The emerging view is that many cancers, due to present therapeutics, may become chronic diseases that need to be managed over many years with diet, lifestyle, and environment changes. Management of the patient that is appropriate for the stage of his or her disease is dependent upon the availability of biomarkers or screening tests that have been validated to define the status of the individual. Traditionally, four types of screening tests have been employed, including early-detection screening such as the Pap test, mammography, dermatology screen, oral screen, and colonoscopy. The second type of screening is the use of gene-based cellular tumor-specific markers such as KRAS, the APC gene, TP53 and BAT26 in stool sample DNA, or cytological examination of cells in sputum samples. The third type of screening test is the use of serum or urine genetic markers including cyclin E, MCM, PCNA, p16, BCL-2, and VEGF that monitor cell-cycle progression, DNA replication, DNA synthesis, cell-cycle control, apoptosis, and angiogenesis. One prime example of this is the use of CA-125 as a tumor marker for women with ovarian cancer. The fourth type of screening test employs soluble serum or urine metabolites to follow the course of disease such as the use of catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA) in the urine of patients with neuroblastoma.

Genetic and molecular biological screening tests traditionally have been used in following the course of therapy in a well-described form of cancer. Beyond these traditional approaches to cancer assessment, however, is emerging another strategy for the assessment of the functional state of the patient's physiology that is related to both his individual predisposition to cancer as well as the design of a personalized program for the chronic management of the cancer survivor. This type of biomarker screening takes its lead from the pioneering work done on the value of prostate-specific antigen (PSA) screening in males for defining the risk and progression of prostate cancer.

The states of cancer from initiation through promotion and progression have different stages of disturbed metabolism associated with them. There are biomarkers that identify these stages of distorted physiology and reflect the state of function that is consistent with cancer. These stages of disturbed physiology include:

- carcinogenic alteration,
- altered cellular proliferation,
- genomic instability,
- epigenetic alteration,
- angiogenesis, and
- metastasis.

These areas of altered cellular physiology in turn are driven by specific cellular processes such as:

- inflammation,
- altered intercellular signal transduction,
- altered mitochondrial bioenergetics,
- altered immune surveillance,
- chronic opportunistic infection, and
- altered posttranslational protein structure.

Each of these areas, in turn, has a series of metabolic markers associated with the degree of distortion or alteration in these processes. It is the systems biology pattern of these markers that defines the "physiological state function" of the individual and aspects of both his risk of and status related to specific cancers. In a sense, the approach for screening using this concept is to develop a genomic, proteomic, and metabolomic profile of the patient that reflects his or her physiological state function.

At first blush, this objective seems daunting and "futuristic" and outside the scope of what is practical or even possible under the constraints of current technology. It could be argued that this concept is conceptually bounded rather than technologically bounded. Many of the tools that are necessary to address the question of the status of metabolic distortion associated with cancer are available today but are not being employed in this conceptual framework. In order to understand which evaluative tools might be needed to properly implement this strategy, we need to ask which types of disturbed physiological functions have been identified to be associated with the physiological state function of many cancers. This list would include, for example, assessment of:

- insulin and insulin-like growth factor signaling;
- detoxification pathways;
- gastrointestinal immune function and enterometabolic
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activity;
- cellular redox, mitochondrial bioenergetics, and oxidative stress;
- lipid signaling and status including CD36 activity, fatty acid status, and eicosanoid signaling;
- steroid hormone status and metabolites;
- immune status including autoantibody analysis;
- inflammatory signaling mediators;
- genomic stability and epigenetic alteration;
- the status of intermediary metabolism; and
- occult bacterial or viral infection in the gastrointestinal tract, oral cavity, liver, and sinuses.

Specific tests are now available for each of these assessment areas and can be employed to define the functional status of the patient that is connected to specific disturbed function associated with tumor initiation, promotion, and progression. The focus of this profile is not to diagnose a specific cancer but rather to better define the physiological state function of the patient that is associated with cancer. As was described in part 1 of this series, cancer is a proliferative disorder that is associated with alterations in physiological function that gives rise to its pathophysiological architecture of dedifferentiation, altered cellular cycling, angiogenesis, invasion, and metastasis.6

Specific tests that could be included in such a panel of assessment of the physiological state function include

- fasting and 2-hour postprandial glucose and insulin, along with hemoglobin A1c, and advanced glycosylated end product proteins (AGEs) and serum IGF-1 levels for aspects of insulin signaling;
- acetyaminophen and benzoate challenge tests to evaluate aspects of phase 1 and phase 2 detoxification;
- lactulose/mannitol challenge testing, fecal calprotectin and stool microbiology to evaluate gastrointestinal immune function;
- serum lipid peroxides, serum 8-hydroxydeoxyguanosine (80HdG) levels, serum isoprostanes for oxidative stress, and mitochondrial bioenergetics;
- erythrocyte fatty acid analysis, plasma CD36, VCAM and ICAM-1 analysis for lipid contribution to cellular proliferation;
- steroid hormone analysis including estrogen hydroxylated metabolite;
- autoantibody analysis including antiTPO, ANA, and antigliadin antibodies along with genetic analysis of DR2 and DR8 polymorphisms for gluten reactivity;
- vitamin D status through serum analysis of 25-hydroxy D3 as part of immune evaluation;
- analysis of plasma hsCRP, LpPLA2, and uric acid as part of inflammatory assessment;
- evaluation of lymphocyte telomere length and serum homocysteine to evaluate genomic instability and epigenetic methylation defects;
- urinary organic acid analysis to evaluate integrity of intermediary metabolism and potential micronutrient insufficiencies;
- serum antibody testing for H pylori, Epstein-Barr virus, hepatitis B and C, chlamydia, and HIV; and
- sputum cytological evaluation for micronuclei alteration and need for increased intake of protective nutrients and phytochemicals.

These represent an ensemble of tests that demonstrate how one might assemble a portfolio of biomarkers for better understanding of the stages of disturbed physiology associated with cancers. The underlying principle for this assessment panel is that specific disturbed physiological state functions are associated with the development and progression of cancer and that by evaluating the parameters that reflect alterations in genomic, proteomic, and metabolomic status, a better understanding of the most appropriate approach to the patient’s long-term management of cancer as a chronic disease can be achieved. This approach might be criticized for excessive reliance upon laboratory testing and therefore thought to be unjustified. Rather than argue for a specific panel that can be rationalized on the basis of economics, I propose that the concept of how best to approach the patient’s physiology that results in an understanding of his or her “oncogenic potential” should be the focus of the debate. The resolution of this question can then be further refined to determine the most appropriate panel of screening and biomarker tests to be included in the management of a specific patient. It is well known that genetics alone account for a very small proportion of the determinants for cancer; therefore, understanding the topography of the patient’s physiology and his or her unique response to the environment seems to be very important in improving patient outcome, from both an early detection and long-term management perspective of cancer as a chronic disease.

EXAMPLES OF HOW THIS APPROACH COULD IMPROVE OUTCOME IN THE CANCER PATIENT

The future of the management of cancer is personalized, preventive, participatory, and prospective in its character, as has been described by Snyderman et al.4 This characterizes the patient-centered fundamentals of functional medicine as presented in The Textbook of Functional Medicine.2 This form of cancer medicine will integrate new genomics science with that of genetic-expression patterns and how they connect to various phenotypic functional biomarkers that serve as “sensors” for understanding the status of the patient and his or her response to personalized intervention/management.30 Recently, the American Institute for Cancer Research published the largest review of the link between diet, lifestyle, and cancer.30 The report estimated that more than 40% of breast cancer cases could be prevented by making relatively straightforward diet and lifestyle changes. The key to this approach is matching the diet and lifestyle of the person to his or her specific needs. This approach to the management of both the risk and the progression of cancer is mirrored in the pioneering work of Josef Issels, MD, which is described in his book Cancer: A Second Opinion.31 His vast experience in managing cancer patients resulted in his conclusion that integrative cancer
therapy employing a personalized approach to managing diet, lifestyle, and the patient's environment were critically important in improving patient outcome. Michio Kushi developed his macrobiotic dietary approach to cancer prevention and treatment upon the same principles of a patient-centered dietary and lifestyle intervention program that adjusts the patient's distorted physiology and doesn't just focus on treatment of the cancer itself. Long-term follow-up studies of breast, prostate, and colorectal cancer survivors have demonstrated that those who follow a personalized home-based controlled diet and exercise intervention program have improved functional outcomes. It is recognized that primary care in the early phase of cancer treatment has a marked effect that results in both reduced mortality risk and improvement of prognostic indicators of disturbed physiological functions associated with cancer. The influence of these interventions on the "oncogenic potential" of the patient can be evaluated by following the specific biomarkers that relate to the physiological trajectory of the patient's phenotype.

SPECIFIC EXAMPLES OF HOW THIS MODEL IS APPLIED TO MANAGING CANCER AS A CHRONIC ILLNESS

An example of this approach relates to the recognition that individuals with insulin resistance/hyperinsulinemia and the resultant type 2 diabetes are at an increased risk for cancer. Insulin is a hormone that stimulates cellular proliferation. It is now recognized that both hyperinsulinemia and the therapeutic use of certain analogues of insulin may promote excessive stimulation of IGF-1 receptors and trigger mitogenic cellular responses. In women, IGF-1 and estradiol and its 16-hydroxy metabolites have been found to multiply their effect on proliferative changes in breast tissue, resulting in increased oncogenic potential. This suggests that evaluation of the patient's insulin sensitivity is important in evaluating oncogenic potential and the sensitivity to therapy in both breast and colon cancer.

It is interesting to note that the association of disturbed insulin signaling and oncogenic potential also relates to the observed connection between the peroxisome proliferator activated receptor (PPAR) gamma agonist medications and their therapeutic influence on colon cancer. Epidemiological studies have indicated that hypertriglyceridemia associated with insulin resistance is related to colon cancer. The PPARs may play a central role in lipid and glucose metabolism and the risk for colon carcinogenesis. Extensive work has demonstrated that the PPAR gamma agonist family of thiazolidinedione medications can reduce the risk of colorectal cancer through their role in modulating aspects of insulin action.

It is also interesting that CD36 is a tissue marker for immune inflammatory activation and the oxidation of LDL is a marker for cardiovascular disease as well as a tumor marker. This demonstrates the important connection between arterial inflammation, immune system activation, and both atherosclerosis and cancer. This once again points to the importance of defining the physiological state function as the "soil" in which the disease ultimately develops.

A second example of the application of this systems biology approach to the management of oncogenic risk relates to gastrointestinal cancers associated with inflammatory bowel disease and its relationship to celiac disease. It has become very well known that celiac disease is associated with genetic polymorphisms of HLA-DQ2 and DQ8 and presents with intestinal lymphogenesis and increased gastrointestinal cancer risk. Mechanisms of oncogenesis and carcinogenesis have been proposed for the relationship between intestinal inflammation and celiac disease. The gastrointestinal-associated mucosal immune system represents more than 50% of an individual's immune system, and specific types of chronic inflammatory activation of this system are associated with increased oncogenic risk. Activation of the inflammatory process within the gastrointestinal system can be determined by evaluating gastrointestinal mucosal permeability with the lactulose/mannitol challenge test or the use of fecal calprotectin analysis. Calprotectin is a protein produced by mucosal-associated immune cells that reflect in situ activation of inflammatory processes. The elimination diet is the traditional treatment recommended for the patient who has been discovered to have his or her gastrointestinal immune system activated by a food-related substance such as the gluten family of proteins in cereal grains. It has been reported recently that certain cultivars of wheat may contain more antigenic proteins than others, and therefore the increasing prevalence of gluten sensitivity may be due to altered plant genetics or posttranslational modification of the gluten proteins that have made them more haptenic. The adage of "food of one is a poison of another" seems very well supported when evaluating the connection among gluten, immune activation, and gastrointestinal cancer. It has been reported that germinating the wheat and activating specific proteases in the grain may lower the immune-activating effects of the wheat through the breakdown of specific immune-activating protein sequences. It has also been reported that certain strains of enteric Bifidobacterium lactis inhibit the immune-activating effects induced by wheat gluten through their influence on the gastrointestinal immune system. The conclusion of this example is that by evaluating the specific immune sensitivity of the patient to a common environmental immune inflammation activator (eg, gluten), a program to reduce the inflammatory oncogenic burden on the patient's gastrointestinal tract can be personalized to his or her specific needs.

A third and final example of the impact on disease outcome by managing the patient's disturbed physiology and not just the cancer itself is that of prostate cancer. In 2005, Ornish et al reported on the results of interviews of men involved in the Prostate Cancer Lifestyle Trial (PCLT) in which men with biopsy-proven prostate cancer with a Gleason score <7 indicated a positive attitude about entering the lifestyle intervention program as opposed to "watchful waiting" as the standard of care. In 2006, a research group from the University of California at San Francisco Medical Center reported that the PCLT group had a significant reduction in PSA levels as compared to the watchful waiting control group, which had elevated PSA levels. The growth of LNCaP prostate cancer cells in culture was inhibited almost eight times more by serum from the PCLT group of patients vs the controls, and these positive outcomes were directly related to the degree of changes in diet and lifestyle. It was further reported that men who made the most significant changes in their diet and lifestyle had the greatest
improvements in their quality-of-life indicators. The dietary program incorporated in the PCLT employed a higher intake of soy foods containing isoflavone phytonutrients and was shown to result in higher levels of IGF-BP-1, which lowers the amount of available IGF-1 with a resultant influence in lowering the oncogenic potential.

A 2-year follow-up study of the PCLT study participants demonstrated that patients with early indicators of prostate cancer who choose a personalized lifestyle medicine program might be able to improve their physiological status and avoid or delay conventional treatment. In examining the patients on the lifestyle therapy, it was found that there was a statistically significant increase in telomerase activity and consequently telomerase maintenance capacity in human immune system cells. Gene expression profiles were obtained from 30 of the participants in the PCLT, pairing messenger RNA samples from control prostate needle biopsy samples taken before intervention with lifestyle therapy to mRNA from the same patient's 3-month postintervention biopsies. Two-class paired analysis of observations of global gene expression using significance analysis of microarrays detected 48 upregulated and 453 downregulated transcripts after the intervention. Pathway analysis identified significant modulation of disturbed biological processes related to tumorigenesis, intracellular tracer protein, and traffic kinase–activated phosphorylation in the lifestyle intervention group. The conclusion of this study is that intensive lifestyle intervention modulates gene expression in the prostate and is associated with the phenotypic indicators of reduced burden of disease.

It is important to point out that in all three of these examples the approach was not to target the specific cancer for therapy but rather to alter the disturbed physiological functional status that is associated with increased oncogenic potential.

Viewing cancer as the outcome of specific types of disturbed physiological function associated with its etiology rather than as a disease that is defined by its pathology allows for the management of cancer as a chronic disease through the appropriate therapy personalized to the patient. This approach relies upon a systems biology approach to conceptualization of the origin of the patient’s cancer and linking genotypic markers with traditional cancer screening tools and biomarkers of disturbed physiological networks to follow the success of therapy.

REFERENCES