings of leafy greens each day experience fewer memory and cognitive issues than people who rarely eat them.

Leafy green and cruciferous veggies (broccoli, cabbage, spinach, kale, Brussels sprouts, Bok choy, arugula, collard greens, and cauliflower.) are excellent; those in the cabbage family contain some cancer fighting substances called indoles and isothiocyanate that have been widely studied.

### Fruits

Some people avoid fruits to avoid sugar, but many fruits are supportive of memory and mental acuity thanks to their high vitamin and antioxidant content. If you are concerned about sugar, choose low glycemic fruits like berries, apples, and watermelon.

The brain appreciates berries like dark cherries, black berries, strawberries – the darker the better.

Be careful of citrus (orange, grapefruit, lemon) during chemo cycles only to avoid having to have your stomach deal with the extra acid. Citrus after chemo cycles are good, but please be aware that grapefruit occasionally interferes with medications doctors may prescribe.

Whole grains (like oatmeal, brown rice, quinoa, whole wheat breads and pasta) are good carbs and 25% of your diet should consist of them. Refined grains (such as white flour, white pasta, white rice, and white breads) are best left on the shelf. There has been some debate about whole grains being bad for the brain. The latest studies do not suggest they are but talk to your doctor or nutritionist on this question.

Legumes (peas, beans, lentils, peanuts, etc.) and starches like sweet potatoes are also excellent sources of good carbs.

### **Antioxidants**

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Even under normal circumstances the brain is most sensitive to oxidative stress. Add some surgery, radiation and chemo, and the brain is really stressed.

An answer to all that oxidative stress is to add some antioxidants. Most of the fruit and veggie items mentioned above are going to provide excellent sources of antioxidants.

Some people feel the need to add more to their diet via supplements of the most powerful antioxidants (vitamins C, E, beta-carotene, selenium, lycopene, and anthocyanins.) Plus, there are supplements that are popular with those dealing with brain cancer such as Curcumin (Turmeric), Boswellia, Berberine, and others.

It is a wise idea to discuss your diet and supplementation frankly with the doctor because during certain phases of treatment (most notably during radiation) the supplementation of antioxidants may undo the beneficial effects of treatment. Consuming antioxidants via what you eat is not an issue (as far as I know), but supplementation via pills/capsules might harm, not help, so the doctor should be involved in deciding what antioxidants you take and when.

Not only that but there is a debate among scientists. It is well understood that as a cancer preventive, antioxidants are beneficial, but once cancer is present, some doctors feel that the antioxidants could aid the cancerous processes and not the person. Again, the issue is not the antioxidants a person is consuming via the diet, but rather the additional amount obtained through supplements. Your doctor or nutritionist would be able to guide you.

## Fats

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We need fats in our diet, but they need to be healthy fats.

Unsaturated fats are the “good” fats, and they are chiefly found in nuts, olive oil, peanut oil, canola oil, avocados, tuna, and salmon... as long as those oils are not superheated by high heat cooking which then changes their chemistry.

There are the saturated fats, which can be found in meat and other animal products, such as butter, cheese, and all milk except skim. Palm and coconut oils are also high in saturated fats and can be found in a variety of the baked goods sold in groceries. (Check the labels!) These are not desirable fats for your diet, so watch your consumption of these.

Lastly, there are trans fats, which are found in limited amounts in meat and other animal products, such as butter, cheese, and all milk, but can be found in large amounts in processed foods, fried foods, some types of margarines, snack foods, and baked goods. If the label says “hydrogenated” or “partially hydrogenated” then that food contains trans fats no matter what else the label says. It is best not to consume any trans fats, but if you do, limit your daily intake to no more than 120 calories (which is probably just one or two commercially baked cookies).

As previously mentioned, the single most important diet principle that someone dealing with brain cancer needs to follow is avoid eating ultra-processed foods, especially those containing trans fats.

## Keto Diet

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Some brain cancer patients believe switching to the keto diet has benefited them. A

few studies in humans with certain types of brain tumors have shown some promise in controlling the growth of those tumors on this diet. Depending on your type of treatment and other personal medical issues, your body may not be able to metabolize the proteins and fats that are used in abundance in a keto diet, so definitely talk to your doctor first before trying this diet.

### **Sugars**

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Some people say that it is essential to eliminate all sugar in all its forms (glucose, glutamate, fructose, corn syrups,) because sugars are thought to fuel cancer. Actually, all of our cells need sugar (glucose) to function, and there is no way for our bodies to give the needed glucose to our healthy cells but not give it to our cancerous cells. The trick is to limit as many added sugars as is possible (and tolerable).

### **Hydration**

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It is vitally important to stay well hydrated, especially during treatment. Drinking lots of water helps to flush the chemo residue from the body and aids in avoiding the constipation that treatment can cause. However, fruit juices, sodas and off-the-shelf ice teas and coffees should be limited because of their high sugar content. The best drink always is good old plain water.

For those looking for some taste to their water, Green Tea, which contains an anti-oxidant that de-toxify cell-damaged free radicals, is an excellent option. If the Green Tea is taken as a supplement by capsule, you should speak to your doctor first because of the antioxidant nature of the Green Tea which may interfere with certain treatments, particularly if you are taking other antioxidants.

### **Alcohol**

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Alcohol consumption should be eliminated or at the very least reduced. Alcohol can cause the liver to be inflamed, can interfere with certain medications (e.g., CCNU/Lomustine and Procarbazine) and could impair the liver's ability to breakdown the chemo. Chances are that your doctor will try to encourage a "no alcohol" policy while during treatment.

## What To Avoid

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The presence of brain cancer means there is a compromise of the immune system. This being the case, it would be wise to avoid foods associated with a high risk of food contamination, including:

- Unwashed fresh fruits and veggies especially those with leaves that can hide dirt raw or lightly cooked sprouts like alfalfa or beansprouts
- Unpasteurized drinks of any kind whether juices or milk and all products made from them (e.g., cheese or yoghurt made from unpasteurized milk)
- Soft, slow-ripened, or blue-veined cheeses (e.g., brie, camembert, Danish blue, stilton, and gorgonzola)
- Eggs that are not fully cooked such as soft boiled, over easy, and poached; raw, unpasteurized eggs; or foods made with raw egg, such as homemade raw cookie dough and homemade mayonnaise. When making a cake, do not lick the bowl
- Refrigerated pate. Pate in a can might be alright but read the label to see if it is safe.
- Rare or undercooked meat and poultry. Investigating in a meat thermometer is smart.
- Cold hot dogs or cold cuts from the deli; if you are going to eat them (despite their overabundance of chemicals), hot dogs must be steaming hot.
- Uncooked shellfish (e.g., oysters).
- Smoked fish and raw fish like that in sushi and sashimi. There are some fish labeled “sushi grade” and “sashimi grade” that might be okay, but ask your doctor first.
- Avoid all the deli prepared salads with egg, ham, chicken, seafood as any of these can teem with bacteria, especially if not properly refrigerated before you get them.

## Strange And Useless

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The following diets or dietary devices have no proven value and may be harmful:

**Budwig Diet.** This is a diet of flaxseed and cottage cheese and includes several restrictions. The flaxseed and cottage cheese may be fine for some people, although the

flaxseed may interfere with the absorption of some medications and the cottage cheese may produce intestinal issues. The restrictions of the diet are a mix of healthy and unhealthy. Taken as a whole, the restrictions of the diet may put you at risk of certain vitamin and mineral deficiencies, so if you want to proceed with this diet, talk to your doctor or nutritionist first.

**Alkaline Water.** There are devices ranging in price from \$50 to \$5,000 to produce alkaline water. While some will claim that alkaline water inhibits the growth of cancer, this concept is unproven. The fact is that the minute the water we drink mixes with the ever-present acid in the stomach, it loses its alkalinity.

**The Gerson Therapy.** This protocol includes thirteen (yes -13) glasses of fruit/veggie juice per day plus many coffee enemas, which can be quite harmful. (This last therapy didn't much help the developer, Dr. Gerson, when he contracted cancer himself).

The bottomline is that there are lots of weird and costly programs out there, some of which are just designed to put your money in their pockets. Talk to your doctor or nutritionist before you buy or start anything that is or seems off the main road.





## .....

## Imaging and Monitoring

### Overview

Brain scans allow doctors to get an idea of what is going on inside the head non-invasively. No scan is 100% accurate, and each is open to interpretation. The more experienced the doctor is at interpreting brain scans, the more confident you can be about the results of that interpretation. Also, the more the doctor knows your personal history, the more accurately that doctor is able to put new scans into their proper context.

As mentioned elsewhere, it is a good idea to get a personal copy of the films (or a CD of them) and the radiology report. You can share these documents with your medical team to make sure they agree on the reading of the scans. Having copies of the scans will also be useful if you need a quick second opinion from another brain tumor center, or if the original scans are lost, as happens more than you would think.

16

### CT Scan

A CT scan (or CAT scan, a computerized axial tomogram) is a non-invasive imaging technology that uses x-rays to generate a computer simulation picture of the cross section of your head. Usually, a contrast agent (a dye) is injected into your arm half-way through the test to enable the tumor to show up better. A CT scan can be readily available and much cheaper than an MRI scan.

A CT scan shows some things very well, such as bleeding into the brain and signs of swelling, and it is sometimes used for planning surgery and radiation. Since CT scans use x-rays, there is a tiny risk with their use, so they are usually limited to only

when they are absolutely needed, especially in children.

If you are having a CT scan performed on a child, ask the radiology technician whether the level of exposure dosage can be reduced appropriately for children. On some older CT scanners, such a reduction is not possible. In such cases, you should select a different imaging facility.

## Magnetic Resonance Imaging (MRI)

### Overview

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Magnetic resonance imaging (MRI) is a non-invasive imaging technology that produces three dimensional detailed anatomical images. It is currently the most used technology for disease detection, diagnosis, imaging support for biopsy and surgery, and treatment monitoring; doctors prefer the MRI because it is more detailed than a CT Scan image and avoids ionizing radiation from X-rays. An MRI also is able to find smaller tumors than a CT Scan.

### Frequencies

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MRIs are usually performed regularly at a frequency recommended by the doctor to monitor the status of the tumor or tumor site. Sample frequencies, subject to the doctor's adjustment, for stable tumors are:

- High grade tumor every 90 days
- Low-grade tumor every 6 months
- Benign every year

Especially after the initial MRIs, the days before any MRI and the time waiting for the results can be a period of extreme anxiety. It is recommended to schedule MRIs and doctor visits as close together as possible to reduce anxious waiting time.

### How an MRI Works

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An MRI scan uses magnetism and radio waves to create a “picture” of the inside of your head. It employs powerful magnets which produce a strong magnetic field that forces protons in the body to align with that field. When a radiofrequency cur-

rent is then pulsed through the patient, the protons are stimulated, and spin out of equilibrium, straining against the pull of the magnetic field. Physicians are able to tell the difference between various types of tissues based on the energy released as the protons realign with the magnetic field.

To obtain an MRI image, a patient is placed inside a large magnet and must remain very still during the imaging process in order not to blur the image. MRI is potentially one of the best imaging technologies for children since, unlike CT, it does not have any ionizing radiation that could potentially be harmful. However, one of the most difficult challenges that MRI technicians face is obtaining a clear image, especially when the patient is a child or has some kind of ailment that prevents them from staying still for extended periods of time. As a result, many young children require anesthesia, which increases the health risk for the patient.

### Contrast Agents

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When an MRI is performed, a contrast dye (usually gadolinium) may be injected intravenously to increase the speed at which protons realign with the magnetic field of the MRI machine. The faster the protons realign, the brighter the image.

Side effects of the gadolinium are typically transient; they may include headache, dizziness, pain at the injection site, rash, itching, and nausea. A severe adverse reaction is extremely rare. A different contrast agent is used for MRI scans than for CT scans, so if you had an allergic reaction to the dye used for a CT scan, you may still be able to use the contrast agent for an MRI scan (and vice versa).

This dye is often used after a round of images have already been taken so that the new images with the contrast dye can be compared to see if there are any important details to be seen. With a contrast agent, non-growing ("non-enhancing") tumors will appear "isotense" meaning that it looks rather dull and dark just like the same as the first series of images taken without the dye.

A growing ("enhancing") tumor will appear hypertense (bright) and show off other changes. Changes may reflect blood perfusion (growth of additional blood vessels), vascular permeability (microleaks of blood) and extracellular space of the tumor. One way to understand these changes is to remember that a tumor needs a lot more blood supply than normal tissue needs, so if there is an increase in blood perfusion

and more blood in the tumor, that is indicative of an enhancing tumor or one that is getting ready to grow.

## Considerations for Use

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When having an MRI scan, the following should be taken into consideration:

- Although an MRI does not emit the ionizing radiation that is found in x-ray and CT imaging, it does employ a strong magnetic field. The magnetic field extends beyond the machine and exerts very powerful forces on objects of iron, some steels, and other magnetizable objects; it is strong enough to fling a wheelchair across the room. As a result, people with implants, particularly those containing iron, including but not limited to pacemakers, vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators, and capsules from capsule endoscopy should not enter an MRI machine.
- Noise—loud noise commonly referred to as clicking and beeping, as well as sound intensity up to 120 decibels (which is loud) in certain MRI machines. If noise bothers you, it is recommended that you inform the imaging technician who can give you ear protection.
- Nerve Stimulation—a twitching sensation sometimes results from the rapidly switched fields in the MRI.
- Pregnancy—while no effects have been demonstrated on the fetus, it is recommended that MRI scans be avoided as a precaution especially in the first trimester of pregnancy when the fetus' organs are being formed and contrast agents, if used, could enter the fetal bloodstream.
- Claustrophobia—people with even mild claustrophobia may find it difficult to tolerate long scan times inside the machine. Familiarization with the machine and process, as well as visualization techniques, sedation, and anesthesia provide patients with mechanisms to overcome their discomfort. Additional coping mechanisms include listening to music or watching a video or movie, closing, or covering the eyes, and holding a panic button.

ton. The open MRI is a machine that is open on the sides rather than a tube closed at one end, so it does not fully surround the patient. It was developed to accommodate the needs of patients who are uncomfortable with the narrow tunnel and noises of the traditional MRI and for patients whose size or weight make the traditional MRI impractical. Newer open MRI technology provides high quality images for many but not all types of examinations.

Other than as may be noted above, MRI scans are thought to be safe.

### **Types of MRIs**

There are different kinds of MRI scans. Here are some of the important ones:

- MRA (magnetic resonance angiography) shows details of the blood vessels.
- MRS (magnetic resonance spectroscopy) shows the chemical makeup of the brain, which can sometimes be used to tell the difference between radiation necrosis, normal brain, swelling, and tumor. Sometimes MRS can distinguish between low-grade and high-grade tumors, a distinction that is helpful when the best area for a biopsy is being selected. MRS can also detect whether a treatment is working much more rapidly than regular MRI can and comparing repeated MRS scans can be especially useful for tracking tumor status. MRS is available at most brain tumor centers and is starting to become available everywhere.
- fMRI (functional MRI) measures blood flow in the brain and is used to map which areas of your brain control which functions. For example, if the tumor is near your speech area, you will be asked to talk while the scan is performed to highlight the areas you use while talking, and to see if the tumor invades that area.
- Diffusion MRI, which measures water movement in the brain, can be used to determine how well the treatment is working.

### **MRI Interpretation Basics**

## Brain Tumor Guide for the Newly Diagnosed

MRI images are taken in sequences. When MRIs of the brain are being made, there are typically two sequences: T1 and T2.

T1-weighted images are produced in shorter repetitions (referred to as TR) and shorter time between the delivery of the RF pulse and the receipt of the echo signal (referred to as TE). T1 is useful for demonstrating the underlying anatomy of the brain and associated structures.

If a structure is dark on the T1 sequence, the image may be displaying additional water (edema/swelling), inflammation, tumor, hemorrhage. If a structure is bright white on the T1, the image may be indicating, among other things, the presence of fat, proteins and protein-rich fluids like slow moving blood, subacute hemorrhage, melanin, necrosis, and gadolinium.

T2-weighted images use longer TRs and TEs than the T1 sequence.

If a structure shows up as dark on the T2 sequence, the image may be displaying melanin, protein-rich fluids like slow moving blood. If a structure shows up as bright on the T2 sequence of images, then it is probably indicating the presence of blood and water (e.g., edema/swelling), inflammation, tumor hemorrhage.

Fluid-attenuated inversion recovery (FLAIR) is contrast technique for the T2 MRI sequence. It shows certain areas revealed in the T2 sequence with the cerebrospinal fluid (CSF) from the ventricles damped or removed. This allows for any brain abnormalities like tumors to appear more conspicuous, while the CSF appears dark or subdued. The FLAIR signal is particularly helpful for detecting subtle changes in tumors.

"Diffusion weighted imaging" is a term that shows up frequently in MRI reports. This imaging simply helps show the cellular structure of the brain.

There are a few new experimental MRI techniques that may be able to better distinguish pseudo progression from true progression, and to tell earlier if a treatment is working or not. See our video library for details: <https://virtualtrials.org/video.cfm>

## **Common Findings**

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The first one or two MRIs following surgery or radiation are likely to be filled with evidence of edema/inflammation, making the MRI inconclusive. In the interest of controlling pre-scan anxiety, it is useful to be aware that MRI results are not always clear, so you should not expect too much from early MRIs. The results are often anti-climactic. Only successive, comparative MRIs will be able to be conclusive.

Sometimes MRIs identify a "suspicious spot." Spots may be tumor recurrence, but it may also be necrosis. Necrosis is the presence of a clump of dead cells. These are deposits of cancer cells that have been killed off by the radiation and/or chemo and that accumulate in a given location. Comparisons to future scans should enable the doctor to conclude what the spot is.

Sometimes MRIs identify an enlargement of the tumor. This puffiness looks like it may be tumor recurrence to the doctor analyzing the MRI without your treatment history, but that puffiness may not be tumor recurrence. In 20% to 30% of cases the enlargement is something called pseudo-progression. The tumor tissue sort of blows up in response to the treatments, shows up as an enlargement in your scan, but subsequent follow-up scans show either tumor stability or shrinkage.

### **Perfusion MRI**

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For this form of MRI, a contrast dye is injected quickly into a vein. A special type of MRI image is then obtained that looks at the volume of blood going through the brain and tumor/tumor environment. Tumors, particularly high-grade tumors, typically require much more blood than normal brain tissue. A perfusion MRI can help detect changes in blood amounts, which in turn can help assess the status of the tumor.

### **Magnetic Resonance Spectroscopy (MRS)**

This test can be done as part of an MRI. It measures biochemical changes in an area of the brain (displayed in graph-like results called spectra). By comparing the results for a tumor to that of normal brain tissue, it can help tell the difference between any dead tissue caused by previous radiation treatments and new tumor cells. The sensitivity, specificity, and accuracy of MRS is 84-87.5%, 75-93.3%, and 81-92.1% respectively. Plus, MRS has a higher sensitivity and specificity than a T2 MRI sequence.

## Pseudo-Progression/ Treatment Effects

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Due to treatments like surgery, radiation, chemos or immunotherapies, fluid soaks the tissues around the tumor site. This fluid (called edema or more medically speaking a "T2/Flair signal") looks very cloudy on an MRI image, and the doctors who look at the image cannot tell if the cloud is itself tumor progression, or if that cloud is hiding tumor progression, or if the cloud is just a bunch of fluid, or if the area being seen is a clump of necrotic tissue. This is why the doctor will say something like "We'll have a better idea after the next MRI" (leaving us biting our fingernails for the next 30 or 60 or 90 days).

In approximately 20% to 30% of GBM cases, the first MRI obtained after radiation therapy and concurrent temozolomide meets the criteria for progressive disease. Additionally, it is not uncommon for MRI images during treatment to have an increase in T2/FLAIR sensitivity, which raises the possibility of tumor progression. The radiologist who first views the MRI images and sends the MRI report to your doctor is probably going to mention the potential of tumor progression.

Your personal doctor, who best knows the phase of treatment you are in and how you have been responding to treatment so far, may tell you he or she disagrees with the report. It is not uncommon for subsequent follow-up MRIs to prove him or her right by showing tumor shrinkage or stability.

This phenomenon has been termed either "treatment effect" or "pseudo progression" and is among the most common causes of misdiagnosed tumor recurrence. This is of concern at most stages of treatment because pseudo progression following chemo can happen in the early months and later there can be radiation-induced necrosis six (6) months or more after radiation, especially for persons with an IDH-1 negative/wild type/unmutated gene in the tumor.

However, development of a new enhancement outside the original tumor site most likely does represent tumor progression and should be treated accordingly.

## PET Scan

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In some cases, to help clarify what is being seen in the MRI images and remove the

doubts caused by pseudo progression, the doctor may order a PET scan.

A PET scan (which stands for positron emission tomography) uses a tiny amount of a radioactive substance injected into your arm. This radioactive tracer is compounded with low dose radioisotope and sugar, making it safe for you with minimal to no side effects, although PET scans can be risky for people allergic to sugar substitutes or iodine, or those with diabetes.

The scan shows how metabolically active each area of the brain is based on how much glucose (sugar) is being used. A PET image is reconstructed by a computer that shows cellular activity broken into "hot spots" or "cold spots". Compared with normal cells, cancer cells are very active in using glucose, so the sugary radiotracer will light up areas of cancer.

Differences in metabolic activity can help distinguish if an area is being affected by a tumor or something else (like necrosis). The use of PET scans is not available everywhere, and it is expensive.

There are a few varieties of PET scan. The types of PET scans most used for aiding in the diagnosing and monitoring of brain tumors are the fluoro-L-phenylalanine (FDOPA or 18FDOPA) or the Fluorodeoxyglucose (FDG). Other options for the doctor are MET and FET.

PET uptake indices based on lesion-to-normal brain tissue ratios are significantly higher for progressive disease than for necrosis making it the strongest predictor of tumor progression. The sensitivity of FDG-PET for distinguishing recurrence of a tumor from necrosis is typically 81% to 86%, although some think its accuracy is nearly 100%.

16

## Blood Tests

Your doctor will probably ask you to take regular blood tests during treatment. This is to monitor the effects of treatment on your blood since treatments like chemo can discourage your bone marrow from producing enough blood cells at the level necessary for a reasonable degree of health.

Each type of blood cell has a range that's considered normal or healthy. Ranges are used rather than a specific number because the number can vary from person to person or within the same person from day to day.

The three blood cell types and their optimal ranges are:

- Platelets, which help blood clot. The normal range for platelet count is 150,000/milliliter (mL) to 400,000/mL.
- Red blood cells, which deliver oxygen throughout your body. Red blood cells may be measured in two different ways. Hematocrit is the proportion of red blood cells in your blood. The normal range for men is 40% to 55% and for women is 36% to 48%. Hemoglobin is a protein in red blood cells. The normal range for men is 13.0/deciliter (dL) to 17.0 g/dL and for women is 11.5/dL to 15.5 g/dL.
- White blood cells, which fight infection. The normal range for white blood cells is 5,000/mL to 10,000/mL.

If your doctor says you're fine but your tests results are somewhat different from the ranges shown here, don't be alarmed. Some labs interpret test results a bit differently from others, so these figures are not absolutes.

If, however, your doctor feels that one or more of your blood cells are too low, the doctor may want to delay your next chemo cycle until your blood cells have had more time to recover from the last treatment.

## SURVIVOR STORY #9

In June 2000, when I was 33 years old, my life quickly changed. I began having headaches that felt as if my skull were going to explode. An MRI scan showed that my brain was hemorrhaging, and I went immediately into surgery. An acorn-sized glioblastoma tumor was found in my left temporal lobe. I was told I had less than a year to live.

I quit my job to be a stay-at-home mom, wanting to spend every precious moment with my boys. I went into conformal brain radiation. I refused chemotherapy because standard treatment at that time had seriously bad side effects and would only add a few months to my life.

In July 2004, the glioblastoma came back. I had awake surgery since the glioblastoma was located in my left temporal lobe and there was a high risk of my losing the ability to speak. After surgery I went on the 5-day, 23-week temozolomide (Temozol) schedule.

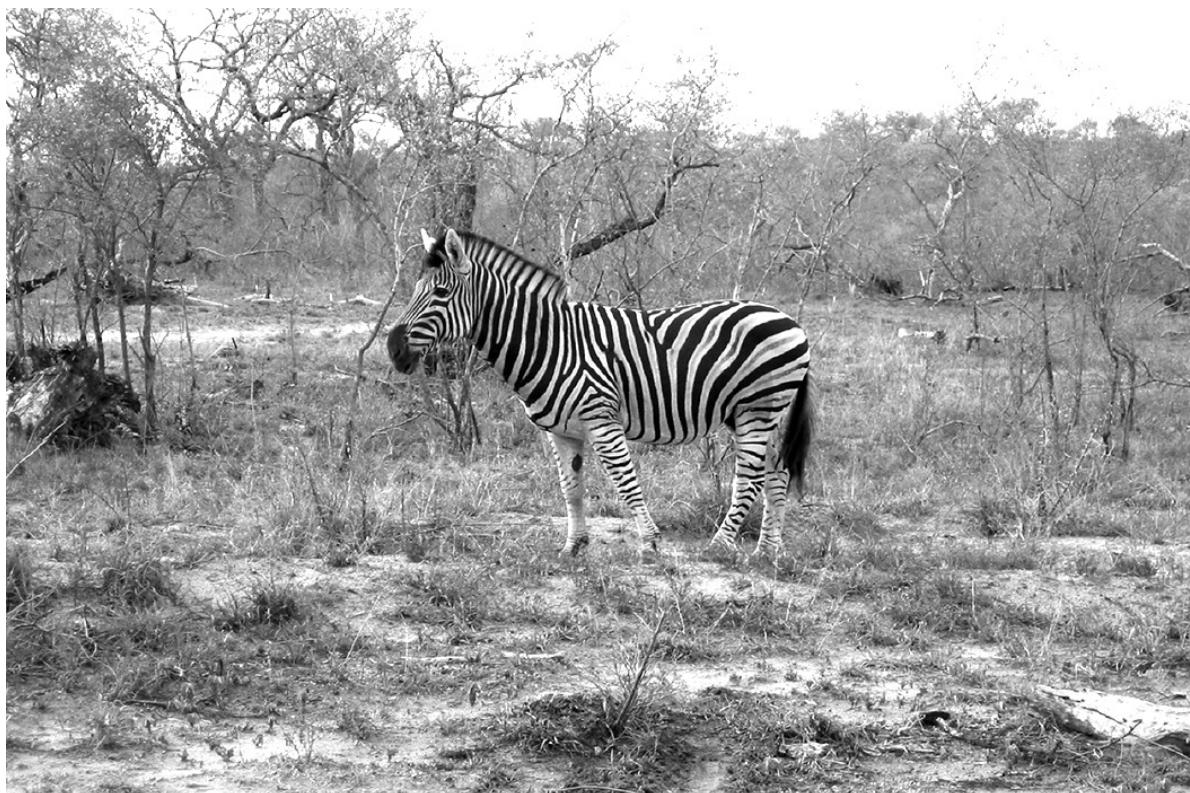
Again, the glioblastoma came back, and I went into brain surgery a third time. The tumor was only the size of a “pea,” but during surgery a buffer around the tumor was removed. After surgery I again went back on temozolomide.

In March 2009, the glioblastoma came back a fourth time. This time the tumor was not even located in my brain but in the meninges (the layer of tissue that covers the brain). I went into surgery a fourth time and all “visible” tumor was removed. The brain itself looked nice and clear, no visible tumor in the brain itself. After surgery, I could not go back on temozolomide since it had quit working for me, and I did not qualify for any clinical trials because of the third reoccurrence of the cancer and my treatment history. We decided to keep an eye on the tumor with MRI scans every 2 months. Now, fast forward to 2018, I have endured three more recurrences of my brain tumor. The last recurrence was last year, when it was discovered that I had a grade 3 anaplastic pleomorphic xanthroastrocytoma (a rare type of anaplastic astrocytoma) located in my pituitary gland. Because the tumor was inoperable I went through four weeks of radiation therapy. At the end of the year, my MRI scan looked clear, with no glioblastoma or xanthroastrocytoma seen.

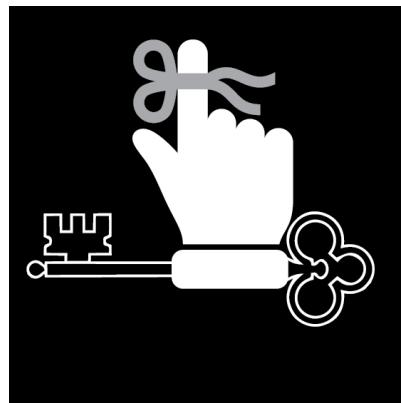
## Brain Tumor Guide for the Newly Diagnosed

Over time I have experienced many deficits. Some of these have been challenging, others I have managed. Most people would never know that I am battling brain tumors. I seem normal. However, my family and good friends know I am seriously suffering in the fight.

But I love life, and I will never regret this fight: it has been well worth it. Since my last recurrence, I have had fun with my family, hugged my boys goodbye at college, celebrated holidays, and enjoyed the beauty around me. During these years, connecting with others battling brain tumors has inspired me so much. Al Musella and the [virtualtrials.org](http://virtualtrials.org) website have been so helpful. Reading survivor stories is encouraging. Please don't feel it is over. Don't listen to the statistics. We can still love life and have fun even as brain tumor patients.



## KEY TAKEAWAYS TO REMEMBER



A good diet may help to stave off some treatment side effects. For this reason, many clinics and hospitals have classes for cancer patients on how to eat better. It's a good idea to check into attending one.

Check with your doctor or nutritionist before using antioxidants. Too many antioxidants or taking them at the wrong time during treatment may not be beneficial.

Keeping well hydrated during treatment is important for flushing any chemo residue from the body and for avoiding constipation that some treatment can cause.

The relationship between diet and brain tumors is not well understood. As studies come out, the Musella Foundation will keep you abreast through its news blasts. You can sign up for these blasts at this link:

<https://virtualtrials.org/newsblast.cfm>

Expect that your doctor will want you to get routine scans to monitor the disease. Usually, these will be MRIs.

The first few MRIs after surgery and radiation may not be very clear owing to inflammation, so the results of these could turn out to be inconclusive.

Pseudo-progression – tumor puffiness caused by treatment – happens in 20-30%

## Brain Tumor Guide for the Newly Diagnosed

of cases. Not being able at the moment to say if this puffiness is tumor growth or treatment effects, the doctor will want to see subsequent scans before providing a conclusive interpretation.

Get copies of your brain scans (or a CD of them) and their interpretations and share them with other members of your medical team to ensure that they agree with the interpretations.





## Side Effects

### Memory and Cognitive Effects

Our brain is our thinking tool. When a tumor damages the brain and treatments like surgery, radiation, and chemo assault it, our ability to remember and think clearly can be impacted. Memory and thinking are susceptible functions that rely on many parts of the brain, so it may not be possible to determine if the issue one is experiencing is related to the tumor or to treatment or is a combination of both.

Regardless of how they arise, memory and cognitive effects can be a frustrating and sometimes debilitating side effect. They may manifest themselves in a general mental fogginess or confusion, and in a slower than normal functioning of these sorts of skills:

- Language (reduced ability to think of a word or name or recall a conversation or event)
- Concentration/focus or ability to pay attention
- Ability to plan and organize
- Decision making
- Controlling impulses

17

In addition to the impact of those functions, there also can be an effect called cognitive fatigue. When the brain is fending off a tumor, it is working very hard and the brain's ability to work at that level is limited. Individuals may signal a halt when their mental stamina reach a subjective limit. They may describe their condition as exhausted, "maxed out", drained or even burned out, or they may say nothing but simply reduce their activities or responsiveness to expectations. Cognitive fatigue is not always easily recognized because it can change from day to day and may be

impacted by needs for sleep, food, a shift in medications or even emotions. Generally, you may find that if you or your loved one have tasks to handle, they are best done earlier in the day, if possible.

Memory and cognitive issues may occur gradually over time. Once your recovery from surgery and radiation have concluded and your life begins to return to normal, you may notice some changes, or you may identify changes shortly after starting a new medication.

In addition to discussing these changes with your doctor, who may suggest a cognitive rehabilitation program or a change in your medications, there are some practical things you can do on a day-to-day basis to reduce the frustration associated with these changes:

- **Pace yourself.** Don't try to do too much and make sure you get regular sleep. Exhaustion does nothing to help a struggling memory.
- **Think When You're Fresh.** Memory often works best when you feel at your best, which is typically earlier rather than later for most, so plan to do your heavy thinking tasks early.
- **Focus on One Thing.** Trying to multi-task only overloads the brain's circuitry.
- **Stay organized.** Do your best to keep essential and common use things in the same place (e.g., like your medications, house keys, TV remote, etc.),
- **Write Notes.** Anyone with a slow memory will tell you they write lots of notes to help them remember things. Make "to-do" lists.
- **Timers and Alarm Clocks.** Use timers and alarms to remind you when you have to do something.
- **Exercise.** Talk to your doctor about starting (or continuing) with an exercise program. Exercise, done safely, can help you feel sharper and somewhat strengthen your memory and cognitive functioning.

## Tumor Side Effects

### Karnofsky Performance Status

A rating system, called the Karnofsky Performance Status (KPS), was developed in the late 1940's by Drs. David Karnofsky and Joseph Burchenal to aid doctors in assess the functionality of a person due to their brain tumor, since a brain tumor can present a complex of conditions. The KPS, which remains in use today, allows a doctor to rapidly classify a patient and their treatment needs. The KPS is presented below.

SCORE	GENERAL CONDITION	COMMENTS
100	Able to carry on normal activity and to work. No special care is needed.	Normal, no complaints, no evidence of disease
90		Able to carry on normal activity, minor signs, or symptoms of disease.
80		Normal activity with effort, some signs, or symptoms of disease.
70	Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	Cares for self, unable to carry on normal activity or to do active work.
60		Requires occasional assistance but is able to care for most of his needs.

50		Requires considerable assistance and frequent medical care.
40	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	Disabled, requires special care and assistance. [In bed more than 50% of the time].
30		Severely disabled, hospitalization is indicated although death not imminent. [Almost completely bedfast].
20		Hospitalization necessary, very sick, active supportive treatment necessary. [Totally bedfast and requiring extensive nursing care by professionals and/or family].
10		Moribund, fatal processes progressing rapidly. [Comatose or barely arousable].

### **ECOG Performance Status Scale**

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A patient's functional status may, as an alternate to the KPS, be evaluated in accordance with the ECOG Performance Status Scale. This scale was developed by the Eastern Cooperative Oncology Group (ECOG), now the ECOG-ACRIN Cancer Research Group, and was published in 1982. This scale, which is also called the WHO Performance Status or Scale, is used by researchers when planning cancer clinical trials to study new treatments. The ECOG Scale is presented below.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Deceased

## Seizures

Roughly 30 to 40% of people diagnosed with a brain tumor will experience some level of seizure activity and will require medical intervention. The nature and severity of these seizures will vary from person to person, depending on the region of the brain that is affected.

In some cases, a seizure will appear as something slight and quick — muscle or eye twitching, or a sense of being “out of the moment” mentally and/or physically for a brief time, or a blank stare or sudden pause without response. These are called focal seizures, which may present themselves prior to a more serious seizure later on, so even focal seizures should be discussed with your doctor. For others, seizures will involve full body activity, often categorized as grand mal seizures. Unprovoked recurrent seizures are a serious problem and can have a big impact on quality of life.

## First Aid for Seizures

- In the US, call 911 and get medical help to your house. (Certain people who routinely have seizures may not need a call for medical help, but if your loved one has a significant seizure, medical assistance is appropriate.)
- Gently roll your loved one onto one side and put something soft under their head.
- Loosen anything tight around their neck.
- Don't put anything in their mouth — the tongue can't be swallowed, and objects placed in the mouth can be bitten or inhaled.
- Don't try to restrain them - you'll only end up injuring them and/or yourself.
- Note how long the seizure lasts so that you can tell the doctor afterwards.

## What To Do About Seizures

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The first thing you should do is discuss any seizure with your doctor. Your doctor is able to prescribe anti-seizure drugs. There are many to select from and it may take some trial & error to find the drug that controls seizures effectively with the least amount of side effects. A list of the most commonly prescribed anti-seizure medications can be seen in the section entitled "Medications for Reducing Seizures".

## What Causes Seizures

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There are star-shaped cells involved with any glioma called astrocytes. The astrocytes that surround the remaining piece of tumor or are in the tumor environment take on a strange shape and act very differently. These weird and dysfunctional astrocytes mimic the response of the brain to some injury or trauma, and they cause swelling. They will do this in reaction to the presence of any part of the tumor, and/or to treatment effects from radiation or chemo. Basically, anything that makes these odd astrocytes unhappy will turn them into swelling producers.

That swelling, which is liquid suspended between brain cells, interferes with the delicate balance brain cells need between excitability and inhibition in order to function properly. That lack of balance can trigger harmful levels of excitability, which in turn can be enough to spark a seizure.

Plus, gliomas try to take over the brain's microvasculature system so that they can get a fresh supply of nutrients to grow. As they grow, they release toxic levels of glutamate, an excitatory neurotransmitter, which can kill off healthy neurons, making space for the cancer to grow. An abundance of glutamate can also cause more neurons to become electrically active, which can result in seizures. Ordinarily, one would expect the astrocytes, which are supposed to protect healthy brain cells from the high levels of glutamate by acting like a mini-vacuum cleaner and vacuuming up the excess glutamate, but the astrocytes are dysfunctional as previously described.

## **Tips For How To Avoid Seizures**

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In addition to taking any anti-seizure medication prescribed by the doctor, here are some practical tips for avoiding seizure triggers:

**Sleep:** goal should be to achieve the number of hours recommended per night (e.g., 8 hours for adults). Need to pick a schedule and stick with it. Sleep deprivation or even changes in sleep schedules can trigger seizures. Sleep deprivation is a \*huge\* trigger. Not getting 8 hours of sleep doesn't immediately mean that you'll have a seizure that next day, but it can make you susceptible.

**Limit Computer Time:** Watch out about getting overly tired by working too much on a computer. An estimated 30% of seizures these days are triggered by people working on their computer. too much. Get up, look away frequently, and limit time spent on the computer and similar electronic devices.

**Stress.** Goal is to avoid as much stress (e.g., emotional drama) as possible. Ideal would be to learn stress management and meditative techniques.

**Avoid use of alcohol.** Some people are fine with a glass or two of wine or maybe a cocktail, but some people cannot have any alcohol. Be reasonable and be guided by the advice from your doctor.

**Avoid drugs** (other than the prescribed ones).

**Avoid flashing lights** or other visual stimulations, whether on TV or elsewhere. Avoid playing videos or computer games, especially those with flashing lights. Avoid even looking at the flashing lights on emergency vehicles or firework finales. Know

also that some people can be triggered into a seizure by flashing lights with loud noises or music (e.g., sensory over-stimulation.)

**Eat a healthy diet.** There are studies that suggest that minimizing carbohydrates (e.g., avoiding gorging on junk food like potato chips) can reduce the risk.

**Avoid getting overly heated.** Saunas, Turkish baths, super-hot showers, Jacuzzis, etc. are not a good idea for those with brain tumors. The heat has been known to trigger a seizure.

**Avoid overindulging in caffeine.** This includes sodas, teas, coffees, and chocolates. Caffeine stimulates the central nervous system. For coffee, overindulging means consuming more than 2 to 4 cups per day (dependent on a person's size and prior typical consumption.) One of the triggers of seizures from caffeine is the interference with sleep, so you should avoid consuming so much caffeine in any form that have insomnia or become irritable and restless.

## **Hiccoughs/Hiccups**

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Hiccoughs (hiccups) do happen in some people. It does help to avoid acidic, greasy, and spicy foods. Really persistent hiccoughs (sometimes lasting days) can be associated with neural dysfunction caused by the tumor (or its residue). When this happens, the hiccoughs are being caused by what could be thought of as a tiny epileptic event. They are not necessarily harmful by themselves but can be terribly annoying and can interfere with sleep. When that occurs, the doctor needs to get involved. Drugs that are used to treat this kind of hiccoughs would be a muscle relaxer like Baclofen (Lioresal/Gablofen, etc.), or an anti-epileptic like Carbamazepine (Tegretol). In really severe cases, the doctor might prescribe even stronger medications like Lorazepam (Ativan) or Haloperidol (Haldol).

# Side Effects of Treatment

## Fatigue

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Fatigue resulting from chemo, radiation, and poor nutritional status is very common in cancer patients. The following describes some ways in which you can get some relief from this symptom:

**Physical Pain.** If you are experiencing a physical pain somewhere, tell your doctor and get it treated. Do not suffer in silence. Pain is a fatigue producer.

**Emotional Pain.** If you are experiencing anxiety or depressive emotions, tell your doctor and get it treated. Certain medications actually can both lift your mood and sensitize the cancer cells so that your chemo works more effectively.

**Get moving.** Planting yourself in a recliner is not a recipe to success; it is a fast track to fatigue. Those with the least fatigue stay active and engaged.

**Eat well.** For its size, even a healthy brain slurps up more than its fair share of calories than the other organs of the body and for a brain fighting back against cancer, the caloric requirements are as serious as if your brain was cycling up a steep hill. There is a section in this Guidebook that covers diet.

**Eat well (again).** Your bone marrow is busy trying to make new blood cells to replace those destroyed by chemo and it needs good nutrition to do that. You need to be eating sufficient, lean, good quality protein in order to have the building blocks (amino acids) required to make new blood cells. Most cancer treatments decrease the number of red blood cells, which causes a decrease in the amount of oxygen that gets delivered throughout the body and when the oxygen in the tissues is low, fatigue follows.

**Sleep.** The brain heals and regroups during sleep, and if it doesn't get sleep, fatigue is sure to follow. However, treatments can really cause problems with sleep. Make sure to go to bed at exactly the same time every night, even on weekends. This is a really important because it programs/reprograms your body into how to go to sleep; sometimes after a trauma like surgery, the body just forgets how to go to sleep and stay asleep for the requisite amount of time.

If you find that you are just unable to restore a good sleeping pattern after two weeks of trying, tell your doctor and get his or her advice for getting you back to your much needed sleep.

## **Behavioral Changes**

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A person who has had a tumor removed from their brain and is potentially facing a tough diagnosis can be expected to have their personality impacted. Not many people would take that sort of an experience with a carefree attitude. Some of the changes you can expect include the following:

**Depression.** Depression is actually one of the first symptoms of the disease owing to the stress the brain is under owing to the presence of a tumor. The reasons for the depression are not clear, but apart from the obvious turbulence on the physical organ-brain from the disease, depression is probably linked to these kinds of factors:

- The psychological/ spiritual load of being diagnosed with this disease;
- Concerns about work and financial concerns;
- The effects of some drugs required for treatment (some drugs, like certain anti-seizure meds can have a depressive effect. If this is noticed and is intolerable, discuss with the doctor.);
- Wanting to return to one's prior normal life and vitality;
- The effects of medical procedures (e.g., some people are offended/humiliated by having to dress into hospital gowns and get transported by wheelchair through hospital hallways in public; others feel demeaned by losing their hair from chemo, having a scar on their head, and having to put up with stares and well-meaning but hurtful comments from others);
- Concerns about possible pain and loss of dignity.

There are probably other factors that others may bring up, but just those are enough for anyone. This is not a symptom that should be ignored but rather should be discussed with the doctor. Some neuro-oncologists report writing more prescriptions

for anti-depressants than for chemo plus some anti-depressants can help sensitize the cancer cells to chemo, so an anti-depressant can provide two benefits.

**Irritability/Anger.** Some medications, notably steroids and anti-seizures, may elevate a person's irritability or anger threshold. Keppra (Levetiracetam), the most often prescribed anti-seizure med, can produce serious levels of anger and irritation in sensitive individuals. Dexamethasone, the most often prescribed steroid, can make a person very nervous, agitated, and unable to get a solid night's sleep leaving them irritable. If you notice unusual levels of irritability or anger, you should discuss the matter with the doctor who may be able to adjust your dosage or switch your medication to a more tolerable one.

## Hair Loss

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Some hair may be lost from radiation, but it is more likely to be lost from high dosages of chemo.

Hair does not suddenly bounce back when radiation or chemo is stopped, because these treatments cause hair follicle loss or injury and it can take a while for the hair to recover.

The fur that returns is called hay-hair. It could be thin, wirey and possibly a different color at first. Over time (6 to 12 months), your normal hair is likely to return, but you could end up with a thin patch where the radiation was at its most intense.

17

During the hair loss period and when your new hair comes in you should avoid all shampoos that are harsh and have alcohol, salicylic acid, grapefruit juice, or strong fragrances in them. Check the ingredients of any shampoo you put on your head. Go for organic, natural shampoos. Some suggested gentle but stimulating shampoos are listed below:

- Ultrax Labs: their shampoo is 5-star rated by those trying to regrow hair after treatment. It has caffeine as a lead ingredient and an antifungal ingredient that knocks out a little fungus which blocks a hormone necessary for regrowth.
- Nizoral Shampoo. First created for dandruff, but it is good for unclogging

hair follicles and thereby stimulating growth. It also has that antifungal ingredient like the Ultrax product. This product is probably a 4.6 star rated product.

- Phytoworx Organic Shampoo. Uses lots of pleasant organic ingredients including peppermint and eucalyptus, both of which are stimulating to the scalp, but gentle. This shampoo gets a 4.4-star rating.
- Pura D'Or Premium Organic Shampoo: includes Biotin. Also has Niacin which stimulates circulation. Gets a 3.5 out of 5-star rating.
- DS Labs Revita Hair Growth Stimulating Shampoo. Gentle on delicate scalps, and has proteins to help circulation. I don't have a consumer rating on this shampoo.
- Lipogaine Big 3 is a gentle shampoo. It smells like peppermint and contains Biotin, important moisturizers, and that antifungal ingredient the same as Ultrax and Nizoral. I don't have a consumer rating on this shampoo.
- Tricomin. Often used by those after chemo to stimulate hair regrowth. I don't have a consumer rating on this shampoo.

Follow the shampoo with a conditioner for fine or limp hair.

Do not use hair curlers. (MAYBE the sponge ones would be okay if applied gently and removed gently, as long as you don't sleep in them.)

Do not color or bleach or otherwise process your hair.

Do not vigorously brush your head/hair.

Avoid hair dryers – or if you cannot, use the lowest possible heat setting.

Avoid using hot water on your scalp; it could damage your incoming hair follicles. Water should be tepid, cool if you can stand it because coolness will be a bit stimulating.

Products advertised to regrow hair are wastes of money. Those products are not designed for loss of hair from cancer treatment.

There is a cap, called the DigniCap, which is designed and advertised to reduce hair loss, however, it is not recommended for use by brain tumor patients. Specifically, it is not recommended for use by those with a CNS malignancy either primary or metastatic.

Keep some of your hair that has fallen out in case you elect to buy a wig. You can take the samples to the wig store, and it will help you find a wig that is closest to your natural color.

If you elect to shave your head, do not use a manual razor. The razor may nick your skin and cause an infection. Use an electric razor instead. Best would be to have someone you trust to be very careful shave your hair for you because they can see what they are doing.

Eating healthy foods will help the hair follicles rebound.

Massaging the head daily with a drop or two of olive oil will stimulate the circulation on the head and will speed up the process, although “speed” will not be so obvious to you. It will only be faster compared to if you did not stimulate the circulation on your head. They make a vibrating head massager that may help.

.....  
: The key to regrowing your hair is stimulating the circulation in your scalp. :  
.....

Use a cotton or satin pillowcase to sleep on to avoid irritating your scalp.

If you go outside without a head covering, make sure you have sunscreen on your scalp. Your scalp will be very sensitive to sunlight.

Most hospitals have wig salons, and most wig salons know of all the special instructions for dealing with sensitive scalps (e.g., they know a patient should have a cotton liner under the wig to avoid irritating the scalp.)

The American Cancer Society in your area will probably be able to recommend a

good wig salon if you call them and they may even be able to help you with the costs of the wig. Your insurance may also cover that cost. Whatever you pay out of pocket, keep the receipt, because wigs may be a tax-deductible medical expense.

## **Effects Of Treatment And Medication On Libido and Sex**

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For patients undergoing treatment for a brain tumor, a decrease in sexual desire or in the ability to enjoy normal sexual activity is common. Deciphering the origin of these changes can be difficult, for many factors can be involved. While surgery causes postoperative fatigue and temporary physical weakness, chemotherapy and radiation can greatly affect and reduce your desire for sexual stimulation because of adverse effects on hormone production. So, too, can medications prescribed for the symptoms of brain tumors, such as swelling, seizures, nausea, anxiety, and depression.

Physical changes, such as hair loss and weight gain, can further undermine your sense of attractiveness and desirability, deepening the emotional separation from sexual contact. Individually or in various combinations, these side effects create in some cases a daunting puzzle that requires patience and communication to piece together.

Depression is common among brain tumor patients, a condition often controlled with antidepressant medication — for example, with selective serotonin reuptake inhibitors like Paxil or Zoloft. These medications can reduce sexual desire. A simple change in dosage or medication may help restore sexual desire and should be discussed with your prescribing physician.

While most treatment-associated dysfunction or lack of desire is temporary, being able to openly discuss difficulties and options for sexual intimacy with your partner and with your medical team can help in managing the extent of disruption and being able to resume normal sexual relations after treatment. Unfortunately, discomfort among health professionals in discussing sex with the same openness and honesty with which they discuss nausea, diarrhea, and even expectations for recovery can complicate your ability to understand — and prepare emotionally for — how treatment might affect sexual desire. For this reason, patients often find it beneficial to discuss issues of intimacy with other members of their medical team, such as counselors or neuropsychologists. These healthcare professionals will be familiar

not only with the impact of brain trauma and the effects of medication but also with the emotional toll borne by the patient.

## **Birth Control**

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If you take birth control pills, it is important to discuss the potential effects of your treatment with your gynecologist and with your medical team for your tumor. Chemotherapy may halt menstrual periods temporarily, but precaution against pregnancy must be maintained due to the devastating effects of chemotherapy for an unborn fetus. Some chemotherapy medications, as well as anti-seizure drugs, can interact with the effectiveness of birth control pills. A thorough discussion with your medical care team is essential.

## **Sex, Surgery, And Brain Tumor Treatment**

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In most cases, there are few reasons why you cannot have sexual relations while undergoing radiation therapy or after surgery. However, you should always consult with your medical team regarding any precautions against strenuous activity, including sex. Both radiation therapy and surgery can result in fatigue, making any strenuous physical activity difficult. As your strength returns, normal sexual activity can resume.

Likewise, unless your medical team specifically warns you against sexual activity while undergoing chemotherapy, normal relations are limited only by the precautions associated with the drugs themselves. Because chemotherapy drugs can be transferred through sperm, in some cases they can also be harmful to sperm and also damage a fetus. Condoms should thus always be used during both intercourse and oral sex to eliminate the possibility of exposing another person either vaginally or orally to the harmful effects of chemotherapy drugs.

Because sperm can live for up to three months, condoms should be used until three months have passed since the last chemotherapy treatment. Although dry orgasms can occur naturally on occasion as men age, chemotherapy can also cause this syndrome. The lack of ejaculation during orgasm is not cause for alarm and should have no adverse effect on pleasure.

Women receiving chemotherapy must take extra precaution against pregnancy, for

birth defects can result from these drugs. Discuss your method of birth control with your medical team and be sure to specifically discuss whether there might be any possible reduction in the effectiveness of your birth control pills during chemotherapy. Chemotherapy can also dry out mucus membranes within the nose, mouth, and vaginal area. Non-petroleum over-the-counter vaginal lubricants can assist with the temporary dryness associated with chemotherapy, relieving the discomfort and pain often experienced during sexual relations while on chemotherapy. Because petroleum-based products can irritate the vaginal area and also weaken condoms, they should be avoided.



## SURVIVOR STORY #10

On June 1, 2005, just five weeks after the birth of my first child, I was diagnosed with glioblastoma. This malignant and deadly type of brain tumor was the size of a woman's fist. Glioblastoma patients are told that "it's not a matter of if, it's a matter of when" the tumor will come back.

I quickly underwent brain surgery to remove the glioblastoma. The problem with brain surgery is that the doctors don't know what they will find until they cut into your head and take a look. After discovering that removing the tumor could cause a loss of mobility on my left side, the surgeons removed only half of it. I was told I would be lucky to live a year. I kept telling the doctors that that couldn't be right, because I had just had my first child.

My husband and I were not going to give up easily. We hit the road to visit some prestigious cancer centers after receiving the worst possible pathology report. Both brain tumor clinics recommended that I "re-do" my brain surgery to complete the removal of the tumor. I chose one of these centers to coordinate all of my treatment. I also went on long-term disability to cover my medical bills and keep my business afloat. In July 2005, surgeons operated again to remove the remaining tumor, a procedure that was successful.

At that time, I entered a clinical trial that involved the implantation of a drug locally at the affected areas in my brain, treatment that required a four-day stay in a neuro-intensive care unit. Most brain surgeries remove the tumor but not all the damaged cells. The new procedure was a way to kill off the remaining damaged cells and prevent the tumor from coming back. I was lucky that my health insurance paid for the hospital stay and all expenses. Frequently, we had no idea whether our health insurance would pay for an experimental treatment if needed.

17

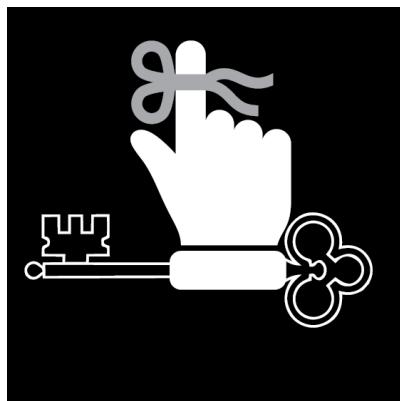
The surgeries and experimental drug procedure were a success. Nonetheless, I lost a lot of my cognitive function, and it took weeks for me to recover.

As if the brain surgeries weren't enough, my family and I moved to the location of the cancer center to receive a complete series of radiation treatment. After radiation, I then began a year of chemotherapy. I returned to work during this important recovery period.

Because of my disability insurance, I didn't have to come back to work, but I love what I do. But without the disability income, I would not have been able to keep my business afloat. It was a life saver.

Now, in 2018, I have had clean MRI scans for 13 years. I attribute my success to mindset, resilience, and tenacity — all of the qualities than enabled me to see beyond a terrible diagnosis in 2005. I strive to continue to set an example to my son, my family, my peers, and my community, in hopes that I can create even a small amount of impact while I am here.

## KEY TAKEAWAYS TO REMEMBER



Both the tumor and its treatment can produce a range of frustrating even frightening side effects. Not everyone will have all the side effects described here and some may have side effects not discussed here. It's a good idea to have a candid discussion with your doctor about what you can expect and what you can do about them should they arise.

If you are in your child-bearing years, talk to your doctors about using birth control and consider using sperm banks or egg harvesting.

Chemo treatment can produce birth defects. Use contraceptive protection.



## Caregiving and Support Groups

It is all too common: You enter your doctor's office with a list of questions, but as soon as your physician has finished his or her comments, you forget your own questions, or worse, forget or misunderstand the answers you receive. Emotions, not your brain tumor, are typically responsible. Emotional support and a second pair of ears can be of tremendous help while you navigate through a new world of tumor terminology.

Even for seemingly routine appointments, whenever possible, take a friend, loved one, or caregiver with you. Aside from taking notes of your session, if you become overwhelmed at any time during your physician's explanation of a particular treatment, necessary tests, or expected results, another person will be at hand to hear (or interpret) the details and will be able to ask questions that you might not think of at that moment.

Encourage your companion to make frequent notations or observations in your personal treatment binder and take an active role in discussing your care options. If your physician will allow recorded sessions, have your companion manage a small hand-held recording device and review the discussion afterwards with you.

In Table 1 (below) there is a list of organizations that can help provide support for caregivers, families, and loved ones.

### Caregiving

Certain types of brain tumors, particularly the malignant ones, require the support of a caregiver. In the final stages of the disease, because the effects can encompass

every aspect of how being human is defined, the challenge can be significant.

Because of its impact on personality, mobility, and cognitive abilities, not to mention the crucial treatment decisions, second opinions, and appointments you probably are having to make, high-grade brain cancer caregiving is considered by many to be the #1 caregiving challenge of all cancers. You should accept that this health challenge may be the hardest thing - physically and emotionally - that you may ever do.

The reason for that unwelcome distinction is simple: The brain is the Master Switch that determines how a person expresses themselves, how they think, how they dream; and it controls virtually all bodily functions. When the brain is compromised by the disease and the effects of treatment (which can leave their mark, too), many abilities are put at risk. Mental and physical decline is a distinct potential, but the one with the disease might not even realize there is anything wrong. Your loved one may exhibit personality and emotional changes that can take a real toll on you.

## Caregivers Fatigue

At times this can be quite a challenge when one is providing care day after day without sufficient breaks, and this can lead to a syndrome called caregiver's fatigue. This can manifest itself in some of the following ways:

### Physical symptoms

- Sleep is no longer regular; routinely fail to get at least seven hours undisturbed sleep per night
- Feeling ill; getting sick more frequently
- Lack of energy
- Change in eating patterns/appetite
- Stomach/digestive issues
- Losing weight or hair
- Having back problems

### Emotional symptoms

- Feeling edgy, irritable, argumentative, or losing your temper more often, even with the loved one you are caring for; displaying episodes of rage (e.g., yelling at other drivers)

- Experiencing crying spells
- Feeling sad or depressed much of the time or having mood swings
- Having a sense of anxiety and hopelessness about the future
- Having a sense of loneliness
- Feeling overwhelmed; want to just curl up into a ball and cry
- Experiencing a decline in your prior level of concern

### **Psychological symptoms**

- Withdrawal from family and friends; not seeking or accepting offers of help
- Not feeling satisfied with support from family and friends
- Not taking, or not having, at least 15-20 minutes of personal time each day; neglecting your own needs
- Feeling like caregiving is running a bulldozer over your life
- Looking for the exit (even to the point of wishing your loved one would perish sooner)
- Feeling strained in balancing work and caregiver responsibilities
- Displaying more forgetfulness than before
- Experiencing more difficulty in concentrating or making decisions (e.g., inability to plan meals, sometimes even when they are sorely needed)
- Needing prescription drugs, alcohol or more coffee, cigarettes, or other substances to make it through the day

### **First Aid for Caregiver's Fatigue**

If you recognize that you are showing signs of caregiver's fatigue, it might be time to apply some caregiver First Aid. Your first aid kit includes:

- **Ask for help.** Do not try to be a hero. Acknowledge you cannot do it alone and recruit people to help you, even if you have to force yourself. Make a list of daily activities and tasks. See if you can delegate any of it. Work hard to delegate parts of your work. Brain cancer takes a village.
- **Give yourself permission to take breaks.** Get out of the house. Visit with friends. Pamper yourself with a long bath. Of course, this means others have to step in to watch your loved one while you are on R&R.

- **Take care of yourself.** Exercise; meditate/pray; eat well; don't sacrifice sleep; take your vitamins; get yourself to your doctor and dentist for regular check-ups or to address any issues. Do not let some urinary tract infection linger until you pee blood or let that back problem get worse.
- **Journal** about your struggles and feelings for a few minutes every day. It helps to get it out. Do a Journal online. Others will read your struggles and be inspired by them or maybe have ideas for you that could lessen your load.
- **Practice Gratitude.** At the end of each day, take a few minutes to write down 3 to 5 things for which you are grateful. If this sounds like a silly waste of time you don't have, don't give in to that thought. This simple, quick step can make a huge difference in your attitude. It literally changes your brain's chemistry to more positive and more energetic thinking.
- **Work/Life Balance.** If you are still working, check into family-leave benefits from your place of work. If available, this might be able to open up your schedule considerably and give you some breathing room.
- **Share.** Keep sharing your frustrations with other caregivers. Communicating with them will remind you that you are not alone and that there really are people who understand what you are going through.

## Mind, Body, Soul: Faith In Healing And Emotional Wellness

While your primary physician may appear anything but spiritual in his or her approach to your brain tumor, some within the medical community are aware, and in support of, the power of prayer. Prayer, while very personal, may be empowering and proactive at times when “control” seems out of reach.

Also do not neglect the rest of your body. When facing a major problem like a brain tumor, the smaller problems sometimes get overlooked. You have enough problems to handle without having a “minor” problem blossom into a “major” problem. Be especially mindful of swelling and/or pain in the legs (which may indicate blood clots, unfortunately common with brain tumors), dental problems (some treatments

may hurt the gums and teeth), and rashes (indicating allergic reactions to treatments).

Your life, as you once knew it, may change throughout the journey. Things may not seem normal, but there will be a new “normal” for you and your family. The new normal will be what you and your family make it. It will take time, but you will settle into a routine that is comfortable for you. As with anything that is lost, you will go through a grieving process. Although everyone experiences grief and loss differently, you will probably experience some of the universal steps in this process, which may include shock, denial, anger, depression, and acceptance.

How you work through this process will be highly personal and individual. As you work through each step, you will probably have some additional feelings that may at times present conflicts for you. These emotions are many and can be unpredictable. Neither right nor wrong, they just are, and you are entitled to feel the way you do. They may include feelings of loneliness, sorrow, anger, sadness, blame, or shame, which may lead to anxiety and stress. Sometimes you will feel helpless.

To combat such emotions, concentrate on wellness and try to work through each of the feelings rather than denying them. Have a set of coping strategies that will guide you through each step. These strategies may include: (1) accept and understand your limitations, and set realistic goals; (2) get as much up-to-date expert information about your condition as you possibly can so you don’t fear the unknown, and be proactive in your treatment plan; (3) take good care of yourself by eating well, getting exercise and rest, and not self-medicating with alcohol; (4) see a mental health provider if you feel it necessary, as he or she can help you handle your emotions and stress; (5) record your feelings in a journal; and (6) try exercise, yoga, massage therapy, and/or meditation.

**Table 1: Organizations that provide support for caregivers**

Organization	Website	Description
Cancer Care	<a href="http://www.cancercare.org">www.cancercare.org</a>	Stories and podcasts on subjects ranging from financial assistance to stress management
Caregiver Hope	<a href="http://www.caregiverhope.com">www.caregiverhope.com</a>	Advice on facing fears and embracing life changes, with stories of hope and help
Cancer Compass	<a href="http://www.cancercompass.com">www.cancercompass.com</a>	Discussion groups and resources
Caring.Com	<a href="http://www.caring.com">www.caring.com</a>	Articles about caregiver wellness and money and legal matters, and a directory of reviewed and rated home healthcare agencies, nursing homes, and hospice facilities
Family Caregiver Alliance National Center on Caregiving	<a href="http://www.caregiver.org">www.caregiver.org</a>	Helps provide long-term care at home by offering national, state, and local programs to support caregivers
Lotsa Helping Hands	<a href="http://www.lotsahelpinghands.com">www.lotsahelpinghands.com</a>	Allows you to organize family and friends for needed tasks via electronic calendars and announcements and provides resources for caregivers
National Family Caregivers Association	<a href="http://www.thefamilycaregiver.org">www.thefamilycaregiver.org</a>	Wealth of informative tips and tools about financial and medical benefits, support groups, respite care, newsletters, and publications
National Hospice & Palliative Care Organization	<a href="http://www.nhpco.org">www.nhpco.org</a>	Resources for caregivers including checklists advance directives
Strength for Caring	<a href="http://www.strengthforcaring.com">www.strengthforcaring.com</a>	Articles and resources just for caregivers, with message boards
Today's Caregiver	<a href="http://www.caregiver.com">www.caregiver.com</a>	Webinars, resources, support groups, caregiver stories, conferences, and even a book club
Well Spouse Association	<a href="http://www.wellspouse.org">www.wellspouse.org</a>	Blogs, articles, and events on an array of timely pertinent subjects

## Palliative Care

Palliative care is medical care that is focused on relieving pain, symptoms, and stress. Unlike hospice which is conducted when all treatment of the disease has stopped, palliative care takes place during treatment. It can be a support mechanism for you, your caregiver, and your family.

It is not new, having come on the scene for patients around the 1970s. However, today it has evolved into so much more and is provided to patients for any diagnosis, at any stage of the condition and/or treatment plan. With palliative care, you, your caregiver, and your family receive emotional support, knowledge, and resources associated with your illness to ensure that your concerns about treatment, medications, side effects, and symptoms are addressed and to enable you to make the most knowledgeable decisions about your care. The first step in seeking palliative care is to ask your doctor or cancer center. Your goals will be to reestablish the quality of your life, to ease stress, and to be more in control. It will take time and patience, but you will find your comfort zone.

At some point, you may want to transition to hospice care, which can be given at home, in hospitals, nursing homes, or inpatient hospice facilities. This highly specialized concept of care — given by a partnership of family members, caregivers, and medical professionals — focuses on providing ongoing comfort, emotional support, and pain management 24 hours a day. It may also include spiritual counseling for the patient and family members. Hospice care will provide medications, equipment, and any medical supplies needed, as well as physical, speech, and occupational therapies to make you feel as comfortable as possible. You will work with an interdisciplinary team including medical professionals, social workers, home health aides, clergy members, and trained volunteers. Because most people see hospice care as marking an end of life, it is often not started soon enough. You can always opt out of hospice care if you wish to re-enter appropriate treatment or if you experience remission. Like palliative care, the main focus of hospice care is to bring quality-of-life and support services to the patient, caregivers, and family members. While palliative care may be given at any time and even through treatment, hospice care is appropriate when life expectancy is six months or less and treatments are no longer an option.

## Impairments And Strategies For Coping

Now that you have been diagnosed with a brain tumor, you may start to experience a variety of impaired functional abilities depending on the size and location of your brain tumor and your treatment plan. You may experience depression, memory and concentration lapses, personality and mood shifts, anxiety, insomnia, difficulties with self-care, poor balance, bowel and bladder incontinence, and conversational speech and word-finding problems. Healing and recovery from surgery and treatment are very important. When you are discharged from the hospital, make sure you are given clear instructions for caring for the surgical site, for what activities you can and can't do for a period of time, for medications and dosages, and for what to do if problems develop. Arrange your ride home from the hospital and have someone at home to help you until you feel well enough to manage on your own.

Each brain reacts differently to treatment, but you can find a way to adjust and compensate. There are strategies you can use that will help you to function and feel better and, in some cases, regain lost functional ability.

First and foremost, speak with your medical team about your difficulties before they become more complicated. They may prescribe some medications to ease your symptoms or refer you for physical, speech, occupational, or hyperbaric therapy sessions. Physical therapists will provide exercises that strengthen your muscles, increase your flexibility and mobility, and help you regain balance. Occupational therapists will work to strengthen small muscle control and gain functionality with self-help daily activities. Speech therapists will help in developing communication skills, vocabulary, and swallowing. Neuropsychologists will help you cope with and assess cognitive and emotional changes, as well as memory, thinking skills, problem-solving and reasoning, and perception. Hyperbaric oxygen therapy sessions may be recommended to aid in healing damaged tissue. Each of the therapists may also recommend adaptive devices to help you regain some degree of functional independence.

Second, speak with your partner or family members and explain how and what you are feeling. It is important to bring people on as part of your team to support you and help make things a little easier for you. However, they need to understand what you are experiencing before they can help. The more informed they are, the better they will be able to cope, understand you, and help you set goals.

The following coping strategies have been used successfully by people in our online support group to regain quality of life. But first you must understand your strengths and weaknesses, identify, or know the problems, and be willing to try a solution. At this point you may be feeling overwhelmed and confused about the changes you are experiencing. You may also feel some grief or denial for the loss of functioning. These strategies will provide the tools you and your loved ones need to help you rebuild your life.

Sometimes, the simplest solutions for what you are experiencing are organization and altering the environment. For cognitive difficulties, making notations on a legal pad, calendar, or day planner will aid memory. Include a check-off sheet or page as needed for each task completed. It will be helpful to use an alarm watch or kitchen timer to alert you of time sensitive activities. You may wish to use a weekly medicine dispenser with slots for am and pm medications. For better concentration, you may need to minimize or avoid distractions such as loud noises. Stay focused on one task at a time or alter a task by breaking it down into smaller parts. Sometimes a daily activity or time-management chart may help organize your day. Set limits and don't schedule too many activities in one day. Rest when you need to. You may find it helpful to follow a routine by keeping a consistent schedule. Keeping daily items in predetermined designated places will make them easy to find and save time locating them.

For physical safety and comfort, be aware of potential dangers in and outside of the home such as clutter, fire hazards, sharp objects, hazardous household products, scatter rugs, inadequate lighting, water heater temperature, and outside hoses. Don't forget to declutter drawers and closets. Switch to plastic cups and plates when needed. You may need to install additional handrails or place brightly colored tape across steps. You may need to conserve your energy or find it safer to use assistive aids such as canes, walkers, or wheelchairs. You may also need to install grab bars in bathroom/shower areas, use a shower seat while bathing, or purchase disposable underwear. Daily movement, which may be as simple as stretching, no matter how limited your ability, will help with improving your night's sleep, reducing negative emotions, and reducing stress, and will also help you focus.

You and your family may find it helpful to communicate with the use of word cues, picture flash cards, simple language, and sentence structure, or by asking only one question at a time and repeating back information to ensure understanding. But

first, make sure you are looking at the person speaking to you, so that you can focus and pick up visual cues. You may also find it helpful to play word games and puzzles.

It is important to recognize that there is no one way of doing things. You will learn to compensate for your deficits by learning new ways. Sometimes, you may feel that you have reached a plateau, but that doesn't mean that you will not progress again. You may continue to experience progress and setbacks in functioning. However, it is important to realize that when one way of doing things may no longer work for you, the strategy needs to be changed. Having patience and flexibility will be essential to your recovery. Your life will feel more normal and on track by using coping strategies that work for you.

## Support Groups

Support groups found on the Internet, or a local support group sponsored by your hospital/regional cancer organization can often assist with nonmedical issues — such as nutrition, relationships, and/or financial concerns.

Most people are shy about joining a support group, but don't be. You will be amazed at how quickly you feel at ease, because the members know and understand what you are going through, something (hopefully) nobody else in your circle of friends knows about.

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There are many online support groups with different focuses. The Musella Foundation runs and manages several online forums, and it maintains a list of many other online support groups. To see what is available, go to: <http://www.virtualtrials.org/lists.cfm>. There is also a list of support groups in the section below.  
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### "Real-World" Support Groups

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We urge all brain tumor patients to try out one or several support groups, whether online or "real world." It is a very powerful experience to speak directly with people who have undergone the same passage. Real-world and even online support groups are typically facilitated by nurses or other caregivers.

## Eighteen:Caregiving And Support Groups

If you live near a metropolitan area, you can attend a support group in person. These support groups provide community, and they can be safe places to open up and share both positive and negative emotions.

Some cancer and dedicated brain tumor organizations provide search engines on their websites that can help you find nearby real-world support groups in your area. These organizations include:

Organization	Website
Musella Foundation for Brain Tumor Research & Information	<a href="https://forum.virtualtrials.org">https://forum.virtualtrials.org</a>
Clinical Trials & Noteworthy Treatments For Brain Tumors	<a href="https://www.facebook.com/groups/13657508258">https://www.facebook.com/groups/13657508258</a>
Novocure, Optune Support For Glioblastoma	<a href="https://www.facebook.com/groups/347097922150691">https://www.facebook.com/groups/347097922150691</a>
Glioblastoma - GBM SURVIVORS TO THRIVERS!	<a href="https://www.facebook.com/groups/197153540892173">https://www.facebook.com/groups/197153540892173</a>
Surviving Glioblastoma (GBM)	<a href="https://www.facebook.com/groups/353827365003">https://www.facebook.com/groups/353827365003</a>
American Brain Tumor Association Forum	<a href="http://www.abta.org/">http://www.abta.org/</a>
American Cancer Society Cancer Survivors Network (for Brain Cancer)	<a href="https://csn.cancer.org/forum/165">https://csn.cancer.org/forum/165</a>

NTSB Brain Tumor Support Conversations	<a href="https://braintumor.org/take-action/brain-tumor-support-conversations/">https://braintumor.org/take-action/brain-tumor-support-conversations/</a>
Smart Patients Brain Tumor Community	<a href="https://www.smartpatients.com/communities/brain-tumor">https://www.smartpatients.com/communities/brain-tumor</a>

The Musella Foundation also maintains a comprehensive list of “real-world” face-to-face support groups, with contact numbers and email addresses, and with meeting locations and schedules. To access that list to find a support group near where you live, go to: <https://virtualtrials.org/support.cfm>.

## Online Support Groups

The Internet and social media sites offer nearly an unlimited resource for brain tumor patients, including online support groups, sometimes called “mailing lists” or “listservs,” chat groups, and message boards for sharing experiences and treatment options with others who understand what you’re going through. Although social media sites like Facebook are a good way to keep in touch with family and friends, and some brain-tumor groups are active there, be aware that Facebook is very public. So be cautious, and be sure to activate privacy settings, if you do not want information about yourself or your medical condition to be available for years to people who do not know you.

### **Common Sense Cautions about Support Groups**

A word of caution: Support groups (both online and “real world”) play an important and, in many cases, vital role in helping participants maintain a positive outlook during treatment and stay up to date on the latest brain tumor issues.

However, you have to be cautious and evaluate how much you can trust anything you find. There are people out there who are simply looking to make money off of your misfortune, and even people who are trying to help might inadvertently supply you with misleading information. NOTHING on the Internet or at a support group

## Eighteen:Caregiving And Support Groups

meeting should be taken as real medical advice. It is important to research anything you find and discuss it with your medical team.

Chat rooms are especially susceptible to problems because they may have few participants and an insufficient number of other people with whom you can discuss the pros and cons of a treatment. On the other hand, in an online support group you can ask for the experiences of many people with a specific treatment and get a broader view of it.

When using the Internet, exercise common sense and discuss information with your medical team to help you make the best possible decisions about your care. To evaluate information found on a website, consider the credentials of the person posting the information, how up to date the site is, whether any contact information is posted on the site, and whether the claims on the site are too good to be true or sound as if something is being sold to you.



## SURVIVOR STORY #11: YARON BUTTERFIELD

Vancouver, Canada

The beginning of 2004 kicked off as a new stage in my life. I had survived the breakup of a 4-year relationship and was ready to move forward. Work was going well and I hoped to move up in my career as a cancer genomics scientist; just 10 months earlier in April 2003, I played a large role in the analysis of the SARS coronavirus genome that made world-wide headlines after we announced our accomplishment. Life was busy with my work and I balanced it out with taekwondo, yoga, art, and my love of ice hockey.

On a Monday morning, February 23, 2004, a day and a half after I had scored 5 goals in the best hockey game of my life, I collapsed in a grand-mal seizure and was subsequently diagnosed with glioblastoma and was given a prognosis of living 12 to 18 months. Analysis also showed that I had the IDH1 mutation of interest and that MGMT was methylated—both good in my case. I decided to follow any treatment plan that was laid before me. The tumour was deemed to be too deep for surgery, so I went ahead with chemotherapy (temozolomide or "TMZ") and radiation.

I focused my emotions and energy on the events of the day without really looking forward. I absorbed the beauty around me, the flowers and trees, the fresh air, even the grocery cashier lady. Friends and family, including my twin brother were there for me 24/7. Rather than rushing to work in the morning and then in the evening to do whatever I had planned, I had a lot of time to think. All my thoughts were directed towards my healing.

Unfortunately, in my third week of treatment, my white blood cells count dropped dramatically so I had to stop chemo and get blood transfusions. I continued with radiation and a couple weeks after it was done, we tried to see if I could handle the chemo but it immediately had an effect on my blood count so treatment was over.

It was time to wait, to see the results of treatment which would be a few months as they wanted to avoid any misinterpretation from possible pseudoprogression. I decided I wasn't going to let my cancer diagnosis and devastating prognosis rule my life. I also realized that life was too short, whether with cancer or not. And so I signed up on a dating website and soon after met someone. We went on a date a week after my

## Eighteen:Caregiving And Support Groups

birthday in July when I turned 30. I warned her about my recent diagnosis and that I hadn't even got results of treatment at that point. She said she wanted to stick around and see how things go, that she saw a fighting spirit in me. We started to date and with her being a big part of my thoughts and energy, I had little time to worry about the cancer. A few months later, the MRI results indicated that the tumour had shrunk.

It felt like a new future was unfolding in front of me. My girlfriend moved in with me, I started fundraising and training for a run, and I became a student again registering for courses in immunology and in bioethics at the local university. My fundraising led to the opportunity to do a marathon in Iceland. I used to be quite a runner and had done many half-marathons but I thought I'd see if I could do a full one.

That August of 2005, I completed the 42km run on the volcanic island and then traveled inland with friends. One night we sat in the hills of Vik, taking in the beautiful Northern Lights, and I felt that I was as far away as can be from the cancer and all that came with it. I had left the tumour behind; I imagined hoping it would never return. But it did. An MRI a couple months after I got back home showed that the tumour increased to double the size. I had to consider further treatment. TMZ is often less successful after recurrence as the new tumour is usually genetically very different from the first tumour. Any cells resistant to TMZ in the first treatment have now multiplied into a new mass. Given that, I was offered a clinical trial drug in November.

Once again, while I subjected my brain to more drugs, I was excited, preparing to getting married at the end of the year. During the ceremony my alarm went off to remind me to take the chemo. That night, I got sick which was a common thing for me since starting the new medication. An MRI in early 2006 showed the tumour had not shrunk. A decision was made to attempt TMZ again. Keeping in mind that I had shown much sensitivity to the drug when I took it before, the thought was that taking it one week per month would be tolerated. Also, I had not initially completed a full round treatment of the chemo; there could still be cancer cells sensitive to the drug.

This was my treatment for first 8 months of 2006 and thankfully by the Fall of that year, the MRI showed that the tumour has shrunk significantly. Around that time, I returned to my hockey team but now, instead of being one of the best players on the team, I was the worst. I also went back to my job at BC Cancer, thrilled to be back to the research, working with colleagues and making discoveries to help lead to more understanding on how to treat cancer. I managed to get involved in various research studies about

## Brain Tumor Guide for the Newly Diagnosed

brain cancer. One such project I was heavily involved in was the analysis of tumour profiles from patients with oligodendrogloma where we identified key interactions with a couple genes of interest and chromosomal alterations (e.g., CIC, IDH, 1p/19q). I also contributed to one of the first research projects <https://www.google.com/?client=safari> demonstrating the benefits of personalized oncogenomics.

In 2008, my daughter was born and she gave me even more motivation to stay healthy and strong. I wanted to give back to the brain cancer community and became coordinator of Canada's Brain Tumour foundation (BTFC) walk/run in Vancouver which I did for 7 years. In 2015 BTFC handed me the David Kelley Award for Community Service. At the ceremony after the award was presented, my daughter came to me and quietly asked, "You had cancer daddy?" I gave her a big hug, held back tears, and told her yes, but not to worry, it was gone.

With my knees a little compromised with all my running, I started to get involved in biking. In 2009, three other brain cancer survivors and I created a team we called the Brainiacs to help fundraise for cancer research leading to a 200km ride over two days every August. Over the years, our team has recruited many each with their own story, and we have raised millions of dollars.

I had graduated over the years from MRIs every three months, to every six and then once a year. Time was moving farther and farther away from my personal cancer experience. Perhaps it was gone but the side effects lingered. In 2014, during a hockey game, I sensed something strange. By the third period, I seemed to be seeing double and my brother drove me home. We were worried that I had experienced a seizure, but it was found that I was getting double vision because of damage to an optical nerve. This wasn't the first long term effect of radiation I experienced; my hearing on the left side of my brain around where the tumour had been, was also compromised. I attempted to continue to play but problems with my vision led to a few bad falls and a couple concussions as a result.

In the Spring of 2016, one morning with my daughter, I had trouble with my balance while walking and fell into the wall. I knew something was wrong and tried to call my brother but couldn't hit the right numbers. My daughter, now 8, called him and then 911 and before I knew it, I was at the hospital and by evening my voice was gradually returning. The next day, I felt much better and was told that I had a seizure. Thankfully, the incident was not a sign that the cancer was back but that my anti-seizure medication

## Eighteen:Caregiving And Support Groups

was too low. I recovered fairly quickly physically, but cognitively; the seizure affected me such that I had trouble doing the detailed tasks of analyzing sequenced cancer genomes. In January 2017, I had to take a break from work.

A couple eye surgeries to try and fix the double vision were not very successful but over time, things improved slightly. After a 2-week trip to Peru with other cancer survivors in November 2019, which included a great day on Machu Picchu, I felt ready to consider returning to work. However, in the Spring of 2020, I had another seizure. Staff at the hospital initially thought I had a stroke but soon realized that there was a blood leak between my brain and the skull: a subdural hematoma. This was another long-term effect of the radiation I had in 2004. One night at the hospital, I woke up and realized I could not move the right side of my body at all. After a surgery, I spent most of the rest of the year in physical and cognitive rehab. Since then, I have been trying to heal in various ways: continuing to exercise with biking and hiking, exploring yoga, tai chi, and qi gong, reading, writing and doing my art. I hope soon I will be ready to return to work and contribute to continued cancer research.

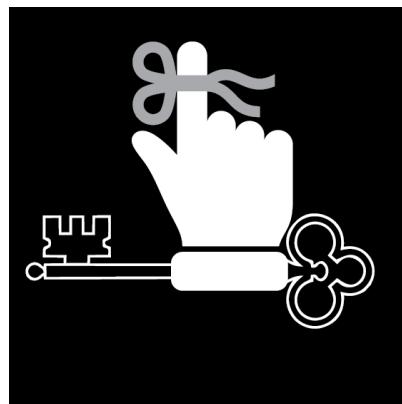
At this point in 2022, it's been over 18 years since my diagnosis of GBM. MRI's have been clear since the Fall of 2006. I am slowly getting my memoir together with the hope readers will be inspired and see that you can move forward past a devastating diagnosis and enjoy the world in your own way. I intend to continue doing that.

<http://yaronbutterfield.com>

Photo Credit Andy Singer



## KEY TAKEAWAYS TO REMEMBER



Whenever possible, go to all appointments with a friend, loved one, or caregiver to help you understand what the doctors are saying to you.

Do not neglect the rest of your body. Do not neglect your emotional health.

Caregivers also need to take extra care for themselves. Caregiver's fatigue is very real.

Support groups can educate you, lift you up, be a place to express both positive and negative emotions, and provide a strong sense of community.

Many cancer organizations and local hospitals offer support groups.

Online support groups can cover a wide variety of topics and issues. To find a support group near where you live, go to: <https://virtualtrials.org/support.cfm>.

Nothing on the Internet or at a support group meeting should be taken as medical advice. If you have any questions, discuss them with your medical team.



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## Late Stage

### Intubation and Ethical Considerations

In certain cases, a loved one becomes critically ill, but owing to their expressed wishes or the wishes of family members, the cessation of treatment and enrollment in hospice is not yet acceptable. However, they are too ill to eat and in order for life to be sustained so that treatment may possibly be continued, the doctor raises the concept of intubation - the insertion of a tube, sometimes a PEG (percutaneous endoscopic gastrostomy), for the purposes of delivering food.

This decision is not to be entered into lightly and without a conscious understanding of the potential consequences. Doctors must be able to provide assurances that the current symptoms are reasonably reversible within the next 2-4 weeks. The issue is that in a few weeks if your loved one does not rebound, you are going to be faced with an even more horrid decision. If the PEG is installed and your loved one does not rebound, the hospital will come to you in a few weeks and discuss its removal. At that point, you will essentially be removing your loved one's life support. No spouse, no parent, no child, no one should ever have to make that kind of a decision on behalf of their loved one.

Unless the doctors can say with assurance there is a reasonable chance your loved one will turn around before they decide it is time to stop the PEG, it is not advisable to agree to its installation, but rather would continue to provide nourishment as best as possible using thickened foods. It's not ideal, but people who are bedridden/asleep can live for a long time without any food.

If you are faced with this decision, you may wish to ask for a meeting with the doc-

tor, a palliative care counselor and if you have a religious tradition, a clergy member to help guide you.

Just as a data point, the intubation of a patient with a terminal illness like GBM is rarely done because of the ethical dilemma that it could cause.

## Hospice

### **Deciding When To Start**

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The decision to begin hospice can be a very painful one. For some people, just the word "hospice" evokes a great deal of anguish. Starting hospice is a very common source of reluctance for those facing the latter stages of this disease and for that reason, most people enroll so late that they are not able to receive the benefit of the comforts and support that hospice can provide.

The great people at Massachusetts General Hospital found in one of their studies that:

- 37% of people with terminal brain cancer fail to receive any hospice care at all prior to their passing thereby depriving them and their loves ones of the numerous benefits available from hospice.
- 60% enroll in hospice with an average length of stay of 21 days. (Typically, the length of time a person with GBM is in hospice prior to passing is 6 to 8 weeks once treatment has stopped.)
- 23% of patients enrolled within a week before their death, and 11 % were enrolled less than three days before their death, which is considered too late to do much good for the patient or their loves ones, according to authors of the study.

The issue we all struggle with is, of course, Hope. But it is essential that our hope is realistic and not unrealistic. If we labor under an unrealistic hope, then we may be depriving our loved ones and ourselves of the compassionate support that is available through hospice.

On the other hand, if there is some turnaround, for instance, if a loved one receives what is thought to be a final infusion, enrolls in hospice, but then rebounds to the point where further medical treatment makes sense, he or she can be un-enrolled from hospice. Hospice is not a one-way street nor is it necessarily giving up; it is simply applying the right support when and how it is most needed.

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For more information about hospice care, go to the following websites:

The Hospice Foundation of America: <https://hospicefoundation.org>

National Association for Home Care & Hospice: <https://www.nahc.org>

The brain-tumor help site for hospice care, Seeking Peace: Brain Tumor  
Hospice Care: <https://www.brainhospice.org>

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## Practical Tips

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### Emotional Support

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Although there are plenty of them, don't get caught up doing tasks. There are only two things a person with a brain cancer (of any Grade) really most wants: to know that they love and to know that they are loved. Make saying kind and loving things a priority every day.

### Pain/Discomfort Control

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Most GBM patients have a low degree of pain, but plenty have an overabundance of sensitivity to stimulation. Consider putting a sign near where your loved one is resting that says "Don't Touch Me! Air Hugs only!" (Obviously, touching your loved one for necessary care purposes or when he/she asks for a hand is excluded.)

If your loved one is uncomfortable in any way, breathing hard, not drinking, or eating, running a fever, or experiencing any other symptoms, tell hospice right away – no matter what time it is - and request their assistance to manage the symptom. That's what they are there for.

When your loved one becomes more and more bed bound, it will probably mess

with his/her lung function. Your loved one may need to have a condenser and be on low level oxygen just to ease their breathing as a comfort measure. Having the O<sub>2</sub> available is important if he/she starts breathing rapidly. When your loved one starts breathing hard, don't assume it will get better later. Just ask for the condenser.

At some point, your loved one will not be drinking as many fluids as he/she needs, and he/she will become disoriented and confused just from being dehydrated. It is suggested you having an electrolyte replacement available (like Pedialyte) to put into your loved one's water, which he/she is more likely to sip on through a bendable straw (so you'll need that kind of a straw, too, if you don't already have it).

At some point, your loved one will just stop eating and drinking. Forcing water or food when the swallowing function has ceased may cause your loved one to aspirate the liquids or food into his/her lungs which may give your loved one aspiration pneumonia. Pneumonia can be a lethal complication at this point, so everyone needs to know that stopping the food and drink is just part of the natural process and not to force him/her. That said, some (but not all) hospice organizations will agree to provide liquids via IV when a person can no longer drink/swallow. If you opt for this, it may give your loved one a few additional days, but then your loved one might not want the discomfort of the IV. Something to think about.

At some point, your loved one's ability to speak may falter, but he/she still wants to communicate. Try and make some kind of sign with little pictures to avoid a lot of frustration for your loved one. For example. I'm cold, I'm thirsty. Try and plan some basic signals.

## **Mobility Management**

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If you are unable to move or properly clean or feed your loved one, tell hospice and request their assistance and/or equipment. Take no chances that your loved one might fall or be dropped or get hurt or that you might be hurt.

One person is usually not enough for handling someone who is bedridden; trying to do so can be inventory for back surgeons. There is a patient hoist (called various things but Hoyer Lift is a common name) that can be provided and used for moving your loved one around in the bed so that your loved one can be cleaned. As with all pieces of equipment, you want this hoist available immediately when the need is recognized.

If your loved one is well enough to use a wheelchair, be aware that your loved one can fall forward out of the chair in the blink of an eye. Watch your loved one as you would a baby.

Keep your cell phone on you (e.g., like in a pocket) at all times. You could end up in an emergency situation (e.g., your loved one falls, no one is around to help and you don't want to have to leave him/her, unless it is to let medical personnel in the door.)

Hospice can provide all the equipment you will need, for instance a hospital-like bed which is essential for lower/raising your loved one so that you can best care for your loved one. That hospital-like bed requires an extra-long twin fitted sheet that no one really has, but twin flat sheets will be fine. You can tuck these. Make sure you have several (4 to 6) sheets and pillowcases. You'll need several to be able to keep your loved one in clean linens.

Hospital beds are designed to be waterproof, not comfortable. The super soft quilt-like bed coverings with waterproof liner will need to be washed, so you might need three or four, used with large, soft, waterproof bed pad (washable or throwaway) on top. That can make all the difference in final comfort.

If your loved one can't turn in bed on their own, consider getting a bed that automatically turns the patient to reduce chance of bed sores.

If your loved one is in a bed in one location of the house and you would just like to go the kitchen or laundry room but still want to keep an eye on your loved one, baby monitors work would great.

It is possible to get a kind of frame around the toilet which provides arm handles for your loved one to lean on for as long as he/she is mobile.

## **Managing Hospice**

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If you don't like your lead nurse, say something to hospice about changing him/her out with another. No medals are available for being long-suffering or more discontented than you otherwise need to be during this highly critical time. You won't "hurt their feelings"; hospice knows that not every nurse works with every family.

Especially during weekends and holidays, hospice can get overwhelmed so if you aren't getting the help you think you need, pester. Be nice but pester. Call at any time of the day or night, but best time to call and alert them to a priority need is early in the morning before shift change (usually 7am).

If you have competent family or a close friend helping you, get them to call hospice for what you need.

Keep hospice phone numbers nearby and easy to locate. Know the name of your assigned nurse's head nurse or team lead just in case you need to escalate a requirement. Do not be shy about your real concerns.

All concerned family members should have the most critical phone numbers on the refrigerator door (or other location) since GBM is famous for creating emergencies at the drop of a hat. Family members that are not in your same location need to keep an overnight bag packed and under the bed/in a closet to be ready to move at a moment's notice.

## **Miscellaneous Topics**

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For ease of clothing your loved one when he/she is very bed bound, you may wish to use soft, cotton t-shirts. If you slit the back of the t-shirt (right in the middle) from the bottom hem of the shirt to the hem of the neckline (but not through the neckline hem), you'll have a shirt you can easily slip on and off to keep your loved one covered and clean. You may need to have a pile of them ready (like 10 or so).

Keep a good, reliable thermometer handy and take your loved one's temperature regularly. If you notice any fever spikes beyond 100.4 (Fahrenheit – 38 degrees Celsius) [or whatever the medical team tells you the magic number is], call them immediately. They will probably suggest you treat your loved one with acetaminophen (aka Tylenol). You should consider tracking your loved one's temperature. The higher the fever and the more constant that fever (absent some underlying reason like an infection) may be indicative of how close your loved one is getting to passing.

Assuming you are caring for your loved one at home, make sure you have plenty of fresh (not expired) acetaminophen and ibuprofen available. Keep all your loved one's

meds in the refrigerator (in a place where children cannot get at them) unless the hospice nurse tells you otherwise. Later, when your loved one can no longer swallow, suppositories of many of these meds can be provided from hospice.

For sponge baths and clean-ups after bowel movements when your loved one is largely bed bound, it is handy to assemble a kit in a small plastic tub of essentials like these:

- Nitrile exam gloves (for you)
- a roll of toilet paper
- pre-moistened disposable wipes\*
- baby powder
- diaper rash ointment or another perineal skin protector
- a spray which is a no-rinse perineal & skin cleanser and/or no rinse body wash/incontinent cleanser
- 1 or 2 replacement pull ups or adult diapers
- 1 or 2 replacement bed pads - nicknamed "chucks"
- Cloth washcloths
- Small cloth towels

\* It is a good idea to put 4 or 5 wipes in a small baggie and then when needed, toss the baggie into the microwave for about 10 seconds to warm them up. You should consider having several of these baggies ready to go at any moment.

Most of these items can be provided by hospice on your request.

Whatever mattress your loved one is on needs to have a WATERPROOF mattress pad.

At some point, the natural saliva flow in your loved one's mouth will decrease and so his/her mouth will get rather sticky/muddy. They make a special mouth cleanser to use for cleaning the mouths of individuals in this situation. Hospice should be able to provide. These cleansers come with a brush, but it is better to just use a damp wash cloth with some of this cleanser in order to really clean the mouth and in particular the cheeks. (GBM patients are famous for storing medications in their cheeks and not swallowing them; if this happens, this mouth cleaning with a washcloth will pick

them up and get them out of the mouth.)

Your loved one's lips are likely to become very dry. You'll probably need to moisten his/her lips frequently with a lip balm or a bit of Vaseline.

It is useful to have a little white board for writing down what medicines your loved one has taken that day and which he/she still needs to take and when. There are usually lots of medicines each with their own schedule and it can get confusing without writing them down.

Don't be surprised if you have to do several loads of laundry a day. Pull ups (while your loved one is still mobile enough) and incontinence pads on every seat help cut down on laundry. Once mobility has ceased, then you'll need to use adult diapers.





## Passing

If you are reading this, we understand that you are facing a very significant loss and for that we extend our deepest condolences. We hope that this description of what you might expect and when will be of help to you for planning, but most of all for diminishing the amount of suffering and heartache that is normally associated with the departure of a loved one from this life.

The following is a summary of the major symptoms you can expect and within roughly what time period. Not everyone will experience all of this, so you should read this as a sort of general idea of what may happen and when.



## Few Months Before Passing

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- May have or continue to have crises that precipitate panicky visits to the hospital. Examples of issues that may arise that may cause one to scurry to the hospital are:
  - Seizures ranging from all out generalized grand mal type to absence seizures where your loved one just sits and stares for some minutes.
  - Brain bleeds which might be minor or serious enough to produce stroke-like symptoms.
  - Sudden weakness in a limb, facial palsy (drooping), eyesight or hearing issues.
  - Infections ranging from pneumonia to urinary tract infections.
  - Uncontrollable nausea/vomiting or even persistent hiccoughs.
  - May have severe headaches from an increase in intracranial pressure.
  - Deep fatigue/ inability to be fully awakened.
- Mounting issues may precipitate a “decision MRI” which, if results are poor, initiates discussion leading to hospice enrollment.
- Likely to display a decrease in facial expressions and verbal expressiveness; may have more trouble finding words.
- May display obsession/compulsive behaviors (e.g., may turn light switches on and off repetitively).
- Sleeping more (e.g., 10+ hours each night, with daytime naps).
- Increased in confusion and memory lapses (may forget how to operate a TV remote control or what toilet paper is for; may change passwords on

accounts and forget those passwords; may put dirty clothes in the refrigerator).

- May start falling with recurring frequency; may need to use a walker/wheelchair; stairs in home become safety concern.
- Likely will need help at home for most if not all waking hours each day; may need to be watched carefully.

## 6-8 Weeks Before Passing

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- Likely needs care 24/7 (Should be enrolled in hospice at this point; early hospice enrollment is best).
- Headaches from increase in intracranial pressure may increase.
- Increasing weakness on the affected side.
- Becomes a fall risk and may have periodic falls due to resistance to accept help.
- May have a need for more assistance with walking and transfers (e.g., from bed to toilet).
- Sleeping much more (e.g., 12+ hours each night, with daytime naps). May also be more likely to just nap or phase in and out of sleep. Sleep disturbances are common at this point.
- Elevated heart rate (e.g., in the 90s) and possibly shortness of breath.
- Increased memory issues and confusion; may not recognize own spouse/children; may not know what month it is.
- May start to become expressionless facially and verbally. (While a few people retain the ability to communicate until very near the end, most do not.)

- Harder to sustain a conversation. May make strange statements.
- Needs more medications to control symptoms.
- Start of loss of bladder and/or bowel control; may experience reluctance to wear protective pants due to loss of ability to understand future consequences.
- May exhibit less tolerance for/interest in food.
- May start to exhibit problems swallowing food.

## About A Month Before Passing

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- Should be enrolled in hospice and needs 24/7 care.
- Will feel safest/less anxious at home on one area of the couch or on one certain recliner.
- Even the side of the body not previously affected is now showing signs of weakness.
- Has likely become a true fall risk and must have support. Legs may just buckle at some point, and they will not be able to support their own weight.
- If still able to walk, may wander around the house. You may find them standing, staring blankly in some room in the middle of the night. May have some level of restlessness/agitation.
- May sleep 18-20 hours a day, but not continuously. Will wake, be alert for a while, potentially will have something to eat, then drift back to sleep. May have sundowner's syndrome - a condition where there is confusion over what time of day it is.
- Memory continues to lag; displays less interest in anything having to do with normal life (e.g., seems detached from family, friends, interests.) No longer interested in activities that require an attention span (e.g., will not

care to watch a TV show, play a video game, or read a book.)

- Conversations become even more difficult to sustain. Word finding may be very slow or be frustrating with words ending up on the "tip of the tongue".
- Speech may become slurred; sentences may be unfinished.
- May make statements indicating they are aware of their impending passing. May describe visions involving deceased relatives or angels.
- May become childlike. Questions only needing a yes/no response work best.
- Urine becomes orange or dark (can be described as "tea-colored").
- May experience less warning before needing to urinate. May have "accidents". May saturate the bed with urine at night and will need an external catheter to control.
- Appetite may start to be sporadic.
- Swallowing problems may increase. (It is important to not force food or drink at this point because they could aspirate the food or drink causing aspiration pneumonia.)

## **Days Before Passing**

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- Totally bedridden and sleeping all the time.
- Decreased food and drink intake (most will stop entirely; swallowing problems will make any efforts to feed downright dangerous). It is important not to force food or water to avoid aspiration pneumonia. Sometimes when/if requested, hospice will start a saline drip for fluids which may provide another extra day or so.
- Dry mouth (will need to keep Vaseline or other softener on their lips).

- Restlessness (if too much, get with hospice to help with this; they can provide a medication).
- Labored breathing (get with hospice to help with this; they can provide oxygen which can help).
- Fever (will probably need to use Tylenol or other med to control fever, but the fever will just go up again when the med wears off).
- Dark orange/brown urine; reduced output.
- Heart Rate: Near the end, heart rate can become very elevated. It is not unusual for someone to have a beats per minute of 140, 150 160 (or more). As the heart rate increases, so may breathing for which they could use some oxygen support. When you see the heart rate start to come down from these peaks (if you are monitoring the heart rate), then you know they are getting ready to pass.
- Communication: Most individuals have not communicated for a long while at this point, but a few may suddenly, a day or so before they pass, awaken, may even sit up, ask for food, tell a few stories, say that they love you, then fall back to sleep and never again wake up.
- Pain and Awareness: Awareness of what is happening, including any pain, is ending. Normally, people who pass from brain cancer do so with very limited amounts of pain. The only real way you may have of knowing they are in some level of discomfort and needs a bit of medicine to alleviate that discomfort will be some very subtle facial expression (e.g., furrows the eyebrows) or maybe some soft groaning.

## **Hours Before Passing**

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- Purple spots on skin start appearing (usually starting around the feet and knees).
- Twitching.

- “Urine dump” (the body could release a large amount of fluid in a short amount of time).
- Perspiration (you'll want to just clean their face, arms, and legs with a clean, cool, moist wash cloth).
- Often in a coma or deep sleep.
- Breathing changes (if there was labored breathing before, it could suddenly calm down before stopping).
- It is recommended that you do not engage in disconcerting conversations around your loved one when he/she is “sleeping” (even if the hospice nurse says he/she is in a coma/ semi-coma). Hearing is the last sense to go, so assume that he/she can hear and possibly even understand everything said in her earshot.
  - One study by a neuroscientist says that the brains of 15-20% of people in a deep coma/vegetative state still show conscious and responsive activity under an MRI. So, if you need to tell your loved one something important, do that; it is possible he/she hears you on some level and understands. Similarly, if someone has something tough to say, it should be taken outside or into another room.
- Keep regular track of your loved one’s heart rate. In the beginning of the transition process, the heart rate may be high, sometimes going very high (like into the 140’s, 150’s, 160’s) and then as the process concludes, your loved one’s heart rate will start to taper. Once it starts, this tapering can go fairly quickly with his/her passing following in a short time.
- Be ready with family, friends, and any clergy you might want to have present.
- It is suggested that you plan your last religious readings and prayers sooner rather than later and have the materials nearby. Be careful not to use your very favorite prayer at the very end because you may not be able to recite that prayer again for a very long time without breaking down emotionally.

## Where Has My Loved One Gone?

The answer to this question is intimately tied to and is best addressed by one's own religious views on the topic. However, for those with a spiritual nature who are craving answers but are not affiliated religiously may find it consoling and useful to review the reports of individuals who have experienced a near death experience. The largest collection of these experiences has been assembled by a radiation oncologist named Dr. Jeffrey Long and is available online at this link:

<https://www.nderf.org>



## Disposal of Unused Medications

### **Disposal of Federally Controlled Substances**

If hospice has been conducted at home and the loved one passes in the home, there is often the question of how to dispose of the unused medications. The question of how to dispose of unused medications should be referred to the hospice doctor, physician's assistant, or nurse.

Some of the medications used during hospice are considered controlled substances (as that term is defined under the US Controlled Substances Act and equivalent laws if hospice occurs in another country), which if not properly disposed of, can be diverted and misused by others.

The most commonly misused controlled substances include opioids (such as oxycodeone) which is used to treat pain and central nervous system depressants (such as diazepam), which are used to treat anxiety and sleep disorders. These and similar types of drugs are commonly prescribed for patients in hospice care.

In 2018, an amendment to the US Controlled Substances Act allows employees of "qualified hospices" to dispose of a patient's unused controlled substances onsite and in accordance with all applicable laws after the patient's death or the controlled substance expires. The employee must be a physician, physician assistant, nurse, or other person who is:

- employed by a qualified hospice (i.e., a business set up to provide hospice services that has written procedures and procedures, and properly documents the disposal of the substances); and
- licensed to perform medical or nursing services by the jurisdiction in which the patient has received hospice care; and
- acting within the scope of their employment in accordance with applicable state law; and
- trained on the disposal of controlled substances by the qualified hospice.

### **Disposal of Medications NOT a Federally Controlled Substance**

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Once qualified hospice personnel have identified to you medications that are NOT federally controlled substances, then you may dispose of the medications following the instructions from the US Food and Drug Administration (FDA) on their website:

<https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know>

## Identify Theft of Deceased

Regrettably, some individuals will attempt to steal the identities of individuals who are deceased. They review obituaries and may try but using these guidelines should help you prevent an attempt, recognize an attempt, and know how to react if an attempt at identity theft is being made.

### What To Look For

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Watch for a letter from the post office saying that your loved one's mail is being forwarded or letters from a bank or banks requesting additional information for the credit applications. These are likely to arrive on or about the time.

### What To Do If You Suspect Identify Theft Of A Deceased Person

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Request a copy of the decedent's credit report. Then, place a flag on the account stating "deceased alert" on the report, as described below.

Notify the police in the decedent's jurisdiction if you have evidence of fraud (collection notice, bills, credit report). A suspicion of identity theft is best when backed with concrete evidence.

Notify any creditor, collection agency, credit issuer and utility company that the person is deceased. Be sure to include a copy of the death certificate. Request an immediate investigation and that they contact you with the results of the investigation. Insist on letters of clearance, which you should keep with the other estate papers.

In the event that the thief is a family member or relative (which unfortunately does happen), seek the advice of an attorney that specializes in estate or family law.

### How to Prevent Identity Theft Of A Deceased Person

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In obituaries, list the age but don't include birth date, mother's maiden name or other personal identifiers that could be useful to identity thieves. Omitting the person's address also reduces the likelihood of a home burglary during the funeral (sadly, this also does happen).

Using certified mail with return receipt, send a copy of the death certificate to each credit-reporting bureau — Equifax, Experian, and TransUnion. Make sure that your letter and/or the death certificate includes the following and any other data needed by the particular bureau:

- Name and Social Security Number of deceased
- Last known address
- Last 5 years of addresses
- Date of birth
- Date of death

In your letter, ask them to place a "deceased alert" on the credit report and mark the file as follows:

"Deceased. Do not issue credit. If an application is made for credit, notify the following person(s) immediately: (list the next surviving relative, executor/trustee of the estate and/or local law enforcement agency- noting the relationship)."

Mail a copy of the death certificate to banks, insurance companies (auto, health, life, etc.), Veteran's Administration (if person was a former member of the military), brokerages, credit card and mortgage companies where the deceased held accounts, membership programs (video rentals, fitness clubs, etc.)

If you're closing an individual account, make sure the institution lists "Closed: Account Holder Is Deceased" as the reason. For joint accounts, remove the deceased's name.

Report the death to Social Security by calling 800-772-1213.

Contact the department of motor vehicles to cancel the deceased's driver's license, to prevent duplicates from being issued to fraudsters.

Keep copies of all correspondence, noting date sent and any response(s) you receive.

## Brain Donation

While considerable progress can be made through the current medical research methods, there is so much more neuroscientists can make given the advantage of working with donated brain tissue. From one brain, dozens if not hundreds of studies can be made.

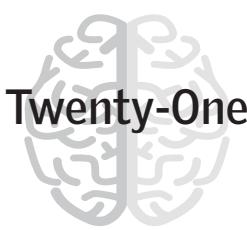
Brain donation makes it possible to advance research into brain cancer that can provide a lasting and significant legacy for your loved one, and families may derive a sense of comfort from contributing to the eradication of this disease with the goal that other families will not have to endure such a loss.

There is no cost to the families for the steps involved in making this donation.

For those interested in making this extremely precious gift, you may find more information at this website:

<https://braindonorproject.org>





## Grieving

### Overview

Even though we know that everyone will die, each death can still have a huge impact those of us who are left behind. Experiencing grief is natural and necessary, and the vast majority of people suffering the loss of a loved one will experience it.

We have neuroimaging studies basically of grief, of the momentary reaction where you have that emotional yearning experience. One thing that we know is that grief is tied to all sorts of different brain functions, from being able to recall memories to taking the perspective of another person, to even things like regulating our heart rate and the experience of pain and suffering. This is why we have a large variety of emotions and why they can be quite intense.

In this section we discuss the three main categories of grief that individuals who have lost or expect to lose a loved one to brain cancer may experience:

- Anticipatory Grief
- Grief after the Passing
- Prolonged Grief Disorder



## Anticipatory Grief

Unlike the grief that happens after a loved one has passed away, "anticipatory grief" is a distinct kind of grief that begins once we realize our loved one is in danger of passing away within the foreseeable future. For caregivers and family members who closely step through the brain cancer diagnosis and treatment journey with a loved one, the growing reality of the impending loss can be all the more intense and real.

Many of the emotions experienced by someone grieving after the loss will be experienced by someone in anticipatory grief. Differing levels of a wide variety of thoughts and emotions like sadness, anger, frustration, denial, guilt, and a clinging to every hope however valid or flimsy can be experienced. Sometimes the experience of anticipatory grief lessens the post-loss grief, but not always. By the time the loved one does pass, a person experiencing anticipatory grief can be very entrenched in the variety of painful emotions that characterize grief after passing.

Anticipatory grief is quite real and should not be ignored. It can sap the energy you want and need to care for your loved one and spend very precious time together making important memories.

You should endeavor to spend time in your normal activities. Staying grounded in your life with your activities and your friends can help. Reaching out to trusted and caring confidants and telling them how you feel can help to "vent" some of the painful emotions you are experiencing. Taking time for yourself is not being selfish; it is recharging your batteries to enable you to be a better caregiver through a very difficult time in your life.

## Grief After the Passing

No matter how long you knew, no matter how much you accepted the loss, nothing can prepare you fully for the reality of the loss.

Grieving is a process that involves your mind, your emotions as well as your body. Many people are surprised to understand that grief is also physical. Here are some practical ideas to help you with this challenging period of your life:

- **Unique.** Your grief will be unique to you, so no one can or should tell you what is right or wrong for you to be experiencing.
- **Find Those Who Understand.** You should find others who understand. Some people cannot relate to anyone who has gone through the brain cancer journey with all its intense complexities, so it is helpful to seek out those who have gone before you.
- **Talk About It.** People who have not gone through such an intense loss will tolerate hearing about it once or twice, but that might not be enough venting for you. Ideally, you should find those who will let you talk about what you have experienced as much as you want.
- **Emotions.** Expect that your emotions will be a stew that will change day by day, even hour by hour. You may visit every emotion like sadness, fear, confusion, depression, guilt, anger, even relief (and then guilt from feeling relieved.)

Others may tell you that something you are feeling is wrong. Do not accept their judgment; accept your emotions unconditionally and seek out individuals who can do the same.

- **Guilt.** Almost everyone who goes through this journey ends up feeling guilty about something they think they could have done or should have done to extend the life of their loved one or to make them more comfortable. This is an unfair and bottomless pit. Accept that you did the very best you could under the circumstances, which were extreme. Caring for someone with brain cancer is the #1 caregiving challenge given all the complexities of the disease.
- **Extreme Emotions.** Some people have difficult reigning in their behavior after a loss. They may be overly angry and engage in road rage. They may experience intense sadness for more than 2 weeks which then migrates into depression. If you experience any long-lasting extremes of emotion that can compromise your normal behaviors in unhealthy ways, please reach out for help to a responsible friend or doctor.
- **Exhaustion.** Grief is hard work and can leave you sapped of strength. Expect fatigue and expect to need to baby yourself with rest. If others want you to do things to take your mind off the loss, do not feel you must go. Maybe a nap will be the best for you at that time.
- **Diet.** It may be hard, but you need to eat, and you may find you have to force yourself a bit to not just eat but to eat healthy foods.
- **Grief Ambushes.** Grief can ambush you when you least expect it. You may have strung 2 good days together and then the third day hits you like a truck and you are overwhelmed again. Or you are holding your own at the grocery store and then you see a food your loved one really liked, and you break down right there in the bread aisle. These ambushes are a normal experience. Over time they should subside in frequency.
- **Funerals.** The funeral is not just to celebrate and honor the life that has just been lost but is intended to support you in mourning. If someone suggests not to have a funeral, talking to a trusted friend or clergy may ease your questions.

- **Relying On Faith.** If you have a religious tradition, make use of it to the maximum extent you want. Faith at a time of grief can be a significant help, so seek out people who share your faith convictions.
- **Anger/Questions For God.** If you have been left with questions or anger at God about why this all happened, please talk to a friend or clergy who will understand and not condemn your feelings. Also, when someone tells you that your loved one is in a better place, no matter what your views are of Heaven, you may recoil from that well-meaning but insensitive comment. You don't have to accept any comments like that.
- **Rebuilding Meaning.** When a diagnosis like brain cancer happens and certainly if a loss happens because of it, it can take a person's sense of meaning and ruin it. As a mourner, you are grieving not just the loss of your loved one, but all the meanings you had in life associate with that person. Your task now is to rebuild your sense of meaning - figuring out why you are getting out of bed in the morning. This is not an easy task, so lean into your support group to help you.
- **Treasuring The Past.** Your memories of your loved one are precious. If you have items of theirs you want to keep, keep them. If you want to put up more pictures of them, do that. This is your loss and your way of treasuring what has been lost. Ideally, you will find people who can share your memories with you.
- **Learning To Bear The Loss.** Grieving is a process of self-paced learning. It takes time and patience to learn how to bear the loss of a loved one and then balance it with the continuation of your life. Your life has been deeply changed by your loss, but with the help and support of those who understand what you have gone through, you will come through and one day the sun will shine again in your life.

## Prolonged Grief Disorder

When a loved one dies, those left behind naturally feel various levels of sadness, anger, guilt, fear, and loneliness. These are the hallmarks of normal grief.

The initial period is intense and for the majority if people (about 93%) is limited to a predictable period of time—about six to twelve months. The exact time will vary from person to person and from culture to culture.

Eventually, the initial grief will slip to the background of the survivor's life and will be integrated into their thoughts and emotions in a way that enables a balancing of the loss with the ongoing life. The mind and heart adapt. The grief does not end, but its sting will lessen and how it is experienced will change.

For about 7 percent of those who are bereaved, however, grief ensnares people, which can prevent them from restoring their capacity to experience life in a healthy fashion. In 2018, the American Psychiatric Association, in the fifth edition update of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), added Prolonged Grief Disorder as a disorder, describing it as grief that persists for one year or more.

Those who lose a central relationship like a parent, child or spouse are more susceptible to Prolonged Grief Disorder.

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If you feel you may be caught in Prolonged Grief Disorder, please reach out  
to a counselor with experience in grief.  
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## Glossary of Terms and Abbreviations

Below you will find the definitions of selected terms and abbreviations used in this Guidebook or that is it expected you will encounter with your doctors.

Access to the complete Dictionary of Cancer Terms is available at the National Cancer Institute website: [www.cancer.gov/dictionary](http://www.cancer.gov/dictionary).

**Alkylating agent:** a type of drug (i.e., chemotherapy) that interferes with the DNA of cancer cells, thereby inhibiting their growth.

**Anaplastic:** An adjective denoting a tumor as cancerous; a term used to describe cancer cells that divide rapidly and have little or no resemblance to normal cells.

**Antagonist:** A substance that acts against or blocks an action.

**Antibiotic:** A drug used to treat infections caused by bacteria.

**Antigen:** Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances from outside the body. Cancer cells also have antigens on them that can cause an immune response.

**Antimicrobial:** A drug used to prevent or treat infections caused by a variety of organisms such as bacteria, fungi, or viruses.

**Aphasia:** A loss or impairment in using words or comprehending what other people are saying.

ASCO: American Society for Clinical Oncology, a US national organization

Astrocytic: Refers to the large, star shaped cells in the brain that form connective tissue between the nerve cells and the blood vessels.

Astrocytoma: A tumor that begins in the brain or spinal cord in astrocytes.

Autologous: cells obtained from the patient themselves.

Avastin: See Bevacizumab

BBB: Blood-Brain Barrier: A network of tissues and blood vessels that helps keep harmful substances from reaching the brain. The BBB can also decrease the ability of certain treatments from getting to the brain, hence the research into nanoparticles.

BCNU: The brand name for the chemo Carmustine.

Bevacizumab: A drug used alone or with other drugs to treat certain types of cervical, colorectal, lung, and kidney cancer, and glioblastoma. It is used under the brand name Avastin to treat these cancers. Bevacizumab binds to a protein called vascular endothelial growth factor (VEGF). This may prevent the growth of new blood vessels that tumors need to grow.

Biopsy: The removal of cells or tissue to allow for evaluation by a pathologist.

Calcification: A buildup of calcium in a tissue causing the tissue to harden.

CBC: Complete Blood Count. The CBC test evaluates the quantity of red blood cells, various white blood cells, and platelets.

CCNU: Another name for the chemo called Lomustine or Gleostine.

## Glossary Of Terms And Abbreviations

Centimeter or "cm": A unit of measure. There are 2.54 centimeters in one inch; said another one, there are .3937 inches in one centimeter. For example, a tumor with a length of 5cms would, therefore, be about 1.97 inches long.

Chemotherapy or "chemo": Treatment with drugs that kill cancer cells.

Chromosomes. Chromosomes are structures found in the center (nucleus) of cells that carry long pieces of DNA. DNA is the material that holds genes. It is the building block of the human body. Chromosomes also contain proteins that help DNA exist in the proper form.

Clinical Trial: A protocol to evaluate the effectiveness and safety of drugs or devices developed in a laboratory by monitoring their effects on humans. Drugs or devices that are being tested under clinical trials have not been approved by the US Food and Drug Administration. In the US, strict rules for conducting clinical studies have been put in place by the National Institutes of Health and the Food and Drug Administration. Other countries regulate clinical trials in accordance with their laws; clinical trial regulations in the United Kingdom are similar to those in the US. See also Randomized Clinical Trial.

CMV: Cytomegalovirus. A virus that infects most adults in the US by the age of 40. CMV is from the herpes family and may cause disease in individuals whose immune systems are compromised.

CNS: The Central Nervous System, which consists of the brain and the spinal cord.

Cognitive: The mental process of thinking, learning, remembering, being aware of surroundings, and using judgment.

Contrast agent or dye: When referring to a medical imaging scan, it is a substance that radiologists use to see tissues more clearly in the images.

Cranium/ Cranial: The bones that form the head and surround the brain.

**Craniotomy:** An operation in which a piece of the skull is removed. A craniotomy may be done so doctors can remove a brain tumor or abnormal brain tissue.

**CSF:** Cerebral Spinal Fluid. It is made by tissue that lines the ventricles (hollow spaces) in the brain. The CSF flows in and around the brain and spinal cord to help cushion them from injury and provide nutrients.

**CT Scan:** Computed Tomography scan. A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the brain or the body.

**Cystic:** A closed, sac-like pocket of tissue. It may be filled with fluid, air, pus, or other material. A cystic glioma is a descriptive term for one form of glioma that contains a large cystic component.

**Debulking:** surgical reduction in the size of the tumor. Debulking may be done in the case of benign tumors to relieve symptoms.

**Dendritic cell:** A special type of immune cell that is found in body tissues and that enhances an immune response by showing antigens on its surface to other cells of the immune system. A dendritic cell is a type of phagocyte and a type of antigen-presenting cell (APC).

**DIPG:** Diffuse Intrinsic Pontine Glioma. A rare, fast-growing, histone-driven tumor that forms in cells called glial cells in a part of the brain stem called the pons. They usually occur in children.

**Diffuse:** Widely spread; not localized or confined.

**DMG:** Diffuse Midline Glioma is a type of brain tumor that is a clarified diagnosis of a DIPG. It is a histone-driven astrocytoma located along the midline of the brain but can also be found in midline structures like the spinal cord or thalamus. Often these tumors start as an “atypical” DIPG and are later formally diagnosed as DMG

## Glossary Of Terms And Abbreviations

DNA: Deoxyribonucleic acid. One of two types of molecules that contain genetic information. The other is RNA. Most DNA is found inside the nucleus of a cell, where it forms the chromosomes.

Edema: Swelling caused by excess fluid trapped in tissues like the brain.

EGFR: Epidermal Growth Factor Receptor. EGFR is a protein found on certain types of cells that binds to a substance called epidermal growth factor. The EGFR protein is involved in cell signaling pathways that control cell division and survival. When mutated, EGFR can be a potent contributor to the development of a brain cancer. Drugs that block EGFR proteins are being used in the treatment of some types of brain cancer. EGFRs are a type of receptor tyrosine kinase. Also called, ErbB1, and HER1.

Eloquent area: The area of the brain which supports language, motor, sensory or other important function.

Epigenetic alteration: A change in the chemical structure of DNA that does not change the DNA coding sequence. Epigenetic alterations occur in the body when chemical groups called methyl groups are added to or removed from DNA or when changes are made to proteins called histones that bind to the DNA in chromosomes. These changes may occur with age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals.

FDA: The US Food and Drug Administration.

GBM: Glioblastoma Multiforme, which is a Grade 4 tumor. See also Glioblastoma.

Generic: Official nonbrand names by which medicines are known. Generic names usually refer to the chemical name of the drug.

GFAP: Glial Fibrillary Acidic Protein, which is a protein that is encoded by the GFAP gene in humans. It is expressed by numerous cell types of the central nervous system, including astrocytes and ependymal cells during development. The finding of GFAP in a pathology evaluation is usually indicative of a primary brain tumor.

Gleostine: The brand name for the chemo referred to as Lomustine or CCNU.

Glioblastoma: A fast-growing type of brain tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Also called GBM, glioblastoma multiforme, and grade IV astrocytoma.

Glioma: Any cancerous (anaplastic) brain tumor. A glioma begins in glial cells (cells that surround and support nerve cells.)

Heterogeneity: Made up of different elements. GBMs have significant inter and intra-tumoral molecular heterogeneity making them tough to treat since one or a few parts of the tumor will be susceptible to a certain treatment, but other parts will remain unaffected.

HIPAA: Stands for the Health Insurance Portability and Accountability Act of 1996, which derives from Public Law 104-191. Sections 261 through 264 of the HIPAA law requires certain standards for the electronic exchange, privacy, and security of health information. As it relates to brain cancer patients, the most common effect of the HIPAA law is safeguarding the privacy of their medical information. As a result, individuals need to designate in writing to whom medical service providers may provide their personal medical information.

Hippocampal avoidance: an advancement in whole brain radiation which uses intensity-modulated radiotherapy, a technique to pinpoint certain regions of the brain while avoiding others, to help preserve a patient's cognitive abilities.

Histology: The study of tissues and cells under a microscope.

## Glossary Of Terms And Abbreviations

**Hyperbaric Oxygen:** Oxygen that is given at a pressure that is higher than the pressure of the atmosphere at sea level. In medicine, breathing hyperbaric oxygen increases the amount of oxygen in the body. It is used in treating certain kinds of wounds, injuries, and infections (e.g., it is sometimes used to treat necrosis). It is being studied in the treatment of some types of cancer. Hyperbaric oxygen may increase the amount of oxygen in cancer cells, which may make them easier to kill with radiation therapy and chemotherapy.

**Immunocompromised:** Having a weakened immune system.

**Immunohistochemistry:** A lab test that uses antibodies to test for certain antigens (markers) in a sample of tissue. Immunohistochemistry is used to help diagnose diseases, such as cancer. It may also be used to help tell the difference between different types of cancer.

**Immunotherapy:** A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight brain cancer. Some types of immunotherapies only target certain cells of the immune system. Others are intended to affect the immune system in a general way.

**Infiltration/ infiltrative:** Infiltration is the movement of cancer cells from their normal location into the surrounding healthy tissue. Another word for infiltration is invasion. Infiltration is an important feature that pathologists look for when trying to decide if a brain tumor is benign (non-cancerous) or malignant (cancerous).

**Inoperable:** an expert neurosurgeon has concluded surgery should not be performed on the tumor.

**Intracranial:** Existing or occurring within the cranium.

**Intracranial pressure (ICP):** Intracranial pressure is the pressure within the cranio-spinal environment, which is a closed system that holds a fixed, optimal volume of neural tissue, blood, and cerebrospinal fluid (CSF). When the ICP increases owing to edema or tumor growth, symptoms like headaches, nausea and others can develop as brain tissues are compressed.

Ischemia: Lack of blood flow. See also Transient Ischemic Attack.

IV: intravenous. IV generally refers to a device to administer fluids into a blood vein.

Lesion: an area of abnormal tissue. A lesion may be either benign (not cancerous) or malignant (cancerous).

Malignant: A term synonymous with cancer. Malignant cells grow in an uncontrolled way and can invade nearby tissues.

Mass: a lump or swelling that may or may not be cancerous.

Meninges: The three thin layers of tissue that cover and protect the brain and spinal cord.

Mesenchymal: Brain cancer that are developed from soft or connective tissues. They are one of four (4) subtypes of GBMs and is one of the most aggressive types.

Metastatic: The spread of cancer cells from the place where they first formed to another part of the body. In a metastasis of the brain, cancer cells have broken away from the original (primary) tumor, traveled through the blood or lymph system, and formed a new tumor in the brain.

Methylation: A complex chemical reaction in which a small molecule called a methyl group is added to other molecules. In the treatment of brain cancer, it is generally believed that having a methylated MGMT gene provides a benefit because it interferes with the cancer's ability to regrow after chemo treatment.

Monotherapy: The use of a single chemo or device during treatment.

## Glossary Of Terms And Abbreviations

**MRI:** Magnetic resonance imaging; a diagnostic and monitoring technique in which radiowaves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue.

**Multicentric glioma:** multiple, widely separated brain tumor masses in different lobes or different hemispheres. These masses arise completely separately from one another; they do not spread by means of any common pathways or cerebrospinal fluid channels or any local metastases via satellite formation

**Mutation:** Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect.

**Myelination:** The formation of the myelin sheath around a nerve fiber. (See also sheath).

**NCI:** The US National Cancer Institute at the National Institutes of Health.

**Necrosis:** The death of living cells. It occurs when too little blood and oxygen flows to the tissue. It can be triggered by injury or radiation. A necrotic area in the brain can grow but will do so at a slower pace than cancer. If the area of necrosis become large enough and symptomatic, surgery may be the best treatment.

**Neuro or Neurological:** Related to or affecting the central nervous system.

**Neuro-oncologist:** A doctor who specializes in diagnosing and treating brain tumors and other tumors of the nervous system using chemical agents.

**Neurosurgeon:** A doctor who specializes in diagnosing and treating brain tumors and other tumors of the nervous system by means of surgical intervention.

**Oncogene:** A gene that, if mutated, may cause the growth of cancer cells.

**Operable:** a qualified neurosurgeon has concluded surgery may be performed on the tumor and is reasonably (based on the doctor's considerable experience) expected to result in greater benefits than risk to the patient, all factors having been carefully considered.

**OS:** Overall survival.

**Palliative Care:** Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, supportive care, and symptom management.

**Pathologist** (may also be referred to as a neuropathologist): A specialized doctor who identifies diseases of the nervous system by studying cells and tissues under a microscope.

**Peer-reviewed Scientific Journal:** A publication that contains original articles that have been written by scientists and evaluated for technical and scientific quality and correctness by other experts in the same field.

**PEG:** percutaneous endoscopic gastrostomy. A tube inserted through the skin and the stomach wall for the purpose of providing food.

**Perfusion:** refers to the passage of blood through the circulatory system. A perfusion MRI, therefore, attempts to identify blood stream activity in a tumor environment.

**PET Scan:** Positron Emission Tomography scan. A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.

## Glossary Of Terms And Abbreviations

Petechiae: Small red spots that may form on the arms and legs as a result of a drop in platelets.

PFS: Progression Free Survival. The length of time during and after treatment that the disease remains stable and does not grow.

POA: Power of Attorney. A power of attorney may be issued/obtained for medical, financial, or other reasons. A POA enables the trusted, designated person to make decisions and perform in place of the person making the designation.

Primary: With reference to a tumor, it is one that is at the original site at which it arose.

Primary endpoint: With reference to a clinical trial, means the result of a trial measured at the end to see if the treatment being tested worked, i.e., that there was a positive and clinically significant difference in survival between the group of patients getting the treatment and a control group of patients who did not.

Progress / Progression: When in the course of a disease, it recurs, grows, or otherwise becomes worse.

Pseudo-progression: a phenomenon in which an initial increase in tumor size is observed but is later followed by a decrease in the tumor; this is often observed in patients receiving immunotherapy but can lead to premature discontinuation of treatment owing to the false judgment of actual progression. Plus, in approximately 20% to 30% of GBM cases, the first MRI(s) obtained after radiation therapy and concurrent Temozolamide meets the criteria for progressive disease, but subsequent follow-up scans show lesion shrinkage or stability, demonstrating pseudo-progression in those cases. Pseudo-progression is among the most common causes of misdiagnosed tumor recurrence.

**Randomized Clinical Trial:** A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial.

**Recur, Recurrence:** The return of a tumor after a period of stability or remission.

**Refractory:** When the disease becomes non-responsive to treatment of any kind.

**Resectable:** Able to be removed by surgery.

**Resection:** surgical removal of a tumor. A resection may be partial (also called "subtotal") or total.

**RNA:** molecules of nucleic acid. RNA is also the genetic material of some viruses used for treatment instead of DNA.

**SEER:** National Cancer Institute's Surveillance, Epidemiology and End Results Program, a national cancer registry that covers more than a quarter of the U.S. population and represents the extensive diversity of the country.

**Sheaths:** when referring to nerves, these are enveloping tubular structures. The destruction of this sheath by disease or injury can slow or stop the impulses traveling along that nerve resulting in a decrease of the function served by that nerve

**SOC:** Standard of Care. Means the treatment protocol that is accepted by medical experts as the proper treatment for a brain tumor and that is widely used by doctors worldwide.

**SSDI:** US Social Security Disability Insurance.

## Glossary Of Terms And Abbreviations

SSI: US Supplemental Security Income.

Stereotactic: Referring to precise positioning in three-dimensional space. For example, biopsies, surgery, or radiation therapy can be done stereotactically ..

Surgically Targeted Radiation Therapy or STaRT: A procedure whereby collagen tiles are inserted during surgery to the tumor site to delivery radiation.

Thrombocytopenia: A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.

TMZ: Abbreviation for Temozolomide, also known as Temodar or Temodal.

Total or Gross Total Resection: Surgical removal of every visible portion of a tumor.

Transient Ischemic Attack or TIA: a temporary period of symptoms similar to those of a stroke. A TIA usually lasts only a few minutes and doesn't cause permanent damage. Often called a ministroke, a TIA may be a warning, so the doctor should be promptly informed of any strike like episodes, no matter how temporary. Those with GBM are susceptible to having TIAs.

Tumor: can be non-cancerous (benign) or malignant (cancerous).

Unresectable: Not able to be removed surgically.

Vascular: Of or pertaining to the blood vessels.

WHO: World Health Organization, which issues the guidance by which brain tumors are diagnosed and classified.



## Al Musella's Story

Al Musella, DPM is a retired podiatrist. He worked his way through school as a computer programmer for medical research projects.

His interest in brain tumors started when his sister-in-law, Lana, was diagnosed with a GBM in 1992. Lana had surgery and radiation, but then the first MRI scan after radiation showed that the tumor had grown even larger. This was before Temodar, the Gliadel Wafer, and Avastin were available. So, the outlook for Lana was bleak. Her doctors also told her there were no clinical trials that would take her because of the size of her tumor. In fact, although they were at a major brain tumor center, they basically gave up on her. She was told she only had a few weeks left to live and there was no treatment options for her other than a standard course of BCNU, which had no chance to help her for more than a few extra weeks.

At that time, there was no world wide web! Version 1 of Netscape was released on December 15, 1994. Al was an active member of Compuserve, and Compuserve had a cancer forum, with sections devoted to the top 10 cancers (but no brain tumor section). Al created and ran the Brain Tumor Forum on Compuserve in January 1993. He organized the members and had them help survey every major hospital in the USA to find what treatments were available. That list was posted on Compuserve and became the basis for the first Internet database of clinical trials!

Back then, the NCI only maintained lists of clinical trials that they funded, not the trials sponsored by the drug companies or the individual doctors or hospitals. (They do most now). And the only way to access them was to call the NCI and they would mail them to you. The NCI invited Al to demonstrate his technology to them, and the clinicaltrials.gov website was partially modelled after virtualtrials.org!

Al found a few clinical trials that would accept Lana, after being told by a few major brain tumor centers that there were none (because her tumor was too large and multifocal). She did very well for a while, getting to see her 4 kids grow up, then unfortunately died of a recurrence on October 25, 2000. She lived over 8 years after being told she only had a few weeks left. Many of those years she was in excellent

## Brain Tumor Guide for the Newly Diagnosed

condition, with her taking care of her kids, working, driving and enjoying life.

In 1998, Al started the Musella Foundation as a not-for-profit charity dedicated to speeding up the search for cures of brain tumors and to helping families deal with the diagnosis of brain tumor. Ironically, Al's father was diagnosed with a GBM in 1999, a year after Al formed the Musella Foundation. Al and his family were more prepared than previously to deal with this diagnosis, but it was still a horrendous experience for Al to go through. His father died quickly, in about 4 months.

Since its inception, a lot has been accomplished by the Musella Foundation:

The virtualtrials.org website continues to expand in terms of services provided and the community served (in 2021 the Foundation had over 250,000 visitors from 217 different countries).

The Foundation's co-payment assistance program has awarded more than \$10 million in grants to over 2,000 brain tumor patients in this life-saving program.

The Foundation created and runs the Brain Tumor Virtual Trial, a study of brain tumor patients, as well as the long-term glioblastoma outcome project.

The Foundation has helped convince Medicare to pay for Temodar, Gliadel, Avastin and Optune. It has helped accelerate FDA approval of Temodar, Avastin, Gleolan and Optune for brain tumor patients.

In the 30 years that Al has been immersed in the world of brain tumors, he has seen an amazing change in attitude among brain tumor researchers. There has been an unprecedented burst of progress in identifying new approaches. He is convinced that we are in the home stretch and a cure is within sight. It is now only a matter of time and money. But although the government now funds brain tumor research at an unprecedented level, many promising projects remain unfunded.

Through the Musella Foundation, we have a chance to speed up the search for a cure, by funding selected research that complements, without duplicating, research funded by the government.

## Al Musella's Story

To that end, Al needs your help. Donations to the Musella Foundation can be general or can be dedicated to specific ends, like its support for brain tumor research or its co-payment assistance program. For more details on how you can help us speed up the search for the cure, please visit the [virtualtrials.org](http://virtualtrials.org) website.



*Photo credit: Paolo Salcido, Salcido Photography, IBTA's First World Summit of Brain Tumour Patient Advocates*

**Al Musella, DPM  
Founder and President  
The Musella Foundation for Brain Tumor Research and Information**

## Recent Grants Made By The Musella Foundation

Below is a listing of recent research grants made since 2020 by the Musella Foundation. The Musella Foundation has awarded investigators with over \$4 million in 126 grants since 2003. We have helped fund the early work on some of the most promising therapies in the pipeline.

Interested investigators should call the Musella Foundation directly to discuss the project(s) for which they seek funding before submitting the formal grant application. To see a list of all grants awarded by the Musella Foundation, please go to the grants page at the virtualtrials.org website: <https://virtualtrials.org/grants.cfm>.

### **2022 (to date) Grant Awards**

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\$100,000 to Dr Nicole Shonka, University of Nebraska Medical School, for the project: **"Phase 1B/2A Clinical trial of APG-157 and Bevacizumab in recurrent high-grade glioma patients"**

\$25,000 to Dr Ekokobe Fonkem, Baylor Scott and White Health Care and Dr. M. Karen Newell Rogers, Texas A&M Health Sciences Center, for the project: **"Eliciting A Specific Immune Response to Glioblastoma (GBM) in the Brain as a Novel Therapeutic Approach for Treatment of Diffuse Intrinsic Pontine Glioma and other forms of GBM"**

\$35,000 to Dr. Huan Yang at Beth Israel Deaconess Medical Center for the fourth year of the project titled: **"Computer Modeling of Tumor Treating Fields Using Single Institutional Data Base"**

\$10,000 to the Central Brain Tumor Registry of the United States for the project titled: **"Provision of the most current population-based statistical information for all primary brain and other central nervous system (CNS) tumors in the United States"** This is our annual grant to help support this important ongoing project.

\$50,000 to Dr Carl Koschman, University of Michigan, for the project: **"Whole Genome Sequencing of Patients Treated on ONC201/ONC206 in PNOC22/23"**

\$35,000 to **Dr. Joelle Straehla** of Dana Farber / Boston Children's Cancer and Blood Disorders Center, for the project "**Preclinical evaluation of a panobinostat nano-formulation for pediatric DIPG**". This is from our DIPG All-In-Initiative, in collaboration with the McKenna Claire Foundation, Live Like a Unicorn Foundation, Prayers From Maria Foundation and the Pediatric Brain Tumor Foundation

\$25,000 to **Dr. Nduom and Dr. Carbonell** for the project "**Utilization of a First-in-Class Anti-CD29 Therapy (OS2966) to Unleash the Potential of Immune Checkpoint Therapy for Treatment of Glioblastoma**"

**Total for 2022 to date: \$280,000.00**

## **2021 Grant Awards**

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\$25,000 to **DIPG Collaborative** to help fund research into pediatric DIPGs

\$50,000 to Dr. Wafa Hassen at The University of Texas, MD Anderson Cancer Center for the project: "**Exosomes for Targeting c-Myc in Glioblastoma Multiforme**"

\$20,000 to Clinwiki, Inc. to continue the project "**ClinWiki Brain Cancer Community Development**" This project will make it easier for patients to find clinical trials, and hopefully increase clinical trial participation! This is the third grant for this project.

\$35,000 to Dr. Eric Wong at Beth Israel Deaconess Medical Center for the third year of the project titled:**"Computer Modeling of Tumor Treating Fields Using Single Institutional Data Base"**

\$25,000 grant to Dr. Jennifer Connelly of the Medical College of Wisconsin for the project: "**Oral Gallium Maltolate for the Treatment of Relapsed and Refractory Glioblastoma**".

\$25,000 grant to Dr. John Prensner of the Dana-Farber Cancer Institute for the project: "**Comprehensive interrogation of uORFs as a source of new medulloblastoma cancer genes**".

## Brain Tumor Guide for the Newly Diagnosed

\$15,000 grant to the Dragon Masters Foundation to help them fund Dr. Seyed Ali Nabavizadeh, Of U. Of Pennsylvania, for the project: **"Pet/ MRI imaging of pediatric brain tumors"**.

\$50,000 grant to Maria Trissal, MD PhD of the Dana-Farber Cancer Institute for the project: **"Identifying the Effect of PDGFRA inhibition on H3K27M Diffuse Midline Gliomas (DMGs)"**. This is from our DIPG All-In-Initiative.

\$12,000 to Dr. Madan Kwatra of Duke University for the project: **Generating patient derived gliomas within Cerebral Organoids to be Treated with Repurposed drugs**

\$30,000 grant to Dr. Andrew Grove, of Dana-Farber Cancer Institute for the project: **"Characterization of a Novel Largazole-Based HDAC Inhibitor as a Potential CNS Penetrant Drug for the Treatment of H3K27M Diffuse Midline Glioma (DMG)"**. This is from our DIPG All-In-Initiative.

\$25,000 grant to the CHOP Foundation for the **"Children's Brain Tumor Network"**

\$75,000 grant to Dr Michael Castro for the project: **Reversal of MHC1 loss in patients with glioblastoma**

\$30,000 to Dr. Sion Ll. Williams at the Sylvester Comprehensive Cancer Center in Miami, FL for the project: **Somatic Genetic Variation in Mitochondrial DNA in Patients with Glioblastoma**

\$10,000 to the Central Brain Tumor Registry of the United States for the project titled: **"Provision of the most current population-based statistical information for all primary brain and other central nervous system (CNS) tumors in the United States"** This is our annual grant to help support this important ongoing project.

**Total for year 2021: \$427,000.00**

## **2020 Grant Awards**

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\$25,000 to DIPG Collaborative to help fund **research into pediatric DIPGs**

\$20,000 to Dr. Tony J. C. Wang at Columbia University's Herbert Irving Comprehensive Cancer Center for the project: "**An Open-Label Phase II Study of Atezolizumab, Tocilizumab and Temozolomide with Radiotherapy in Patients with newly Diagnosed Glioblastoma without PTEN loss or mutation**"

\$20,000 to the Jaime Leandro Foundation for the project: "**Therapeutic Cancer Vaccines**"

\$25,000 to Oncoceutics,Inc, (by way of the Dragon Masters Foundation) for the project "**Onc-201 expanded access program for DIPG and High Grade Gliomas with the H3 K27M mutation!**"

\$33,000 to Dr. Eshini Panditharatna at Dana Farber Cancer Institute for the project: **Inhibition of chromatin complex activity as combination therapy for H3.3 K27M DIPG**

\$35,000 to Dr. Eric Wong at Beth Israel Deaconess Medical Center for the second year of the project titled:**"Computer Modeling of Tumor Treating Fields in the FORWARD Trial "**

\$24,432 to Dr. Anne-Marie Carbonell, of Oncosynergy, for the project "**Development of a tissue-based receptor occupancy assay to verify target engagement and determine optimal biological dose of OS2966 delivered via convection-enhanced delivery in a phase I glioblastoma trial**"

\$250,000 to Oncoceutics,Inc, as third payment of a \$1 million grant, for the project "**Onc-201 for DIPG and High Grade Gliomas with the H3 K27M mutation!**" This grant is a collaborative effort between the Musella Foundation, The Cure Starts Now Foundation, Dragon Master Foundation and the Finn Family Foundation. A special thanks to Lisa Ward for helping bring the brain tumor community together on this project!

\$25,000 to Cure Glioblastoma, Inc, to help fund startup costs and get started on their first research project involving the drug **OS2966 in the Treatment of Recurrent High-Grade Glioma**

## Brain Tumor Guide for the Newly Diagnosed

\$32,860 to Dr. Katherine Warren at Dana Farber Cancer Institute for the project: **Targeting Epigenetic Silencing Mechanisms in DIPG**. This was from our DIPG All-In-Initiative fund!

\$10,000 to the Central Brain Tumor Registry of the United States for the project titled: "**Provision of the most current population-based statistical information for all primary brain and other central nervous system (CNS) tumors in the United States**" This is our annual grant to help support this important ongoing project.

**Total for year 2020: \$500,292.00**

Photo Credit Andy Singer



## APPENDIX A: MOLECULAR CHARACTERISTICS OF A GBM

### Subtypes of GBMs

In 2010, a landmark study led by Professor Roel Verhaak, Ph.D., of the Jackson Laboratory, identified fundamental differences in the molecular (DNA) characteristics of GBMs. Dr. Verhaak's group found there are four (4) subtypes of GBM, each with their own collection of molecular traits. Those subtypes are: proneural, mesenchymal, neural, and classical. In real life, there are few thoroughbred representatives of these 4 subtypes, but each tumor will substantially align to one of these subtypes.

- Proneural GBMs, sometimes demonstrating changes in the PDGFRA pathway, are usually associated with a better outcome, particularly when harboring mutations in the IDH-1 gene (or the IDH-2). Mutations typical to the proneural GBM are TP53, DLL3, DCX, TCF4, SOX, ASCL1 and OLIG2.
- Mesenchymal GBMs are enriched in mesenchymal markers such as CHI3L1, YKL40, MET, CD44, MERTK, co-mutation of the NF1 and PTEN genes, loss of CDKN2A, and expression of SERPINE, TRADD, RELB and CTGF.
- Neural GBMs strongly resemble the signature of neural cells, with strong expression of neuronal markers such as NEEL, GABRA1, SYT1 and SLC12A5.
- Classical GBMs are characterized by Chromosome 7 amplification (some people will have two chromosome 7 strands), Chromosome 10 loss, EGFR amplification, lack of TP53 mutations, NES expression and oftentimes deletion of CDKN2A.

Treatments today often target key tumor drivers found in a GBM's molecular structure. A great and promising treatment that the GBM does not contain, is not likely to be an effective fit. Conversely, if a GBM has a particular molecular trait for which a targeted treatment exists, then the match may result in a good candidate for treatment. An example would be the identification of the EGFR variant III mutation which the immunotoxin D2C7 treats.

Moreover, it is possible that transitions between these subtypes to occur during treatment of patients, which can lead to a need to shift treatment strategies and may lead to a less favorable prognosis. It is unclear if these transitions are due to tumor cell plasticity or the late eruption of pre-existing cell factors that have been previously inactive.

## Immunosuppressive Environment Differences in GBMs

In addition to the molecular variables identified by Dr. Verhaak's group, studies over the last few years demonstrate that GBMs can be expected to respond differently to treatment because of differences in their immune landscape.

The latest studies identify four distinct immune landscapes in GBMs:

- Type 1 tumors with a high number of macrophages and a few T cells.
- Type 2 tumors with a moderate number of macrophages.
- Type 3 tumors with high numbers of T cells and a few macrophages.
- Type 4 tumors that the researchers call an immune desert, because they have few or no immune cells of any type.

What is emerging from the latest study is that GBMs subtypes vary significantly in the percentage of immune cells in their microenvironment.

## APPENDIX B:

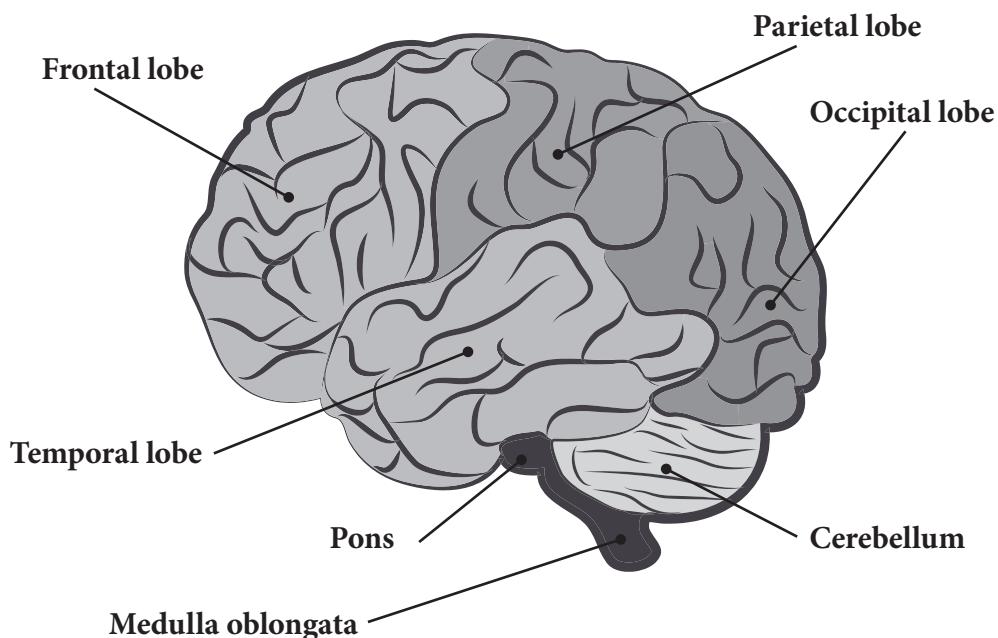
### Brain Functions and Dysfunctions by Location

To understand what symptoms you may experience as a result of the tumor and its treatment, it is helpful to specifically understand the tumor's location. Symptoms depend on the tumor's location, the amount of edema (swelling) it produces and also its size and development rate. Tumors that are less than 2 centimeters in diameter or that develop very slowly may be asymptomatic. Larger tumors, those that rapidly develop (over weeks or months rather than years), and tumors that simultaneously affect both hemispheres are more likely to become symptomatic.

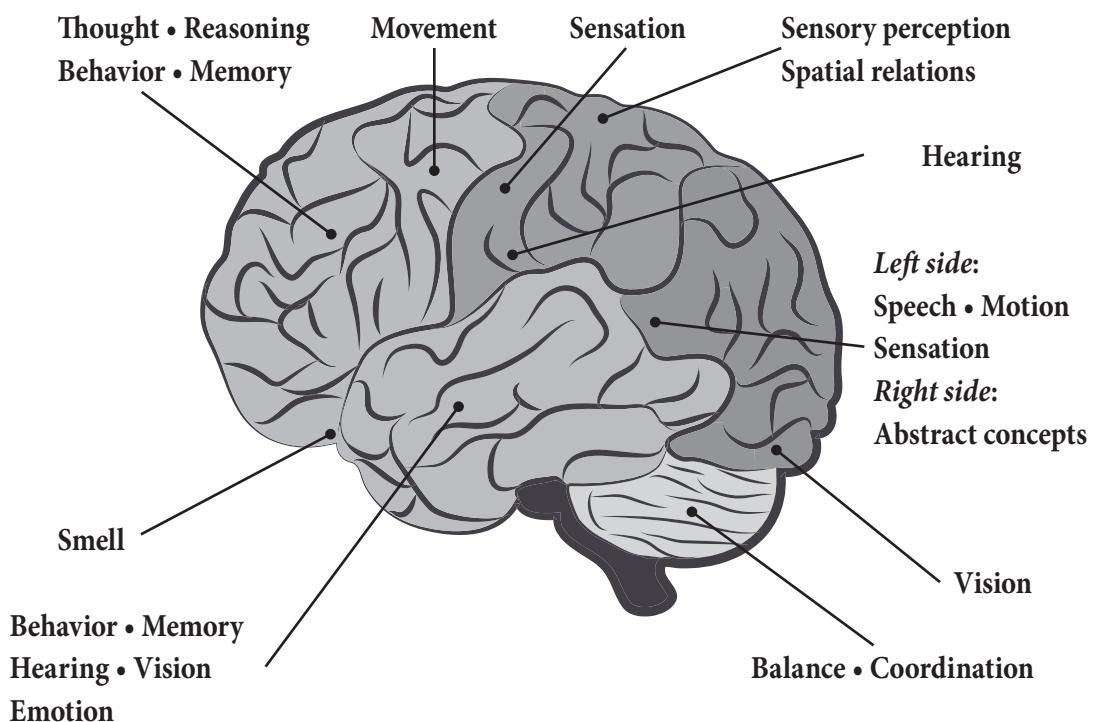
Your neurosurgeon or neuro-oncologist would be able to help you identify the tumor location. The doctor may provide you with a diagram of the brain with a penciled-in identification of your tumor site. Alternatively, you may use the images of the brain provided below in discussions with your doctor.

The top part of the figure (1A) shows the major parts of the brain. The bottom part of the figure (B) shows some of the functions associated with each of the brain parts.

**Figure 1A: Major parts of the brain**



**Figure 1B: Associated functions of the parts of the brain**



## Hemispheres Of The Brain

The brain is divided into two halves called hemispheres. The hemisphere affected by the disease is important because the functions of the two halves of the brain are not identical. Some functions are performed exclusively by one hemisphere. For example, movement and sensation on one side of the body are controlled by the hemisphere on the opposite side. Other functions are performed mainly by one, dominant hemisphere. In those cases, damage to the single, dominant hemisphere may cause complete loss of a function.

However, most functions, like memory, require the cooperation of areas in both hemispheres. For such functions to be completely lost, both hemispheres must be damaged or the connection between the hemispheres (usually through a connecting point like the Corpus Callosum) is damaged.

The most classic symptoms occurring when the connection between the hemispheres is disrupted are:

- left hand anomia (unable to recall names of everyday objects)
- left upper limb ideomotor dyspraxia (problems with gross and fine motor skills; affects coordination, playing sports or driving a car)
- left visual field dyslexia (making the person easily frustrated, angered, or annoyed) and
- dysnomia (inability to recall words, names, or numbers; they may be "just on the tip of the tongue").

## Diagnosing Dysfunctions

Specific dysfunctions are usually related to an area of the brain that has been damaged. In many cases, doctors can diagnose the dysfunction in conjunction with, and using the same techniques as needed in diagnosing brain cancer (e.g., MRI and interview questions).

## Frontal Lobe Damage

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The frontal lobes are responsible for a multitude of functions such as:

- Initiating many actions,
- Controlling learned motor skills, such as writing, playing musical instruments, and tying shoelaces,
- Controlling complex intellectual processes, such as speech, thought, concentration, problem-solving, and planning for the future,
- Controlling facial expressions and hand and arm gestures, and
- Coordinating expressions and gestures with mood and feelings.

Often, damage to the frontal lobes causes loss of the ability to solve problems and to plan and initiate actions, such as crossing the street or answering a complex question (sometimes called "executive functions"). Some specific impairments can occur depending on which part of the frontal lobe is damaged.

If the back part of the frontal lobe (which controls voluntary movements) is damaged, weakness or paralysis can result. Because each side of the brain controls movement of the opposite side of the body, damage to the left hemisphere causes weakness on the right side of the body, and vice versa.

If the middle part of the frontal lobe is damaged, people may become apathetic, inattentive, and unmotivated. Their thinking becomes slow, and their responses to questions are very slow.

If the middle back part of the left frontal lobe (Broca area) is damaged, people may have difficulty expressing themselves in words—an impairment called Broca (expressive aphasia).

If the front part of the frontal lobe is damaged, any of the following may result:

- Difficulty temporarily holding information available for processing (called working memory),

- Reduced fluency of speech,
- Apathy (lack of emotion, interest, and concern),
- Inattentiveness, and
- Delayed responses to questions.

A striking lack of inhibition, including socially inappropriate behavior. People who lose their inhibitions may be inappropriately elated (euphoric) or depressed, excessively argumentative, or passive, and vulgar. They may show no regard for the consequences of their behavior. They may also repeat what they say, not unlike individuals with dementia.

### **Parietal Lobe Damage**

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The parietal lobes have the following functions:

- Interpreting sensory information from the rest of the body,
- Combining impressions of form, texture, and weight into general perceptions,
- Influencing mathematical skills and language comprehension,
- Storing spatial memories that enable people to orient themselves in space (know where they are) and to maintain a sense of direction (know where they are going), and
- Processing information that helps people know the position of their body parts.

Certain functions tend to be controlled more by one of the parietal lobes (usually the left). The left is considered the dominant lobe. The right lobe (nondominant) has other functions, such as enabling people to be aware of how the body relates to the space around it.

Damage to the front part of the parietal lobe on one side causes numbness and impairs sensation on the opposite side of the body. Affected people have difficulty identifying a sensation's location and type (pain, heat, cold, or vibration). People may have difficulty recognizing objects by touch (that is, by their texture and shape).

If the middle part is damaged, people cannot tell the right from the left side (called right-left disorientation) and have problems with calculations and writing. They may have problems sensing where parts of their body are (a sense called "proprioception").

If the nondominant (usually right) parietal lobe is damaged, people may be unable to do simple skilled tasks, such as combing their hair or dressing—called apraxia. They may also have trouble understanding how objects relate to each other in space. As a result, they may have trouble drawing and constructing things, and they may get lost in their own neighborhood. These people may also ignore the serious nature of their disorder or deny its existence, a condition called "anosognosia". They may neglect the side of the body opposite the brain damage (usually the left side).

## **Temporal Lobe Damage**

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The temporal lobes have the following functions:

- Generating memory and emotions,
- Processing immediate events into recent and long-term memory,
- Storing and retrieving long-term memories, and
- Comprehending sounds and images, enabling people to recognize other people and objects and to integrate hearing and speech.

In most people, part of the left temporal lobe controls language comprehension. If that part is damaged, memory for words can be drastically impaired, as can the ability to understand language—an impairment called Wernicke receptive aphasia.

If certain areas of the right temporal lobe are damaged, memory for sounds and music may be impaired. As a result, people may have trouble singing.

### **Occipital Lobe Damage**

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The occipital lobe contains the main center for processing visual information and have the following functions:

- Processing and interpreting vision,
- Enabling people to form visual memories, and
- Integrating visual perceptions with the spatial information provided by the adjacent parietal lobes.

If both sides of the occipital lobe are damaged, people cannot recognize objects by sight, even though the eyes themselves are functioning normally. This disorder is called cortical blindness. Some people with cortical blindness are unaware that they cannot see. Instead, they often make up descriptions of what they see (called confabulation).

Seizures that involve the occipital lobe can cause hallucinations involving vision. For example, people may see lines of color when they look in a certain direction.

### **Limbic Lobe (Limbic System)**

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The limbic lobe includes structures located deep within the cerebrum and some parts of the adjacent lobes, such as the temporal lobe. These structures have the following functions:

- Receiving and integrating information from many areas of the brain, enabling people to experience and express emotions,
- Helping form and retrieve memories, and
- Helping people connect memories to the emotions experienced when the memories form.

Damage that affects the limbic lobe usually results in a variety of problems. If seizures result from damage to the temporal lobe area in the limbic lobe, people may not be able to control their feelings or to think clearly. They may smell bad odors that are not there (a type of hallucination). Occasionally, these seizures cause personality changes such as humorlessness, extreme religiosity, and obsessiveness. People may also have an overwhelming urge to write.

## **Other Locations**

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Many functions of the brain are performed by several areas of the brain working together (networks), not by a single area in the brain. Damage to these networks can cause the following:

- Agnosia (loss of the ability to identify objects using one or more of the senses)
- Amnesia (total or partial loss of the ability to recall experiences or events)
- Aphasia (partial or complete loss of the ability to express or understand spoken or written language)
- Apraxia (loss of the ability to do tasks that require remembering patterns or sequences of movements)
- Dysarthria (loss of the ability to articulate words normally) may be caused by damage to areas of the brain or cranial nerves that control the muscles involved in producing speech or by damage to the nerve fibers that connect these areas.

## **Rehabilitation**

Recovery of some portion of an impaired function may be possible through the action of neuroplasticity. Neuroplasticity is the ability of the neural networks in the brain to change as a result of their biological, chemical, and physical capacities.

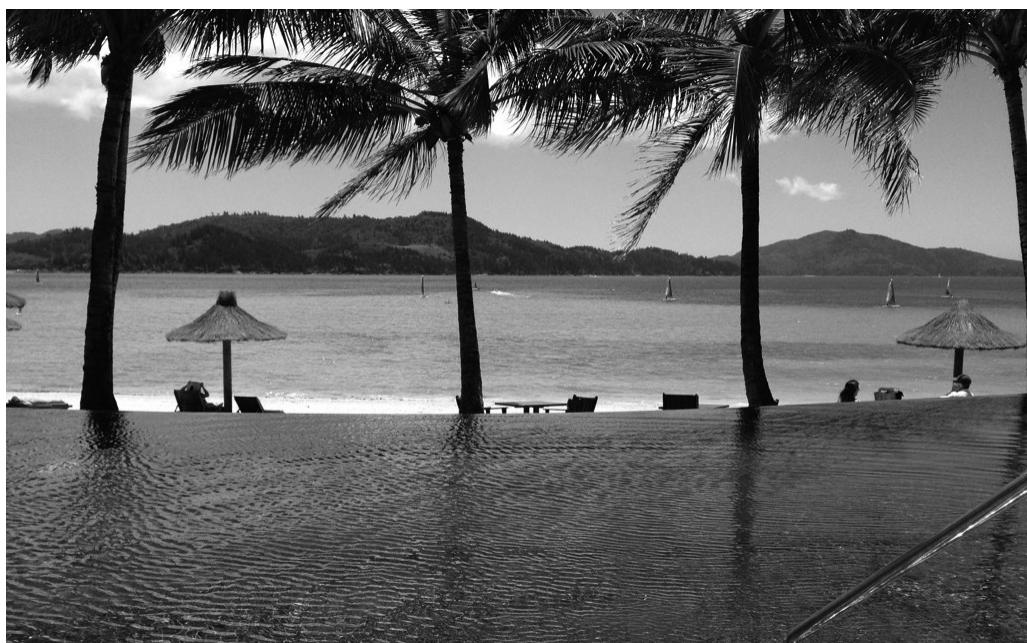
## Brain Functions And Dysfunctions By Location

When certain neural networks in the brain are damaged by disease, those networks may be encouraged by experience or learning to rearrange themselves to adapt to the changed situation as they continue to try to function normally.

After a brain injury such as damage from a tumor, the unaffected brain areas may adapt and take over the functions of the affected parts. This can enable individuals with brain damage to regain some of the past capabilities. For example, case studies of stroke victims who have experienced brain damage and lost some brain functions have shown that the brain has an ability to re-wire itself with undamaged brain sites taking over the functions of damaged brain sites.

This potential for neuroplasticity declines with age, however, efforts like rehabilitation ("rehab"), which is intended to encourage the brain to re-wire itself, can help to regain lost or degraded functions. In order to take advantage of this capacity of the brain, a person should begin rehab as soon after the loss of a function as advised by the doctor.

In addition, studies have found that Gamma waves are associated with enhancing the coordination of neural activity in the brain. Levels of gamma brain waves are far higher than normal in individuals who practice meditation, suggesting that daily meditation for 15-20 minutes may be a helpful routine.



## APPENDIX C: CAUSES OF BRAIN TUMORS

### Overview

One of the most troubling issues faced by anyone diagnosed with a brain tumor is: where did it come from? This question is even more urgent and frustrating for those who are otherwise healthy, have led a relatively healthy lifestyle for a long time, are youthful and have no such cancer in their familial bloodline. The disease just seems to have come out of nowhere.

So, where does a brain tumor, especially a cancerous one, come from?

In most cases, the cause of an individuals' brain tumor is never determined.

As it relates to GBMs, about 90% of them will go through a lengthy multistep development process. Researchers theorize that a cancerous kernel may take up to seven (7) years to develop into a GBM before it becomes symptomatic and requiring medical attention. The other 10% of GBMs develop from a pre-existing tumor of a lower grade (e.g., an AA3).

The factors that contribute to the development of brain cancers are described below.

### **Immune System Escape**

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Our bodies are guarded from microbials that causes disease and flawed cells that could become a problem by a complex immune system that includes powerful defenders like lymphocytes, macrophages, mast cells, dendritic cells (DCs), and natural killer (NK) cells. These components are ever vigilant and eliminate the risks to the preservation of our well-being.

Sometimes, however, our immune systems become tired or lazy due to us being overstressed and instead of eliminating risky intruders, our immune system no longer see when the intruders loiter around. One of the strategies for brain cancer treatment is to re-train the immune system into being able to recognize intruder cells again so that the immune system can function properly again.

When the immune system is unable to see intruder cells, eventually they break down the powerful defensive line of all the earlier mentioned components of our immune system. Brain cancer is, first and foremost, a breakdown of the immune system. The intruder cells develop genetic and epigenetic changes to camouflage themselves, which misleads all the defender cells we have, and an invasion of intruder cells starts. Once that invasion is large enough, we will call it a tumor.

When the intruder cells reach enough critical mass, they begin sending out chemical signals that convince some of the defending components of our immune system to join their ranks. Because the intruder cells have been entrenched for a long time and have hijacked some of our best defenders, the battle is fierce, employing a multitude of therapies: surgery, radiation, chemo and more.

Our growing understandings of how our immune system falters, allowing the breakdown and how cancer cells co-opt parts of our immune system for their own purposes provides considerable research opportunities for eventually reversing the process that started the cancer in the first place, and is encouraging the development of combination therapies such as CAR T-cell plus oncolytic virus treatment to attack the tumor in different ways.

### **Triggers that May Lead to Immune System Escape**

A brain tumor is a perfect storm of a variety of factors. Below are listed some of the factors that are believed to be contributors:

- Size - the bigger the brain, the greater the risk. (This is why a slightly greater percentage of men will get this disease.)
- Overweight - Doctors don't know exactly why being overweight may help trigger this disease, but the evidence it does is piling up. Some guesses are things like hormones and inflammation. What is known at the DNA level is that a cancerous gene (c-Myc) is present in visceral fat, which is found around the inner organs of the body as opposed to subcutaneous fat, which is located under the skin.
  - o Additionally, it appears that there is a deep connection between our

## Brain Tumor Guide for the Newly Diagnosed

metabolism and fat and how our brains regulate our immune systems. Brain cancer is, fundamentally, a failure of the body's immune system. For an interesting description of what we know of the connection between visceral fat and cancer, please see this article:

<https://www.inverse.com/mind-body/visceral-fat-study>

- Viruses - There may be links between certain viruses (e.g., Cytomegalovirus). Plus, there is an apparent association between having an Epstein-Barr virus infection or mononucleosis in the case of gliomas and an association between the human papilloma virus (HPV) and head and neck squamous cell carcinoma (HNSCC).
- Oxidative Stress - When our oxidative stress exceeds our defense system, cellular stress occurs and that can lead to the development of a tumor. Excessive oxidative stress can result from a variety of sources: metabolic complications, ionizing radiation from being a pilot, ionizing radiation due to being a frequent passenger on airplanes, heavy metals exposure as a machinist might experience, food or water with triggering substances, cigarette smoking, or other environmental exposures.
- Autoimmune Conditions- Autoimmune diseases can make someone more susceptible to the development of a brain tumor. These conditions arise from an overactive immune response of the body against various substances. They include (but are not limited to) Addison disease, ALS, Ankylosing spondylitis, Bechet's disease, Celiac disease, chronic rheumatic heart disease, Crohn's, diabetes, hyper and hypothyroidism, Lupus, multiple sclerosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, ulcerative colitis. In Sweden, doctors have even found increased brain tumor risks in patients with psoriasis.
- Carcinogens - Exposure to pesticides and herbicides (like RoundUp that was recently featured in a \$2 Billion award to a couple who claimed their cancer was caused by that product) and fertilizers are believed to make a person susceptible.

## Appendix C: Causes Of Brain Tumors

- Working with elements such as lead, certain plastics, rubber, petroleum, and some textiles can add to the equation that produces cancer. Inhaling the smoke from these materials (such as when working as a firefighter or first responder) is a brain cancer risk. Many firefighters and first responders pay for their selfless service by getting brain cancer.
- The Department of Defense estimates that roughly 3.5 million military members could have been exposed to burn pits (excavations filled with any and all waste from a deployment and set aflame with jet fuel or diesel) during wars in the Middle East and Afghanistan, and it is believed that some of them have or may develop brain cancer from those burn pit exposures.
- Pollution - Researchers in the UK concluded that there is a growing body of evidence that exposure to air pollution, notably arising from the carcinogenic components of vehicle exhausts, such as PAHs, 1,3-butadiene, and diesel particulate matter generally, may be associated with increased risk of brain tumors in both children and adults.
- Environmental- Currently, there is only one (1) established brain tumor environmental risk factor: exposure to ionizing radiation. This association is strongest for meningioma and glioma in younger patients. Patients who also received cranial radiation as treatment for acute lymphocytic leukemia in youth are also at a higher risk for subsequent brain tumors.
- Genetics - Even if a person has exposures to one or more of the factors above, the right genetics eventually need to be present for brain cancer to develop. Genes either "break" because of an exposure or were always in a condition that could develop into cancer.

More than 50 genes have been identified and associated with increasing an individual's lifetime risk of developing some form of cancer. We do know that about 5% of brain cancers occur in people with certain inherited genetic syndromes such as neurofibromatosis type 1, Turcot syndrome and Li Fraumeni syndrome.

Some of the genes noted for causing brain cancer that are thought to be passed from generation to generation are these:

<b>Gene</b>	<b>Syndrome</b>	<b>Features</b>	<b>Brain Tumor Type</b>
CDKN2A	Melanoma-neural system tumor syndrome	Predisposition to malignant melanoma and malignant brain tumors	Glioma
MSH2, MLH1, MSH6, PMS2	Contributes 40-50% of all cases of Lynch syndrome	Elevated risk of cancers of the brain, as well as colon, endometrium, ovaries, upper urinary tract, stomach, and small intestine	GBM and other gliomas
NF1	Neurofibromatosis 1	Neurofibromas, schwannomas, café-au-lait macules	Astrocytoma, optic nerve glioma
NF2	Neurofibromatosis 2	Acoustic neuromas, meningiomas, neurofibromas, eye lesions	Ependymoma
PMS2	2% of Lynch Syndrome Cases	Elevated risk of cancers of the brain, as well as colon, endometrium, ovaries, upper urinary tract, stomach, and small intestine	GBM and other gliomas

## Appendix C: Causes Of Brain Tumors

<b>Gene</b>	<b>Syndrome</b>	<b>Features</b>	<b>Brain Tumor Type</b>
POT1	Predisposition syndrome	Associated with longer telomeres in familial melanoma	Glioma
SMARCA4/ Brg1	Atypical teratoid/rhabdoid tumors (ATRTs) predisposition syndrome	Increased risk of developing cancerous tumors in many parts of the body.	Medulloblastoma
TP53	Li-Fraumeni syndrome	Predisposition to numerous cancers, especially breast, brain, and soft-tissue sarcoma	GBM and other gliomas
TSC1, TSC2	Tuberous sclerosis	Development of multisystem nonmalignant tumors	Giant cell astrocytoma

An organization called Gliogene through the Dan L. Duncan Comprehensive Cancer Center of the Baylor College of Medicine is engaged in a study of familial brain tumor. A link to their site is:

<https://www.bcm.edu/academic-centers/dan-l-duncan-comprehensive-cancer-center/research/gliogene/participate>

We also know that a high percentage of those with GBM have an extra Chromosome 7, but we cannot say from that, that everyone with a pair of Chromosome 7s gets GBM.

Add to all those external factors and those genetic factors, the following:

- Chronic Inflammation. Can be caused by virtually anything. One major thing that causes it is chronic stress and the typical American diet: too much red meat, too many sugar/glucose laced foods, too many grain-based products with gluten. Chronic inflammation can also be caused by harbor-

ing certain viruses or parasites (e.g., toxoplasmosis).

AND

- **Cancer Cell Survival.** Cancer cells, like all normal cells, have a shelf life. The process by which cells remove themselves is called apoptosis. Apoptosis is a highly regulated mechanism of cell death for the removal of unnecessary, surplus, aged or damaged cells. Dysregulation of the process of apoptosis can result in the persistence of mutated cells, leading to cancer. This dysregulation can occur as a result of an over or under expression of required proteins, peptides, hormones, or the presence of other body chemicals that have become out of balance owing to the factors described above.

AND

- **Proliferative Factors.** There are several factors that collaborate with the cancerous cells to proliferate and coalesce into a tumor. For example, in GBMs, approximately 45% of adult human cases harbor amplifications or activating mutations in the epidermal growth factor receptor (EGFR). Approximately 29% and 21% of pediatric and adult high-grade gliomas, respectively, harbor Platelet-derived growth factor A (PDGFRA) amplifications. Approximately 18% of adult GBMs show mutations or homozygous deletions of the NF1 gene. These and other factors help the cancerous cells to survive and proliferate into tumors.

In summary, the development of a brain tumor is not the result of bad luck or something that you or your loved one did or did not do. A brain tumor is the result of often continuing external assaults on the body which the body could no longer defend against and/or a significant misstep in the body's formidable ability to suppress the formation of a tumor. It is the intent of research for tumor treatments to understand how to un-do the effects of these assaults and missteps.

## ACKNOWLEDGMENTS

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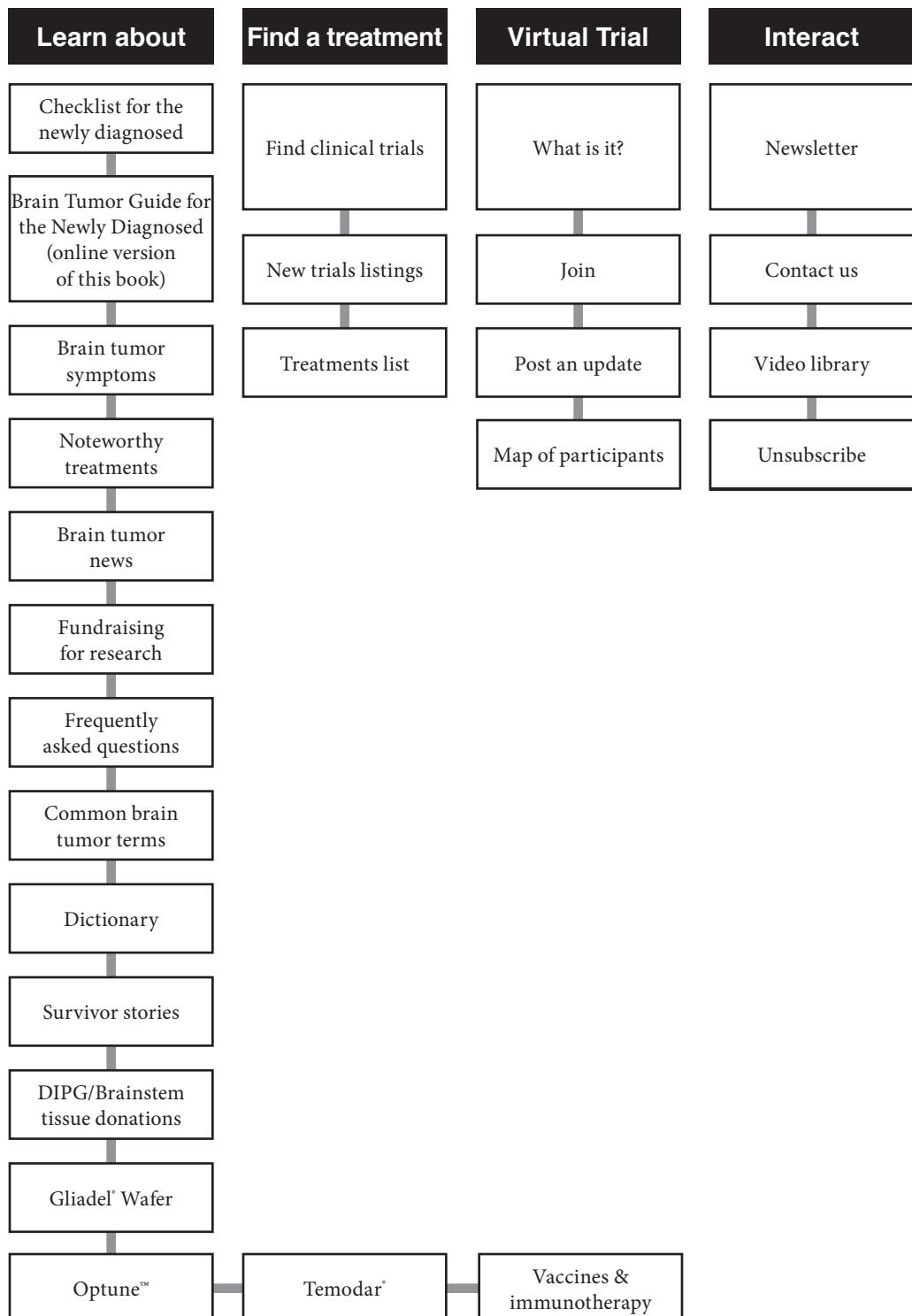
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The Musella Foundation is a 501(c)(3) nonprofit public charity dedicated to speeding up the search for the cure of brain tumors and to helping families deal with brain tumors.

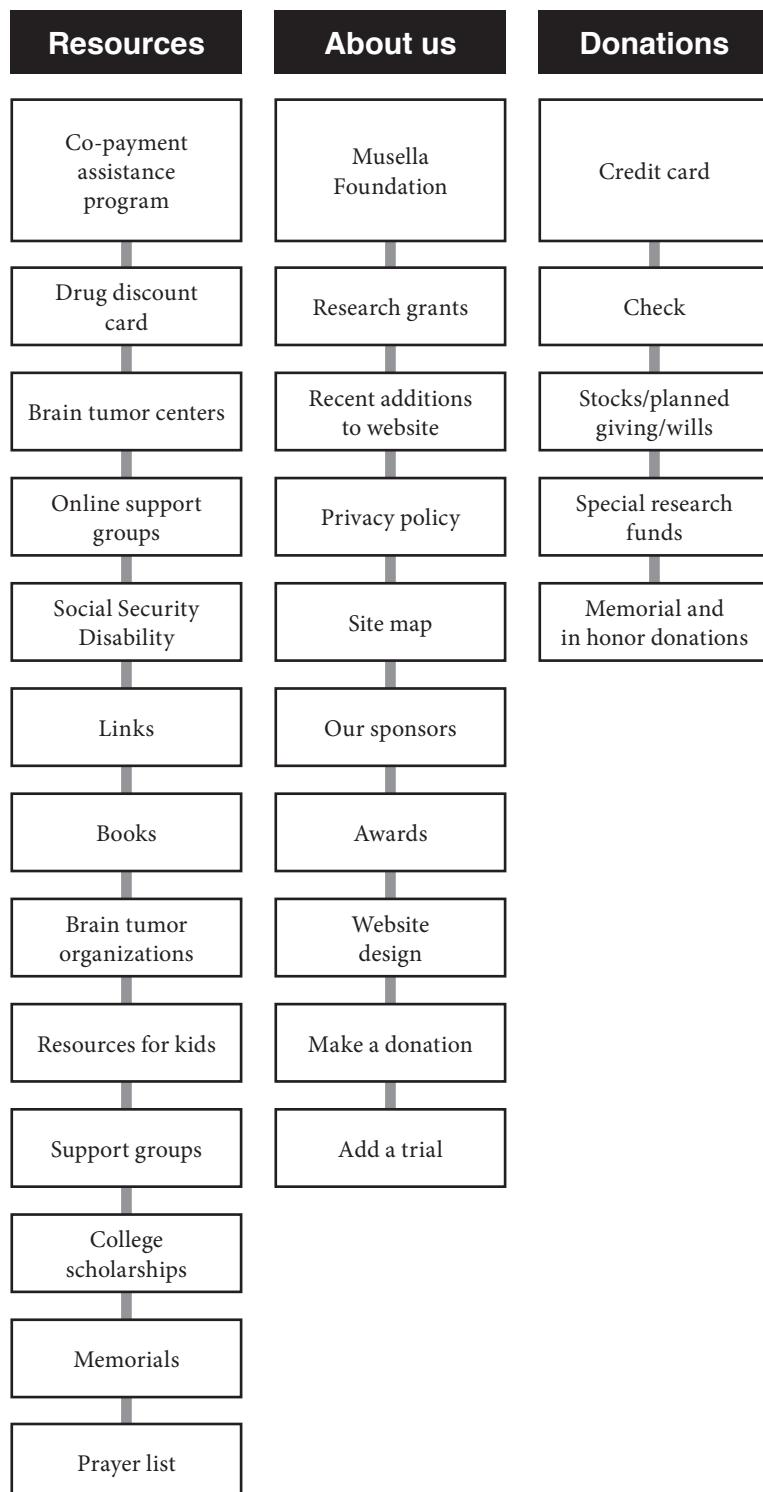
For brain tumor information or make a donation, please go to: <https://virtualtrials.org>.

All proceeds from the sale of *Brain Tumor Guide for the Newly Diagnosed* are used to fund brain tumor research.

# Site Map of Virtualtrials.org



# Site Map of Virtualtrials.org



# BRAIN TUMOR GUIDE for the NEWLY DIAGNOSED

IF YOU HAVE TIME TO READ ANYTHING IN THIS BOOK,  
PLEASE READ THE MUSELLA FOUNDATION NEED-TO-KNOW  
CHECKLIST, STARTING ON PAGE 82.

Al Musella, DPM



The diagnosis of brain tumor is a life-shaking event, compounded by the need to make crucial immediate decisions. What doctors to choose, where to be treated, what treatments are available, what clinical trials can be entered — to make the most rational decisions for yourself or for a loved one, you need to become as informed as possible as soon as possible.

The goal of *Brain Tumor Guide for the Newly Diagnosed* is to provide a vital first resource with tools for organizing and engaging with a medical team and the complex array of treatment options.

Represented here in readily actionable form is the wealth of helpful and hopeful information accumulated over the past two decades by the Musella Foundation for Brain Tumor Research & Information, an organization dedicated to the cure of brain tumors.

*Brain Tumor Guide for the Newly Diagnosed* was written with explicit reference to the Musella Foundation's influential virtualtrials.com website that since the 1990s has served as a clearinghouse for information related to brain tumor clinical trials and treatments while hosting multiple online support groups. The Musella Foundation also awards investigators with research grants to study brain tumor treatments.

**The Musella Foundation for Brain Tumor Research & Information, Inc.**

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