

## "No Stone Unturned: Medical Advocacy Techniques for People with Cancer and Other Serious Conditions"

Healing Circles workshop, Commonweal – June 5, 2015

Presented by: Mark Renneker, M.D.  
Associate Clinical Professor, Department of Family and Community Medicine,  
University of California, San Francisco

...this talk dedicated to Jared Lipsker, and Laura Sobell

[Note: this is an update of the "No Stone Unturned: Seeking Optimal Cancer Care" handout first written for the 11/23/99 Jenifer Altman Memorial Lecture at Commonweal. It is targeted to the Commonweal community.]

### **INTRODUCTION**

**Goal:** The goal of this workshop is provide the members of the Commonweal community (patients, family and friends, health professionals) with practical informational content and ideas as well as advocacy strategies to implement those ideas so as to achieve the best possible, most comprehensive care

**Background:** I have developed a full-time, San Francisco-based medical advocacy consultation practice which, since 1988, has provided intensive, case-specific research and advocacy services to thousands of patients, family members, and other health care providers. Referrals come to me from all over the country, and sometimes internationally, largely by word-of-mouth, often from fellow physicians. Although my practice is named "Patient-Directed Consultations," my nickname came to be "The Medical Equalizer," in that I provide help to people who are in a medical situation where they can't seem to get the help or information they need. Most all of my work is by phone, mail, fax, email and other electronic means. I do not bill or work through insurance companies or health plans; patients pay me directly, on a sliding scale. From when I first began this practice, there has been far greater demand for my help than I can provide; unfortunately, there are an untold number of patients needing these kinds of services. It has been gratifying to finally see other health professionals enter this field. I have been selectively training fellow health professionals, including medical students at the University of California, San Francisco, in a senior elective course started in 2014, entitled "Advocacy Medicine" (with Eric Jamison, M.D.). And, I recently co-coordinated (with Sandee Birdwell, M.D.) the First National Conference on Clinical Advocacy, in October 2012, at Commonweal.

I do not assume care for patients; nor do I treat them, in the conventional sense. I provide rigorous case analysis, personalized medical research, help in understanding and making decisions based on that information, and navigation strategies to implement such strategies. I seek to work within the patient's existing structure of caregivers; only rarely does my work lead to confrontation - it is about enhancing, expanding, and building bridges between people. I am empathetic to both physicians and patients: the world of medicine has become so complex, time so scarce - emails 24/7!, reimbursement mechanisms so confining, internet information so mixed.

About half of the cases I work with are cancer-related, most often dealing with high-risk, recurrent, and metastatic disease, often for unusual tumor types. Non-cancer problems are most often gastrointestinal, rheumatic/immunological, endocrinological, neurological, and pain-related. 93% of all cases are in adults, the average age is 52, and about 2/3rds are female. Patients have already seen or worked with 7 physicians on average (range 1 to 30), 70% are from outside of the Bay Area, 30% are themselves M.D.'s, PhD's, or lawyers. Family members are on the line about 50% of the time (e.g., conference call). I average about 10 hours of work per case (range 1 to 50 hours)- that could all be in one day or week, or spread out over months or longer. 2/3rds have tried alternative or complementary/integrative therapies - the other 1/3rd want to, often specifically seeking my help to evaluate and implement such strategies.

The general approach I take in my practice is to try to help a patient (and family) take charge of their overall case, by first identifying their own hopes (and fears), confidences (and misgivings), level of knowledge (and misinformation), and direction they would like their case to go in. This usually necessitates their coming to "own" the facts of their case, and to reasonably get up-to-speed on pertinent cutting-edge work.

My process is to try to go to where the patient is, meaning that I need to do everything possible to understand their feelings, fears, confusion, frustrations, hopes, strengths, and desires, as well as their physical symptoms and suffering; I need to take up their side in dealing with the disease, their doctors and the health care system - my alliance, my bond, is to them, less so the medical profession. I find that doing this work by phone actually facilitates empowerment and intimacy, e.g., their being at home (not in some doctor's office), using such a familiar communication medium as the telephone - which many of them use professionally and with great authority.

The circumstances in which a patient decides to ask for my help is often when the treating physician has reacted negatively, indifferently, too briefly (the most common problem), or not at all, to a patients' questions about and interests in additional or different therapies - whether they be mainstream, experimental (such as clinical trials), integrative, or unorthodox, and whether they be local, or elsewhere in the country or the world. In the worst of circumstances, a physician may have said that they have nothing more to offer the patient. Every patient wants to know that everything possible is being done or has been tried; they can't help but wonder if there aren't treatments somewhere else they might learn about and consider. I find that these needs of patients and their families are usually met once time is spent investigating and discussing with them the therapy or therapies under consideration, and how those therapies may be pursued practically and safely. In addition to patients not receiving enough time from their physicians, the other problems I commonly see are: family ignored, under-treated pain, incorrect or absent diagnosis, no prognosis given, hasn't consulted elsewhere, and false hopelessness.

Specific areas that most often need to be addressed include: (1) completeness and accuracy of the medical record, (2) additional tests, consultations, and research that may be needed, (3) mainstream, experimental, integrative treatment possibilities, (4) nutritional and physical considerations (including exercise, sleep, and sexual function), (5) psychological, spiritual, and family considerations, (6) primary, preventative, and wellness care, (7) quality of life, pain and symptom control, end-

of-life planning, (8) quality of care to date, (9) communication with health care providers, (10) advocacy within the health care system.

## **A CONTENT FOR ADVOCACY ONCOLOGY**

### **Stones Often Unturned**

**Completeness and Accuracy of the Medical Record:** it is imperative for the patient, or at least someone in the family or close to them, to obtain and reasonably comprehend the key medical records, if not the complete medical record. Most patients have only scratched the surface on this, though HIPAA laws and MYCHART online portals finally give greater access to such information. At most, usually because they wanted a second opinion and needed to bring key documents, patients sought or were provided with a pathology report of a biopsy or surgery, imaging reports, and sometimes some laboratory and tumor marker records. It can be a real eye-opener to read the various physicians' written history (be prepared to find errors!) and see their assessment of what should be done – which often may include many suggestions as yet unimplemented. Factual errors and omissions of important facts can be crucial at the outset of a case, especially in this early era of Electronic Medical Records, which so assuredly carries all such errors forward, ever misleading future consultants. For instance, errors as to where a tumor is (i.e., left or right lung), potentially relevant etiologic factors (family history, exposures), results pending that never made it into the medical record; speculations or cautions from a radiologist or pathologist that you were never told, unfair characterizations of the patient (difficult, in denial) that clearly will bias future physicians. (For this reason, I think it important to first have talked with a patient (i.e., taking their history) before examining their medical records – though I do like to see beforehand a single page summary of dates and treatments, and the key pathology reports.) I find the patient's thoughts on what may have caused or contributed to the cancer often never makes it into the record, particularly if it deals with psychological/relationship/stress factors, intuition, nutrition, chemical exposures, and especially iatrogenesis (physician-caused illness). Don't assume the record is complete, no matter how high a regard you may have for the doctor or hospital: what is hardest to discern from one's medical records is what is NOT there – certain procedure notes or reports of test results are often missing.

**Incomplete Testing:** hard to believe for cancer patients, I know, but it may turn out there was never any cancer there in the first place (I've done several such cases!). Or it may be a different cancer than was thought originally (often turned out to be a neuroendocrine cancer). Or it may be that there are two cancers (making it seem that there is metastatic cancer – multiple primary cancers is not all that rare). All pathological diagnoses of cancer should be independently double checked, and that second opinion should be in writing (don't take just a verbal report!). The best pathologist to give a second opinion is the one who specializes in that disease, wherever in the country (or world) they may be – they will have seen the most variants and falsely appearing cases. A tip-off that the diagnosis is wrong is when virtually all the treatments that usually work haven't worked. As a case goes on,

beware of physician's tendency to have diagnostic anchoring, which will keep them from questioning their initial diagnosis.

Even such bedrock-seeming tests as hormone receptors (estrogen and progesterone) and HER2 testing have considerable source of error, depending upon what part of the tumor was sampled (there is considerable cellular and geographical heterogeneity in a tumor), testing techniques used, and cut-off values to say if a result is positive or negative.

**Molecular and Genomic Testing:** as of the late 1990s, there has been a molecular and genomic revolution underway in all fields of medicine, but especially oncology. Even so, molecular profiling in cancer cases is underused, even for the most agreed upon tests, such as (depending upon the type of cancer) HER2, EGFR, BRCA, MGMT, Microsatellite Instability, and many other markers that, together, comprise the basis for what is presently called Personalized Medicine or Precision Medicine. Physicians and patients alike often have trouble understanding the different types of molecular and genomic testing. Most major hospitals fancy themselves fully able to do genomic profiling (with the advent of relatively low-cost, high-throughput machines), but most are not as thorough as larger, better established commercial companies, such as Caris in Phoenix (doing both genomics/gene testing and IHC/protein testing, leading to chemotherapy and targeted therapy recommendations), and Foundation Medicine in Boston (only genomics, and generally only leading to recommendations for targeted therapies, often only available in clinical trials.). Both are generally held in reasonably high-regard by oncologists, and are usually covered by insurers (though that may change). When a tumor's behavior changes (say, going from localized to metastatic), that is an indication for re-profiling a tumor, since it is likely that new, genetic changes have occurred (a tumor that was HER2 negative before may now be positive). Dr. Patrick Soon-Shoing's new enterprise, in Los Angeles, called Omics, is recently offering still more comprehensive genomic profiling, of both the tumor and the patients' regular cells.

My favorite molecular profiling service, though, and the one I find most useful for clinical and integrative applications, is Consultative Proteomics, out of the Department of Pathology at the University of Texas, Houston. Founded by clinical pathologist Robert Brown, M.D., this in depth testing and written analysis is, unfortunately, usually out-of-pocket, at about \$4000. Dr. Brown and his associate, Jamie Buryanek, M.D., are cutting-edge when it comes to interrogating a tumor's proteins (i.e, proteomics), using special stains to look for the key pathways that are driving the tumor. They also will test for immunological parameters, such as tumor-infiltrating lymphocytes, PD-L1, and PD-1 expression. Their tumor testing leads them to recommend consideration of using various medications but also natural medicines, and their highly referenced research and professional standing gives validity to such recommendations.

**Individualizing Chemotherapy: Live Cell Chemosensitivity Testing.** In the interest of better choosing chemo/targeting therapy, many scientists and physicians attempt to extrapolate from genes (what is called "the genotype", which is largely obtained from dead cells' DNA). It makes so much more sense to use live tumor cells for chemosensitivity testing. This involves sending overnight a piece of tumor tissue, immediately after it is removed and when the cells are still alive, to a lab that can test which chemotherapies and targeted therapies will kill the tumor cells. This kind of testing has been commercially available since the mid-1990s, and is better validated than genomic testing as a predictive test, but is seldom used by most

oncologists (unless requested by a patient). Numerous studies show it is about 90% accurate at determining what drugs will not work singly or in combination (which can save a lot of false starts, and attendant toxicity), and is about 40 – 90% accurate at indicating what will work. It is rarely done with a first surgery, since for most cancers the type of chemotherapy (“first-line”) is “standard,” and most oncologists feel uncomfortable (and malpractice vulnerable) deviating from that standard. But if there is an additional surgery, or a person develops lung or abdominal fluid containing cancer cells, or the tumor has recurred or become widespread (indicating a change in its behavior, mandating consideration of re-analyzing the tumor), consider sending a specimen for testing (fine needle aspirate or core biopsies don’t usually result in enough tissue – at least 0.5 grams is needed, more is preferable). My favorite chemosensitivity testing lab is Dr. Robert Nagourney's Rational Therapeutics, in Long Beach, Ca. (1 562 989-8128; see his book). Dr. Nagourney’s former partner, Dr. Larry Weisenthal, is also good: Weisenthal Lab, in Orange County, Ca. (1 714 894-0011). This kind of testing costs about \$4000, and is only rarely covered by insurance companies. Dr. Weisenthal can also test for some immunologicals and natural medicines.

**Protecting Future Options: Cryopreserving Tumor:** tumor removed by a surgeon or removed for biopsy is routinely sent down to the pathologist, but pathologist very often only need a small piece of the tumor to do their testing – the rest of the tissue is killed by formaldehyde, placed in paraffin wax, and stored away. I strongly recommend, pre-surgically, that one seek to have at least some of the live tumor tissue cryopreserved (freezing it, but by a careful process in the proper medium) for later possible vaccine and/or cell-line development for testing as new therapies arise. Some major hospitals have an in-house Cryo lab, usually for their own research, so they are often reluctant to accept specimens unless as part of a research project, such as adding to their Tumor Bank. My favorite private cryo/biological tissue facility is called Incell, in Austin, Texas, run by Mary Pat Moyer, Ph.D. Without much difficulty, once you have your surgeon’s agreement, a specimen can be set aside right after a surgery or biopsy procedure, and overnighted to them.

**Additional Imaging:** In general, ultrasound, CT, MRI, and CT/PET imaging is uniformly of high-quality, and, if anything, is overused (which, with the exception of ultrasound and MRI, understandably worries patients as to radiation exposure). What varies most, though, is how those scans are read. One would think it would be fairly objective, for instance simply measuring the size of a tumor, but inter-radiologist studies show as much as 50% variance in sizing the tumor – the only consistency being intra-examiner measurements (i.e., each radiologist consistently “errors” in the same way). So if one uses the same reading radiologist, at least there will be reliability as to whether a tumor is smaller or larger. In some centers, more often in rural areas and smaller hospitals it may be possible to request the same radiologist to read your scans each time. Note, most radiologists – cooped up in a dark room most all day, every day – welcome fellow health professionals’ calls or emails, and even enjoy meeting in person with a patient and family to go over scans, if kindly asked.

There are some underused and new scanning techniques worth being aware of: MRI with gadolinium, for abdominal and pelvic problems, particularly for what is called peritoneal carcinomatosis (not uncommon with ovarian cancer, but also appendiceal, colorectal, stomach, and pancreas cancers). Randall Low and Robert Barone’s published work shows this to be superior to standard CT or CT/PET for peritoneal

carcinomatosis. Clever, alternate forms of PET abound (most originating from Washington University, in St. Louis), such as with carbon acetate (for prostate cancer) and gallium 68 (for neuroendocrine tumors) can make all the difference in deciding what direction to go therapeutically. It is probable that the new MRI/PET machines will be revolutionary as to differentiating live from dead tumor and immunological and inflammatory processes – but there are as yet only a handful in America. There is a fascinating MRI technology variously called Combidex or ferro-MRI, which allows determination of tumor involvement in lymph nodes (even if normal sized). These imaging methods are not yet available in most of the best known medical centers, but it may be worth journeying to the closest imaging center that has such capabilities.

A simple but often overlooked low-radiation test is DEXA testing for Bone Density. Bone density often wanes, sometimes precipitously, due to cancer and its' treatments, especially chemotherapy. And short of knowing that it is occurring, one can be at risk for devastating fractures of the hip and spine, plus miss the opportunity to use bone-building strategies. A cancer immunotherapy called gamma delta T-cell therapy can be instituted by combining IV bisphosphonate treatments (Zometa, Boniva), with low doses of IL-2 (read Raymond Chang, MD., at the Meridian Clinic in NYC).

**Additional Laboratory Testing, Immunological:** until quite recently (2013-2015) the field of oncology had little interest in the role of the immune system in cancer, but with the advent of powerful new immunotherapies, such as anti-PD-1 and anti-PD-L1 approaches (e.g., pembrolizumab/Keytruda, nivolumab/Opdivo), oncologists are now scrambling to learn more about cancer immunology, with Cancer Immunology 101 lectures regularly being offered (usually indirectly by Immuno-Oncology Big Pharma), at professional meetings. Those in the integrative and naturopathic field have long been interested in immune function tests, and through companies such as Pharmasan have been testing natural killer cells numbers and activity, and T and B lymphocyte numbers and function. Those values can then be used as serial biomarkers to see if specific immune-enhancing interventions are effective. Mainstream labs such as Quest now offer many of these tests: Natural Killer Cell absolute number (test code #43786N), Natural Killer Cell function (#34184), Mitogen-induced Lymphocyte (T and B) Proliferation Panel (#91976). Key cytokines such as IL-6 are often worth measuring, and mirror pro-inflammatory states, which can wear a person down and give the edge to a cancer. A key marker can be found in every CBC (complete blood count), which is the absolute number of lymphocytes – if that is below normal, as is often the case after several rounds of chemotherapy, it means the Natural Killer Cells and T-lymphocytes numbers are likely lower than is optimal, and may need help rebuilding. Conventional oncologists are usually at a loss as to what to do about that, holding that only with time will the bone marrow recover, but most integrative physicians, naturopaths, and TCM/acupuncturists will know of many strategies that can be tried (and something as simple as a CBC can be used to measure success).

As mentioned above, there is now great interest in testing tumors for expression of PD-L1, but this is tricky to do. George Coukos at Univ. of Pennsylvania some years ago documented the importance of testing ovarian tumors for tumor-infiltrating lymphocytes (TIL), as a measure of how well the body's immune system is recognizing the tumor. Tumors with low TIL are riskier than those with high TIL – high TIL tumors are far less likely to recur. This year, Edith Perez at Mayo reported

similarly for breast cancer. Consultative Proteomics (described above) is one of the few labs who will measure and report TIL.

**Additional Laboratory Testing, Tumor Markers, Circulating Tumor Cells and Liquid Biopsies:** with the advent of molecular sciences, there are an ever expanding number of quite remarkable tests that can be used to help evaluate a given cancer patient. This allows finding more useful tumor markers for more cancers or for when a given cancer's usual tumor marker is not proving reliable (not solely relying on just CA-15.3/27-29 for breast, CEA or CA-19-9 for colon and pancreatic, CA-125 for ovarian, and PSA for prostate cancer). Tumor cell markers are proxy measurements (that can help lessen the need for scans) to better gauge whether a cancer has recurred, or how well a cancer is responding to a given treatment. The use of tumor markers is oddly idiosyncratic, for instance some oncologists never seek them for lung cancer, while others routinely do so.

To most everyone's shock, even early stage cancers (for instance stage 1 and 2 breast cancer) often generate circulating tumor cells, which can be culled and quantified (and even genomically tested) from a single tube of blood, as per Veridex with their CellSearch technology (available from Quest, but only FDA approved for breast, colon, and prostate cancers). And a simple blood test can be done for circulating tumor DNA, such as from Guardant 360, in what is called a "Liquid Biopsy." Tumor genetic material can be used, for instance, to identify the tissue of origin of a cancer of unknown origin (cancer of unknown primary is surprisingly common), and can be used to test for mutations. Also, pharmacogenomic blood testing can be done, indicating how well a cancer drug will be metabolized, such as for irinotecan, Taxol, and tamoxifen, and how they might optimally be dosed. But the exigencies of insurers' cost-containment attempts loom largely. Increasingly, these kinds of tests are being denied by insurers, and thereof are pre-emptively not even requested by an oncologist (tired of spending time unsuccessfully asking that they be covered). Collectively, patients and families voices will need to increasingly be heard on this as we enter the cancer treatment cost-wars that are just now heating up.

**Additional Testing, Terrain Panels and Functional Testing:** some oncologists have become interested in what is called "the stroma," which is another way of saying terrain, namely the normal tissues (and their inherent natural processes) surrounding the cancer, harkening to a seed-and-soil model (cancers are less likely to grow if the soil – the body's terrain – is healthy). Keith Block, M.D, an integrative oncologist in the Chicago area – really, the founder of the whole field of integrative oncology and a longtime friend of Commonweal, has for years been routinely doing what he calls "Terrain Panels" on most every patient he sees. This includes testing the blood for levels of key antioxidants and vitamins (not just vitamin D) and micronutrients, and markers for inflammation, coagulation markers (cancer quite often leads to heightened risk of serious blood clots), and immune function. Keith outlines these tests in his writings (see his Website and book "Life Over Cancer"). The test results can then guide nutritional and nutraceutical/supplement interventions. Most oncologists, on being asked to do these kinds of additional tests, will refuse, defaulting to the tried and proven clarion call for "Evidence-based Medicine," no matter that such evidence reasonably can be produced. The main reason is usually simply that they aren't sure what to do with the results (it has taken nearly a decade for vitamin D testing to find its way into regular use in oncology), and also it makes them uncomfortable to not provide the same standard of care to all their patients. Plus, it often won't be covered, and it is painful to say

so, and have to answer why that is. Some will order the tests, though, if the patient agrees to pay out of pocket (or one can go to a health professional more fluent in these strategies, naturopathic physicians particularly so).

Oncology is just now realizing that the gut terrain may play a role in how well some cancer therapies work. Genova Lab has long offered remarkably comprehensive testing of what is now called the "microbiome," namely, the various subpopulations of gut bacteria, including recommendations on how to treat pathogenic bacteria (with sensitivity testing for both standard and natural antibiotics).

Thyroid function is not checked often enough, particularly with the widespread use of targeted therapies, most of which can affect thyroid function. Be on the watch for drops in thyroid functioning, which is a not uncommon result of the body's innate response to widespread cancer, that the energy from thyroid hormone is, in effect, co-opted by a cancer. This has been shown by research and a clinical trial on glioblastoma at the Cleveland Clinic, which showed that inducing hypothyroidism can lead to tumor shrinkage. So, be mindful of most doctors' knee-jerk response to supply thyroid supplementation to normalize thyroid function, unless one is clearly symptomatic from being on low thyroid.

As a gauge of bone loss, leading to osteoporosis, a nifty urine test can be done, called N-telopeptide (also a blood test, but urine testing gives more complete information). This can be a functional guide as to how often to use bone-builders, such as Zometa/zolendronate or Xgeva/denosumab, so as to lessen the risk of getting osteonecrosis of the jaw (an unfortunate side-effect of those treatments).

One last consideration, and that is that if a patient will have to pay out of pocket for any such blood tests, to look at the rapidly ascendant company, Theranos, which has a fascinating disruptive technology of only needing a drop of blood (which can be obtained at places like Walgreen's, and may eventually not need a doctor's prescription) to do most every standard blood test, at a fraction of the cost (less than \$5 for a complete blood count, or metabolic panel).

**Additional Research:** most patients are under-educated about cancer, in general, and their cancer, specifically. But an understandably large number of patients do NOT want to read about their cancer, whether on Wikipedia or American Cancer Society or National Cancer Institute supplied summaries. It is just too scary, the thought of coming upon sections on prognosis - especially if this wasn't discussed before with one's oncologist - and worse, fear that their state of cancer will be described as incurable (never mind that many patients with metastatic cancers DO survive their cancer and could even be called "cured." As mentioned earlier, this is often a good time for a family member or friend to volunteer for being the Researcher on the case, chasing down articles, news items, etc.

When it comes to medical topics, I find that Wikipedia entries are often biased towards science and technology, and are not very clinical or patient-centered. For the clinical aspects of cancer, the best resource to start with is the head-and-shoulders best textbook in the field: DeVita's Cancer - Principles and Practices of Oncology, now in its 10<sup>th</sup> edition (2015).

A basic Medline search through what is called PubMed (just enter that into Google and go there) is essential to see what has most recently been published in a peer-reviewed journal. Various commercial computer search companies exist, especially

for cancer, but often are not on-point (too broad a search yields too much "junk" information), and are often assembly-line produced. If you do your own search, it will take longer, but spending a few hours sorting through the information and trying to make sense of it will serve you well, and help you begin to map the field: who is doing what and where.

The major professional oncology organizations in this country (and the world) are the American Society for Clinical Oncology (ASCO, annual meeting every late May/early June), and the American Association for Cancer Research (AACR, annual meeting every mid-April). At each of these meetings will be 1000s of presentation (some only as poster presentations, some only electronically presented), and none of them will appear on PubMed, and often won't turn up on Google, unless it made the news. To access these key, cutting-edge presentations, go to the respective website for each organization, looking for the "Proceedings" from the Annual Meeting. You can then enter what subjects you are interested in, whether a specific cancer or type of treatment. Their indexing has always been idiosyncratic, so be prepared to try several search terms. If you are imagining that, well, my oncologist will be reading this stuff, that is hardly the case – most don't attend these meetings, and even if they do, they mainly will be exposed to plenary presentations (key, possibly practice-changing studies, but only a couple handfuls of them). The drug companies put on regional ASCO summary meetings after each year's annual meeting. This is for practicing oncologists who didn't attend, but again only a tiny fraction of what was presented is covered. To spend time reviewing the actual proceedings - the many abstracts, is to come upon a gold-mine of information, ideas, and new developments to follow up on.

Each November, in NYC, a remarkable, several day meeting takes place, called "Innovative Cancer Therapy for Tomorrow." It is put on by The Chemotherapy Foundation, with The Mount Sinai School of Medicine. The speakers are, for the most part, the shakers-and-movers and the mavericks in the cancer field. There are proceedings for the meetings, and they can be obtained [call Jaclyn Silverman, 1 212 241-6772].

The key journals to consider accessing are the Journal of Clinical Oncology (pairs with ASCO), Clinical Cancer Research (pairs with AACR), Cancer (the American Cancer Society's journal), the Journal of The National Cancer Institute, and Lancet Oncology (the most fun to read). When it comes to integrative oncology, the best peer-reviewed journal is still Integrative Cancer Therapies, edited by Keith Block, M.D., and published by Sage.

The role model for taking on the task of researching one's own case is Ben Williams, a non-physician now 20 years out from having had glioblastoma multiforma, including several recurrences. His book, "Surviving Terminal Cancer," is a manifesto as to the value of doing one's own deep research on both conventional and unconventional therapies, and developing one's own portfolio of treatments.

**Additional Consultations:** most cancer cases haven't been presented before a tumor board: a multidisciplinary board, consisting of a pathologist who reviews the slides, a surgeon or surgical oncologist, radiation therapist, medical oncologist, and other specialists as may be available (immunological oncologist, nutritional oncologist or dietician, psycho-oncologist or social worker or psychologist, physical and rehab specialist). Private hospitals' tumor boards are less often where true, unfettered-by-referral-economics discourse takes place; regional cancer centers are

best. The San Francisco Regional Cancer Foundation makes available free-of-charge an all-volunteer, all tumor types reviewed, independent tumor board. UCSF has a superb weekly Brain Tumor Board, through their Department of Neurosurgery.

Local second and even third or more opinions are rarely a waste of time – each consultant seen will usually contribute to your case. As to choosing whom to see, from Websites and Yelp style online commentary you may be misled - better to ask friends, fellow patients, and trusted health professionals. In general, try to choose persons who didn't train with (or who is at the same institution) as your present doctor. In fact, seek those who may hold different views, or may be of a different specialty – for instance, surgeons and medical oncologists rarely tell you much about the possible uses of radiation therapy, and not until you were to meet with a radiation oncologist would you hear of ways to perhaps avoid surgery or chemotherapy.

A comprehensive second opinion can be indispensable, ideally conducted at a major cancer center, such as M.D. Anderson in Houston, or John Hopkins, in Baltimore.

**Seeking Additional Types of Therapies:** The way I think about comprehensive cancer therapy is that all of the following therapies be actively considered –

1. Surgery, which accounts for the most cases of cure - don't forget that over 50% of all cancers are being cured in 2015, and surgery accounts for the lion's share of those successes. Surgical techniques just keep getting better. There is world of difference between a general surgeon and a surgical oncologist. For peritoneal carcinomatosis, seek consultation with a surgeon who uses the Sugarbaker technique, involving meticulous removal of the peritoneal lining (most gynecological oncologists don't do this) and then using HIPEC (heated intraperitoneal chemotherapy). Regional anesthesia is being found to lead to less cancer recurrences compared to general anesthesia, for reasons which are still under investigation.
2. Radiation therapy, including external beam (ie., Intensity Modulated Radiotherapy), interstitial/brachytherapy (placing radiation-containing needles or pellets into the tumor), stereotactic radiosurgery (such as Gamma knife and Cyberknife), proton and photon beam, high-intensity focused ultrasound (HIFU), and radioimmunoconjugates (radiation attached to monoclonal antibodies, such as alphasarin for prostate cancer and PRRT/peptide-receptor radioconjugate therapy for neuroendocrine cancers).
3. Interventional Radiologist techniques, such as radiofrequency ablation, microwave ablation, and cryoablation of tumors in the liver, lung, and bones. Also, vascular delivery of treatments, such as chemoembolization of liver metastases and placement of radiation particles (ie., Sirspheres).
4. Chemotherapy (usually referring to cytotoxic - cell-killing - therapy) and also targeted therapies (technically chemotherapy, but with these treatments a specific, known molecular feature of the tumor is being targeted, such as HER2 amplification in breast cancer (trastuzumab/Herceptin, Lapatinib, pertuzumab/Perjeta, T-DM1/Kadcyla – all HER2-targeting, patented medications), ALK translocation in lung and some other cancers (crizotinib), and VEGF (bevacizumab/Avastin, and other anti-angiogenics). The use of **chromomodulated chemotherapy** should be considered. This involves

giving chemotherapy at optimal time windows in the 24-hour clock, based on circadian rhythms, ideally so that it runs in gradually at first then peaks then tapers off (a bell-shaped curve) See Francis Levi's work, out of Europe, where chronomodulated chemotherapy is most available. For instance, Levi showed that, for colorectal cancer, if one receives intravenous chemotherapy with 5-fluorouracil (5-FU) at 4 in the afternoon it will be twice as toxic and ½ as effective compared to receiving it at 4 in the morning (which is possible with programmable pumps, allowing it to run in while you sleep). Levi and others have determined optimal time windows for most chemotherapies. At present, in the U.S., it is only possible to receive IV chronomodulated chemotherapy at Keith Block's center near Chicago.

5. Hormone therapy: a key adjuvant therapy to prevent recurrence of many types of breast cancer, now recommended for ever-lengthening periods of time (10 years or longer). Also, it is a key, frontline treatment for metastatic breast cancer that is estrogen receptor positive. Hormone therapy has long been used for prostate cancer, but now there are newer, highly specific types of androgen blockers, such as abiraterone and enzalutamide (which may also play a role in breast cancer treatment). Hormone therapy has a little known but actual track record with ovarian cancer as well.
6. Immunotherapy: the most exciting form of cancer therapy at present, proving more long-lasting ("durable" remissions) and less toxicity than most chemo- and targeted therapies, notably including anti-PD-1 and anti-PD-L1 therapies, which are given intravenously every 2 to 3 weeks. Two anti-PD-1's now have limited FDA-approval (as a second-line melanoma treatment, and for squamous cell lung cancer), but the number of cancers they will be approved for will rapidly grow, perhaps coming into first-line use for some cancers, and even for adjuvant therapy. They already can be used (and are being used) off-label, with a willing physician and an ability to self-pay; far lower, less expensive doses may be equally effective. There are a bewildering array of PD-1/PD-L1 studies underway (most so recent or else deliberately not even listed in ClinicalTrials.gov), including many that combine them with other treatments, including chemotherapy, targeted therapy, radiation therapy, stereotactic radiosurgery, antivirals, and a wide range of other immunotherapies, including checkpoint blockade inhibitors (such as ipilimumab/Yervoy), interleukin-2, dendritic cell and other cancer vaccines. CAR (chimeric antigen receptor) immunotherapy has shown stunning results, as at the University of Pennsylvania, mainly with hematologic cancers such as leukemia and lymphomas, but it is quite complex to prepare and administer, and is only gradually being studied with other cancers. The remarkable Steven Rosenberg and his team at the National Cancer Institute have developed highly effective immunotherapeutic methods to treat advanced melanoma, and is pioneering an already successful method of using gene probes to find specific cancer driver mutations and then using a patient's own T-cells as a medicine, once the T-cell receptor (TCR) is genetically reprogrammed with a viral vector to go after the cancer. Dendritic cell vaccines in of themselves can be effective for many cancers, as can long-term use of low-doses of interleukin-2 or bacterial stimulants (OM-85) combined with cis-retinoic acid/Accutane, as with the Recchia Protocol, from Italy's Francesco Recchia, M.D., as presented at AACR in April 2012.

7. Gene therapy, getting close to living up to its promise, but still not quite there, as to being a readily available therapy. However, the above mentioned TCR work of Steven Rosenberg at the NCI can be seen as a form of gene therapy. If you apply to be in one of his immunotherapy studies, it is possible you will be accepted. They are free-of-charge.
8. Stem cell therapy, similar to gene therapy, in terms of being hugely popular in concept but not yet in practice, at least as far as cancer therapy and being a therapy unto itself. Obviously though, for recovering from high-dose chemotherapy and for bone-marrow transplants, stem cells are essential. The greatest advances ever in chemotherapy may come when therapies are developed that effectively targets cancer stem cells.
9. Nutritional therapy: food can be medicine, and is as important as any of the above therapies. This is a complex subject and not one to be taken lightly. Finding a knowledgeable nutritionist is not so easy as it sounds – most clinic and hospital-affiliated nutritionists are kept on pretty short leashes. Self-employed nutritionists are more likely to be out-of-the-box. Rebecca Katz's book, "Cancer Fighting Kitchen," is a good place to start.
10. Nutraceutical therapy: supplements and natural medicines such as herbs and plant extracts. They continue to make most physicians uncomfortable, and patients, if any, take ever more of them. Suffice it to say, I think supplements can favorably affect the behavior of cancer cells, and most assuredly can improve the ability of normal cells to contain and eliminate cancer cells. I recommend, though, trying not to shotgun by being on every supplement every well-meaning family member or friend or a Website points you towards. Consider how much of that may be fear-driven (and work psychologically on that fear). Instead, with supplements, try to proceed rationally, based on valid published research and experts you trust. Again, look at Ben William's book, "Surviving Terminal Cancer," and Keith Block's publications (notably his take-downs on oncologists recommending avoidance of anti-oxidants during chemo- and radiation therapy).
11. Physical therapy and rehabilitation: talk about underutilized. Physical therapists and physiatrists (physicians specializing in physical medicine and rehabilitation) are invaluable. Add to this consideration having regular visits with a manual-medicine oriented osteopathic physician, such as a cranial osteopath (see listings on the Cranial Academy website). I've also found Atlas Chiropractic quite helpful to some cancer patients.
12. Pain Treatment and Palliative Care: initial research out of Harvard, and now replicated and validated elsewhere, has shown that palliative, symptom-oriented care – in addition to regular care, such as chemotherapy - results in longer survival, and should begin as soon as a patient is diagnosed with an advanced cancer, and not wait until they are at the end of their rope. This makes good sense, and means having greater focus on symptom-management (pain, breathing, nausea, anorexia and weight loss, bowel movements, fatigue, sleep). Most medical oncologists imagine they are already doing a good enough job with this – they are not. It usually requires seeking a separate consultation with a palliative care physician. Pain specialists can help greatly with pain.

13. Acupuncture and Traditional Chinese Medicine: even the least integratively-minded oncologists have come to accept and often recommend acupuncture, particularly for the side-effects of chemotherapy, such as nausea and fatigue. Michael Broffman, LAC, and Michael McCulloch, LAC, PhD., through their Pine Street Clinic, in San Anselmo/Marin county, have for years been supplying first rate TCM-based guidance and therapy for patients dealing with cancer and other complex illnesses. Their publications in Integrative Cancer Therapy on using a TCM-based portfolio of treatments in a sizable case-series of patients with advanced colon cancer, and advanced lung cancers, is, to this day, the only large studies validating multi-therapy, integrative portfolios in the treatment of patients with cancer.
14. Homeopathy: still hard to explain how it works, but there is peer-reviewed published literature supporting the use of homeopathic remedies as a cancer treatment. See Chatterjee's work with psorinum, for pancreatic, gall bladder, liver, esophageal, and lung cancers.
15. Psychological: psycho-oncology is probably the most unrecognized and under-dosed cancer therapy. Some cancer centers, such as Memorial Sloan-Kettering in NYC, and Lombardi in Washington DC, have Departments of Psycho-Oncology! Lawrence LeShan's work (read his classic book, "Cancer As a Turning Point") spawned a number of good psycho-oncologists. Many LeShanian therapists will work by phone. It seems to me that the cancer help programs at Commonweal and Smith Farm have psycho-oncology at their core.
16. Family and spiritual considerations: family members and close friends often need a lot of support, and classically it is the patient who usually ends up being the one who provides that support. Sometimes that helps the patient, often it is more than they can bear. Seek outside help – social workers and case managers, support groups, spiritual and church organizations can make a huge difference. Meditative approaches and prayer are of tremendous value to patients and family members alike.
17. Off-label and over-the-counter therapies: a number of widely prescribed medications are actually being used off-label, meaning they don't have FDA-approval for the condition they are being prescribed for. Cancer-related examples are metformin, celecoxib/Celebrex, statins (cholesterol-lowering medicines), cis-retinoic acid/Accutane, and Low Molecular Heparins/Lovenox. There are also a number of over-the-counter medications to consider, such as cimetidine/Tagamet, aspirin, and melatonin. Read Albert Reichtle's papers.
18. Unconventional and underground therapies: This is something that often makes most physicians cringe, sometimes for good reason – there are sharks out there just doing it for the money, but in my experience, many such therapies are legit. Better known ones for which I have personally seen one or more patients have actual remissions, prolonged stabilizations, or who kept a likely-to-recur cancer from recurring, include (not a complete list): artemisinin, anvirzel, Vitae Elixir, psorinum, Iscador, gcmf, Newcastle Virus, copper chelation with TM, cannabis extracts (CBD/THC), alpha-lipoic acid and low-dose naltrexone, phenylbutyrate/anti-neoplastons, and others. Keep in mind, though, that most such compounds were being given as part of a cocktail of other such therapies, but in the above cases it was when this

specific therapy was added in that things began to change. Also, keep in mind, I've seen many more patients unsuccessfully try these therapies, and sometimes they had severe toxicity (a patient who had a crashing anemia from copper chelation, one patient died from intrathecal gcmf), and not inconsiderable costs. When a patient decides to pursue out of the country therapies is when many physicians want to wash their hands of them, but really, that is a form of abandonment, and instead should be a key time to stay in close contact with the patient and family, to watch their back and help make sure everything goes as safely and as well as possible.

19. The choice of no therapy: some patients have a strong sense of when to stop treatment of their cancer, often a lot earlier than an oncologist thinks reasonable. Most often the patient is right. Too often, hospice care is initiated too late. I've seen many patients actually get stronger and live longer once they stop treatment, probably because they finally have a chance to recover from the toxicities of the treatments. Sometimes they later go off hospice and back into treatment. Some patients will not accept hospice care, wanting to go down swinging; most often patients die the way they have lived. They deserve support in that choice. Some patients, after being diagnosed with cancer, will refuse any treatments, including simple surgery. That is their right. Most often, I think them wrong, but I will support and help them in every other way possible.

**Other Important Considerations:** (1) **Exercise** is a forgotten modality in all too many cases; if you aren't using your body, it will stop working and give up on you. Even hospitalized patients need frequent use of muscles (if only leg isometrics) to avoid blood-clots (more common in cancer, called Trousseau's Syndrome). Walking, swimming, and yoga are excellent. Exercising right up to the moment (and even during) you receive chemotherapy, may lessen toxicity and improve effectiveness. (2) **Sleep:** in recent years, numerous studies have associated poor sleep with cancer. Many cancer treatments negatively affect sleep, while also increasing the need for sleep. Optimizing sleep is a key component to optimizing recovery from cancer. Consider going to a sleep specialist. (3) **Sexual functioning:** although all physicians are taught to take a sexual history and ask questions to determine if sexual dysfunction is present, few do so - and most patients are too embarrassed to bring it up. (4) **Emotional disassociation** with those body parts affected by the cancer - it is important to realize that cancer cells are only a minute portion of your organ(s) and body and that they are continually being attacked and for the most part are being held in check by your body's (and organs' and tissues') own natural healing abilities. Try not to dissociate from any part of your body. (5) **False hopelessness** is epidemic. False hopelessness is most often due to how a patient has been informed by their oncologist as to their prognosis, or if they are being treated with little hopefulness. Many patients say to me that they are being treated like "a dead man walking." However, in most oncologists' practices there will always be a group of "exceptional" patients who are long term survivors who had metastatic cancer, and are now years, sometimes decades, out from when they were first diagnosed. As for metastatic breast cancer, at the time it is diagnosed, many women are hit over the head with the oncologist's pronouncement that it is incurable. Get a copy of the editorial in the August 1996 Journal of Clinical Oncology, by George Sledge, M.D., entitled "Should We Dream the Impossible Dream? The Meaning of Long-term Survival in Metastatic Breast Cancer," in which he points out that there are consistently women who do survive metastatic breast cancer, so why must oncologists continue to insist that it is incurable? (Just in the last month he was

called upon in a cancer publication to again debate that point.) The number may be low - about 3% of patients diagnosed with metastatic breast cancer who began chemotherapy and went into complete remission and were still in remission at least 5 years later (up to almost 20 years!), based on studies by Aman Buzdur and Gabriel Hortobagyi and other colleagues, at M.D. Anderson, largely using older forms of chemotherapy, during the 1970s. On an updated analysis in 2010 from M.D. Anderson, Aman Buzdur reports that the 10-year survival rate for metastatic breast cancer has risen to 22% from just 3% 50 or more years ago. So, why shouldn't a woman with metastatic breast cancer aim for and believe in her ability to be in that growing group of survivors? (6) **Intentionality** is vital, namely believing in your own ability to recover. It is crucial that your doctor also believes in your ability to get well. If it rings a bell that you feel your doctor is treating you "like a dead man walking," it is time to get a different doctor.

[Talk given 6/5/15, this handout drafted 6/4/15 and presented with the talk, final corrected draft 6/10/15]

\*\*\*\*\*

**Note:** the following information is attached to this handout to allow better analysis of my viewpoints and observations. It is not intended as a means of gaining more patients; the wait for new patient appointments with me is unfortunately long, currently at about 3 to 4 months, though I have trained other physicians who can start work on a case a lot sooner. My hope would be that anyone thinking they might need my help would instead be able to use the information in this handout to navigate on their own; and for those health professionals considering doing this kind of work, reading over my background could help them see a path to adding clinical advocacy strategies into their practice.

For anyone wanting further information on my practice, if you email, write, call, or fax my office, you can request to be sent a comprehensive, 17-page write up on the kinds of cases I work with, and how to go about setting up an appointment to work with me. My address/phone/fax is: MARK RENNEKER, M.D. 4637 ULLOA STREET SAN FRANCISCO, CALIFORNIA 94116 phone (415) 681-5357 fax (415) 681-9734. My email address is mark.renneker@ucsf.edu.

### Personal Background

Undergraduate work in biology, education, and communication at the University of California, Santa Cruz (Gregory Bateson, mentor). Medical school at the University of California, San Francisco (graduated/M.D. in 1979). Post-graduate training in the School of Public Health, University of California, Berkeley (1979-80). Residency in family medicine at UC San Francisco, at San Francisco General Hospital (completed 1984). Diplomate of the American Board of Family Practice (i.e., board-certified), since 1984.

Faculty appointment at the University of California, San Francisco, School of Medicine, as an Associate Clinical Professor in the Department of Family and Community Medicine (since 1984). Attending physician at the Cancer Education and Prevention Center, Summit Hospital, Oakland, California (1984-92); Principal Investigator of a three-year (1989-92), \$600,000 national American Cancer Society demonstration project that provided comprehensive cancer education and screening

services to the poor, at West Oakland Health Center. Attending physician at the South of Market Health Center (an inner-city clinic; 1982-98). Attending physician at Laguna Honda Hospital (geriatrics, rehabilitation, hospice; 1983-2008). Founder, Patient-Directed Consultations (case specific research and clinical advocacy; 1988 to the present).

American Cancer Society volunteer (local, state, national; 1974-98), Member, Planetree Board of Directors (1993-98). Member, the American Association of Cancer Education (since 1986), Association of Teachers of Preventive Medicine (since 1978). American Society for Clinical Oncology, and the American Association for Cancer Research. Author/editor, "Understanding Cancer," a textbook for college students and the public (3<sup>rd</sup> edition in 1988), and author of numerous medical and lay articles and other books. Editorial board member, "Integrative Cancer Therapies." Former member of the editorial boards of "The Journal of Cancer Education" and "Physician and Sportsmedicine." Founder of the Surfer's Medical Association (in 1986); Former Editor, "Surfing Medicine" (the Journal of the Surfer's Medical Association).