

Systems Modeling in Integrative Oncology

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Abstract

Systems modeling provides an integrated framework to capture and analyze diverse and multidisciplinary data in a standardized manner. The authors present the Integrative Oncology Systems Model (IOSM) to help assess the impact of behavior modification and various therapeutic interventions on cancer development and progression and the resultant effect on survival and quality of life outcomes.

Keywords

cancer, prevention, recurrence, progression, systems modeling, systems dynamics, integrative oncology, integrative medicine, complementary medicine

Integrative oncology is the approach to oncology that combines conventional interventions (ie, surgery, radiation, chemotherapy, etc), nonconventional modalities (ie, acupuncture, massage, meditation, etc), and behavioral/lifestyle education to help patients improve their quality of life (psychological, spiritual, and physical) and disease-specific outcomes and prevent disease. Integrative oncology is personalized medicine that takes into account each individual's unique circumstances and disease process to customize treatment programs. The concept of integrative oncology creates the significant challenge of trying to understand the complex relationships and effects of numerous dynamic, interdependent parameters (eg, psychosocial and biological factors, comorbidities, treatments, etc) that occur before, during, and after a diagnosis of cancer.

The Society for Integrative Oncology's recently formed Integrative Oncology Systems Modeling Working Group is developing the Integrative Oncology System Model (IOSM), an integrated framework to capture and analyze diverse and multidisciplinary data in a standardized manner. The IOSM is based on both analysis and empirical data and will eventually be used to simulate how various interventions and behavioral changes might dynamically modulate cancer-specific and other health-related outcomes. The IOSM is in the earliest stages of development and, currently, is only a visual/graphical representation of the complexity of a whole systems approach to integrative cancer care. At this time, the present version of the IOSM can be used as an educational tool to demonstrate potential

interactions among numerous parameters that may affect outcomes. As the IOSM becomes more sophisticated and robust, we expect that it will become a helpful tool for tailoring individualized integrative oncology recommendations for our patients.

Introduction to Biological Systems Modeling (BSM)

Systems models can be qualitative and/or quantitative representations of the system under study that are designed to assess how changes in parameters may affect outcomes. Systems modeling is an approach for developing models that can be used to assess the interactions of parameters within a complex system to better understand how changes in any variable (or parameter) modulate the overall direction of the system.¹ This methodology was first described by Forrester in *Industrial Dynamics* in 1961.² Groups such

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as the System Dynamics Society,³ the Center for Disease Control and Prevention's Syndemic Prevention Network,⁴ and others continue to advance the BSM field. Since the 1970s, BSM has been implemented to enhance our understanding of numerous complex health problems (ie, cardiovascular disease, diabetes, HIV/AIDS, etc) and to help project ways in which various interventions and public policies may improve outcomes.¹

These models consist of an underlying set of equations that are derived from measured and experiential data.⁵ Whenever possible, the assumptions inherent in the model are evidence-based; however, inclusion of parameters in which limited or no data exist is often a critical first step in identifying potential critical parameters.⁵ In the absence of strongly supporting data, if the subject matter experts agree that a particular variable is likely important, it may be incorporated into the model. Attempts to quantify these parameters is done by taking into account all available information and assigning greater weighting in the following preferential order: recorded measurements, inference from recorded data, logic, educated guesswork, or adjustments needed to provide a better simulated fit to history.^{5,6} Calibrating and establishing confidence and reliability in the model is accomplished by testing and refining the model until it satisfies numerous requirements: realism, robustness, flexibility, clarity, ability to reproduce historical patterns, and ability to generate useful insights.^{2,5,7}

BSM is an evolving, iterative, and collaborative process (hypothesis generation, causal diagramming, quantification, reliability testing)⁵ that uses a model in which modifications to the structure, parameters and connections of the biological system can be easily made. Ideally, the models are scalable, so that one can either zoom in or zoom out to examine varying degrees of detail and to demonstrate narrower or broader perspectives of the overall system and its relationship with adjoining systems.

Adopting a standardized BSM approach offers the following benefits: (1) The community can establish a common language for capturing, sharing, and analyzing the results of diverse studies and analysis; (2) a BSM can be better supported by software tools that can capture the information in a more formal manner (compared with informal diagrams in a word processing document); (3) the information in the model is repository based, allowing it to be queried and readily scalable to accommodate increasing levels of detail; (4) a robust modeling language can integrate multiple views of the biological system (ie, static parametric models, signal pathways, and anatomical relationships); and (5) a modeling standard can be maintained through an organization that specifies standards (ie, the Object Management Group⁸) to meet the evolving needs of the community.

A general purpose graphical modeling language, such as the OMG SysML, is the Systems Modeling Language adopted

by the Object Management Group⁸ to specify, analyze, and design complex systems. SysML includes basic block diagramming constructs for describing systems in terms of the system components, the interaction between the components, and their performance and physical characteristics.^{8,9} With customization, SysML could provide a standard and robust language for describing human system physiology at the system to cell level in terms of their constituent biological components, interactions, and behaviors as well as performance and physical characteristics. This allows investigators to focus on various aspects and levels of abstraction in the system, to explore potential interactions, and to integrate published data into the modeling framework. In addition to SysML, other BSM tools are available, such as the SBML (Systems Biology Markup Language), which was developed through an international collaborative effort among multiple organizations.¹⁰ Regardless of the specific modeling language or tool that is used, a community of subject matter experts should be formed to develop a common language for capturing, sharing, and analyzing systems biology processes and data.

Application of Systems Modeling to Integrative Oncology

The ability to make reliable, safe, and effective integrative oncology care recommendations is challenging for many reasons (ie, lack of pertinent studies, poor study designs, inadequate statistical power, conflicting study results, etc). Much of the evidence is based on a simplistic, reductionist model of single interventions rather than a whole systems approach. Furthermore, each individual is uniquely defined by a complex set of dynamic, interdependent psychosocial, biological, and treatment parameters that are redefined at each stage of their disease process (ie, before, during, and/or after their diagnosis of cancer). The interactions between these parameters may lead to significant affects on cancer-specific and other outcomes. To address these challenges, the Society for Integrative Oncology recently established the IOSMWG. The main objectives for the IOSMWG are as follows:

1. A community of cross-disciplinary experts—psychologists, neurophysiologists, biologists, oncologists, nurses, bioinformaticians, statisticians, oncology nutritionists, and health care economists—should be created, who will work through a standards committee to develop a common language for capturing, sharing, and analyzing systems biology processes and data. Numerous systems biology collaborations have been established and can play a significant role in establishing and guiding this standardization effort.¹¹

2. A reliable and integrated systems model(s) should be developed for the following purposes:
 - to help researchers better understand the complex biological and psychosocial interrelationships among various parameters that may be involved in pathways leading to cancer development, progression, and recurrence;
 - to provide an integrated framework to capture and analyze diverse and multidisciplinary data;
 - to identify knowledge gaps and thereby help focus future research efforts;
 - to help providers develop tailored integrative oncology recommendations and simulate how they affect outcomes;
 - to estimate the economic impacts of implementing various interventions and health behavioral changes; and
 - to support education in the interactions of complex biological systems.

To reach consensus on each stage of the BSM process, we are using the Delphi technique.^{12,13} This method uses repeated rounds of systematic questioning, including feedback to responses gathered during previous rounds, to develop consensus. The compiled responses from each round are circulated back through the process 3 to 4 times to each member privately for consensus development. Experts then reconsider their initial positions in light of the group trends and make any adjustments and comments felt to be appropriate. The final result is an informed consensus insulated from the forces of face-to-face group or individual interaction.¹⁴ Because the individual responses are kept anonymous, there is little chance of a panel member being influenced by the opinions of other members of the group. One of the advantages of the Delphi technique is that the expert participants are more likely to generate thoughtful and independent opinions in the absence of exposure to the “persuasively stated opinions of others.”¹⁵ Each round is conducted via anonymous Email communication with the panel coordinator. This both helps maintain anonymity and minimizes the participants’ commitment in terms of time and travel.

Contributions to each systems model are made by the consensus of so-called experts. The experts’ primary evidence source is from systematic reviews of clinical trials, using the Jadad Scale.¹⁶ Because the highest level of evidence is not always available, expert analysis using a Delphi consensus model is used to provide the “best” evidence available. Future iterations can strengthen the confidence in the weighting between linked inputs and outcomes. This system of providing the best evidence available concurrent with expert feedback is similar to the practice guidelines loop model developed by Browman et al.¹⁷ However, the systems model is more complex because it integrates multiple

components using both preclinical data as well as clinical trials outcomes. We believe that the systems model contains greater external validity because it deals with real life complexities.

The Delphi method is a systematic, interactive forecasting method, which relies on a panel of experts.¹⁸ The experts selected for the Delphi technique are chosen by consensus from practitioners and researchers in the specific field of interest. This is similar to the selection of experts who derive practice guidelines. In our initial model, selected experts were practitioners and researchers in integrative oncology. We admit that this may introduce some bias in the process. The experts answer questionnaires in a number of rounds, the facilitator providing an anonymous summary of the experts’ forecasts after each round. The experts are encouraged to revise their earlier answers in light of the replies of other members. In view of the subjective nature of part of the process, we agree that weightings can vary depending on individual opinions. We agree that in areas such as science, forecasting the degree of uncertainty is so great that exact and always correct predictions are impossible, so a high degree of error is to be expected. However, we also expect the variation to diminish as objective evidence is derived from clinical studies. The expression of systems analysis can be improved by weighting each connection within the network with a confidence measure that expresses the relative contributions of opinion, preclinical data, and the various strengths of clinical trials. We believe that some data, even weak, is better than no data at all and may provide pragmatic guidance in the context of multiple data inputs.

The first iteration of our Delphi panel was limited to a small group of experts from the Society for Integrative Oncology as well as invited academic and clinical colleagues. Establishing a community of subject matter experts is essential in BSM. Future panel experts will include recognized leaders in relevant fields (eg, radiation oncology, medical oncology, surgical oncology, oncology nursing, naturopathy, nutrition, psychology, traditional Chinese medicine, Ayurveda, massage therapy, and biostatistics) who are renowned national and international lecturers, authors, and educators. It is crucial to select experts from different areas of specialization because they offer unique perspectives of the problems, hypotheses, model structure, and causal relationships, leading to a cross-disciplinary synthesis of data.

Integrative Oncology Systems Model (IOSM) Overview

Our group has developed the IOSM (Figures 1, Figure 2, available online at <http://ict.sagepub.com/>; see appendix for further details on examples of parameters included within the IOSM domains and subdomains), a draft model to illustrate how complex interrelations can represent the impact of

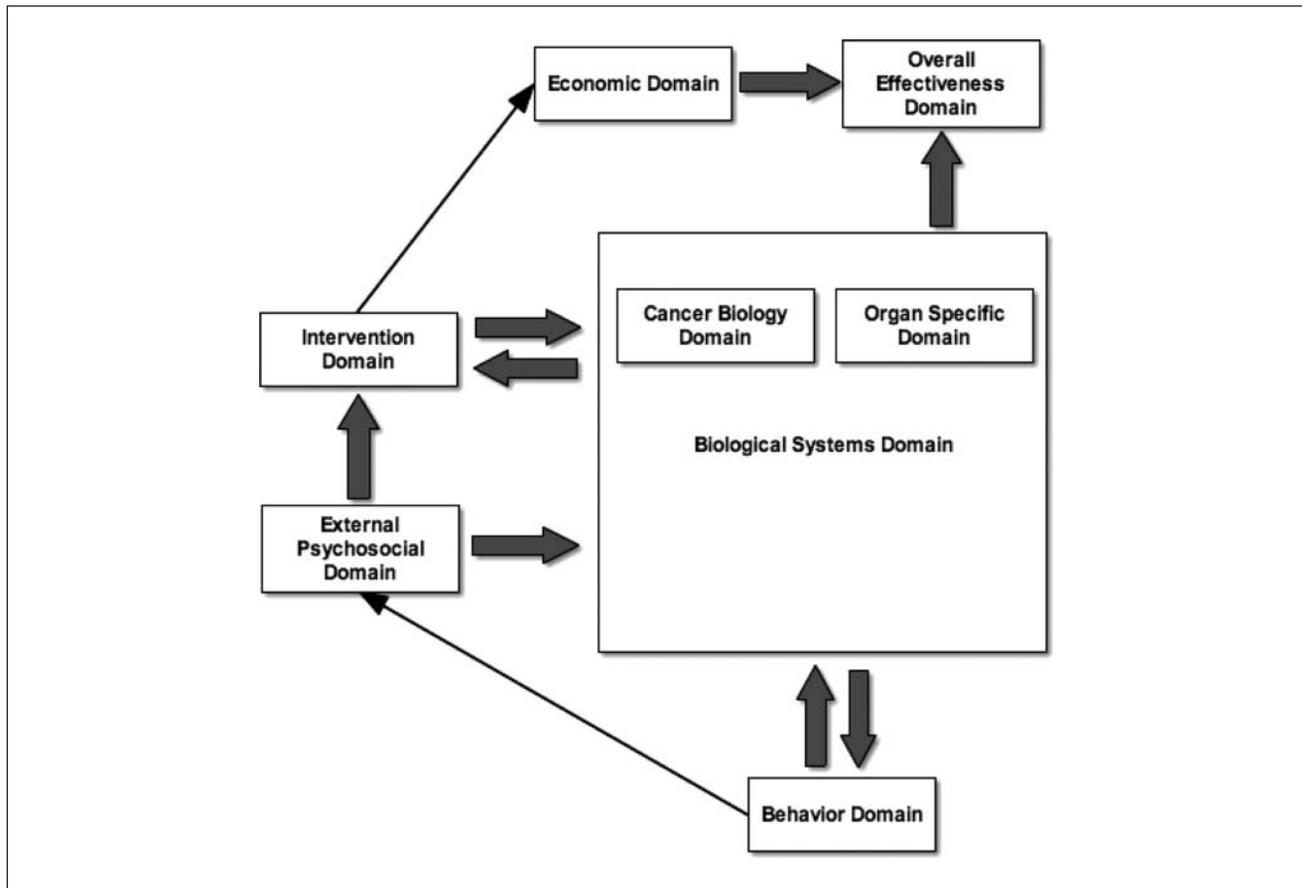


Figure 1. Integrative Oncology Systems Model, top level view (basic structure)

multiple variable parameters on cancer-related outcomes. The goal of this initial effort is to demonstrate a modeling approach that can serve as an abstract integrating framework to relate multiple detailed models and empirical data to one another. Eventually, the IOSM will be able to incorporate numerical data, so that quantitative predictions of outcomes can be calculated. Furthermore, we envision the use of the IOSM as a structural framework for helping researchers and clinicians develop an extensive database of information from patients around the world that can be used to test, validate, and modify future versions of the model. Patients will eventually be able to enter information (ie, details of their cancer, lifestyles/behaviors, treatments, side effects, comorbidities, etc) into an online program that will analyze these data and generate individualized recommendations and outcome information based on a whole-systems integrative cancer care approach that is specific to them.

The initial draft of the IOSM is not intended to be complete or accurate but merely to highlight the modeling approach. The IOSM currently represents one view of a system that can be represented in SysML. Other SysML views can be leveraged in the future.

The IOSM is based on the hypothesis that behavioral and lifestyle modifications (ie, improving nutrition, reducing stress, and increasing physical activity, etc) can cause biological changes that may influence the risk for cancer development and progression as well as other health problems (ie, cardiovascular disease, diabetes, etc).¹⁹ Furthermore, the effects of the cancer and/or its treatment can lead to serious medical complications and exacerbation of existing comorbidities and adversely affect healthy behaviors and lifestyles. These changes also influence parameters in the systems model (eg, cancer treatment→neuropathy→reduced physical activity→weight gain→deep vein thrombosis→lethal pulmonary embolism). One of the roles of an integrative oncologist is to identify these issues and make recommendations (ie, a combination of pharmaceutical, physical, psychological, and behavioral/lifestyle interventions) that may prevent these and other adverse outcomes. Capturing the complex interdependent relationships among various parameters is one of the principles used in BSM to develop the systems model.

Figure 1 shows the basic structure of the IOSM that includes a Biological Systems Domain with subdomains

for organ-specific physiology/pathophysiology and cancer biology. The IOSM incorporates an Intervention Domain, with subdomains (not shown) for conventional and nonconventional approaches for treating cancer and/or mitigating the untoward effects of cancer and/or treatment as well as behavioral counseling interventions (ie, smoking cessation, dietary counseling, etc). Additionally, the intervention domain includes a subdomain for diagnostic screening exams used to identify precancerous/cancerous conditions.

The IOSM also includes an External Psychosocial Domain, which represents a variety of parameters that introduce external stressors that may influence parameters within the Biological Systems Domain. Finally, the IOSM incorporates a Behavior Domain with subdomains (not shown) for specific behaviors (ie, diet, physical activity, smoking, etc) that may affect biological systems and lead to the development and progression of cancer. These domains interact with each other and modulate top level effectiveness measures related to survival and quality of life.

Figure 2 (see the magnified view at <http://www.integrativeonc.org/model/>) is the IOSM as it appears in the modeling tool (SysML). It includes each of the domains along with their parameters. (appendix describes examples of parameters included within the IOSM domains and subdomains.) Each domain is represented by a graphical node in the model. A domain, such as the Nervous System Domain or Inflammatory Response Domain, is an abstraction of a set of relationships among the parameters, such as the relationship between a growth hormone level and the tumor burden level in the Cancer Progression Domain. The tumor burden level is the representative output parameter for the Cancer Progression Domain. The other parameters contribute in some way to this output parameter.

Many of the domains have one or more parameters that correspond to a response level (eg, immune response level, tumor burden level, physical activity level, etc) that is a quantitative or qualitative measurable value, derived from the composite effects of other parameters on the domain and across domains. The concept of a measurable response level is unique to BSM and will one day allow researchers and clinicians to quantify (using an evidence-based formula) the effects of parameter modification on the system. Treatment level is an aggregate representation that refers to any of a number of different interventions that may be implemented. Future IOSM versions will incorporate specific intervention subdomains and corresponding treatment levels.

At this time, based on the limited quantitative and/or qualitative data available to input into this model, the *level* remains a conceptual value. As more data become available to add into the model, the interrelations between domains and the effects of the parameters on the domain levels will become more robust and will move us closer to being able to accurately calculate both the *level* values and the strength

of validity among the interparameter relationships. The lines connecting each domain establish equality between the parameters in the respective domain. The arrows indicate direction of causality by showing an output parameter from one domain connecting to an input parameter in another domain. These abstract relationships can be specified by more detailed models, which include mathematical equations that might appear in a dynamic simulation model, or by empirical data. Future versions of the IOSM will elaborate the model with additional views of the biological system (ie, structural views such as the composition and taxonomy of the different physiological systems, behavioral views of the system that highlight specific interactions and signal pathways, etc).

Diet and Nutrition in Integrative Oncology

Within the Behavior Domain are subdomains that represent dietary factors, such as the Nutrient Domain (Figure 2), which include a complex array of parameters that have been postulated to modulate risks for developing specific cancers and cancer recurrence/progression. Many plants and foods are exceptional sources of nutraceuticals, molecules that have been shown to prevent cancers from developing and/or progressing.²⁰ These compounds may work independently and/or synergistically with other compounds to target a variety of anticancer functions, including angiogenesis inhibition, tumoral invasion and metastasis inhibition, growth factor–receptor inhibition, inflammatory enzyme inhibition, transcription factors inhibition, chemotherapy medication resistance inhibition, antiestrogens, immune system modulation, cellular signal cascade inhibition, toxicity toward cancer cells, cancer cell cytoskeletal perturbation, toxin metabolic action inhibition (ie, via cytochrome P450, etc), and so on.²⁰ Theoretically, by eating a diverse diet rich in foods containing a variety of anticancer compounds, an individual is establishing a tissue microenvironment that is not conducive to tumor cell growth. Furthermore, limiting certain foods or preparations (ie, red meats, smoked/barbequed meats, foods with nitrites, saturated fats, and omega-6 fatty acids, etc) may reduce the risk of developing cancers.²⁰

Numerous studies of varying degrees of quality and reliability have investigated the affects of dietary intake of various macronutrients (lipids, proteins, and carbohydrates) and micronutrients (phytochemical compounds, fibers, vitamins, and minerals) on risks of cancer outcomes, tissue microenvironment and intratumoral changes, and modulation of inflammatory, endocrine, and immune factors. Through the Delphi method, these data will be critically assessed to determine their level of weight and relevance in the model. SM will need to account for the specificity of different cancer subtypes and the conditions and stage at which these parameters coexist within the system (ie, individuals

with cancer-induced cachexia will have different nutritional requirements from those who are in remission). One suggestion may be to create variant system models for each cancer subtype and stage of disease. Although this significantly increases the complexity of the model, it may be necessary for developing quantifiable domain levels.

Psychosocial Factors in Integrative Oncology

The External Psychosocial Domain includes multiple stress-related parameters that when factored together (defined by a psychosocial stress level) may influence changes within the nervous system.^{21,22} These effects have been shown to affect the neuroendocrine, immune, and inflammatory systems and may eventually lead to complex physiological changes that may increase susceptibility to cancer development, recurrence, and progression.²³ Although many epidemiological studies identify psychosocial stressors as potential risk factors in the development of malignancies, this remains an area of controversy.^{24,25} Several thorough review articles have been published on this topic,^{23,26-29} including a recent meta-analysis of 165 studies, which indicate that stress-related psychosocial factors are associated with an increased cancer incidence.³⁰ This hypothetical association is supported by a recent randomized controlled trial reporting that women with breast cancer who are taught strategies to reduce stress, improve mood and health behaviors, facilitate cancer treatment compliance, and ensure medical follow-up have significant reductions in the risk of breast cancer recurrence (hazard ratio [HR] = 0.55), death from breast cancer (HR = 0.44), and death from all causes (HR = 0.51).³¹

The definitive answer as to whether psychosocial stress influences the risk for carcinogenesis and subsequent survival from cancer is not known. Although promising data suggest that efforts to reduce psychosocial stress may affect cancer-specific outcomes, there is little doubt that many of these interventions greatly improve quality of life.^{30,32-34}

Individuals living with and beyond a diagnosis of cancer are frequently affected by various untoward psychosocial symptoms that affect their quality of life (ie, fatigue, sleep quality/quantity, anxiety, depression, etc). What is important is that treatment and follow-up compliance have been reported to be significantly worse in patients experiencing distressful psychosocial symptoms.³⁵⁻³⁷ It is quite possible that treatment outcomes could be reduced in these patients as a consequence. The IOSM not only demonstrates the complex relationships that modulate these psychosocial symptoms, but it also highlights how various therapies may help in mitigating them. We provide a few examples below:

- increased physical activity may reduce cancer-related fatigue and sleeping difficulties and

- massage, yoga, meditation, and acupuncture may reduce stress, anxiety, and depression.

Physical Activity in Integrative Oncology

Numerous studies support the association between physical activity and improved outcomes in individuals prior to and after a diagnosis of cancer (ie, reduction in cancer development, progression, recurrence, and survival rates).³⁸⁻⁴¹ Exercise causes physiological and psychological changes that have been postulated to explain these positive effects (eg, reduction in tumor-stimulating growth factors, reduction in estrogen, reduction in oxidative stress, increase in immune function parameters, reduction in inflammatory molecules, improvements in sleep function and fatigue, and reduction in anxiety and depression).⁴²⁻⁴⁷

In the IOSM, physical activity is represented as a subdomain within the Behavior Domain. The physical activity level parameter (within the Physical Activity Domain) defines the individual's ability to perform physical activity. This subdomain comprises parameters that further characterize the details of the activity: the time ("when") in which the exercise was initiated (ie, before, during, or after a cancer diagnosis), the type of activity (ie, walking, resistance exercise, etc), the volume (ie, total weekly dose), and fractionation (ie, weekly frequency, intensity, and duration).

The physical activity level influences other subdomains within the Biological Systems Domain (ie, Cardiovascular Domain, Pulmonary Domain, Nervous System Domain, etc), and they are affected by other coexisting factors (ie, cancer treatments, cancer effects, nutritional state, etc). A vast amount of research has been published on the individual effects and mechanisms supporting these complex interactions. These data will need to be vetted through subject matter experts and incorporated into the model, based on consensus opinions. As new data emerge, they will be considered for future versions of the model.

Conventional and Nonconventional Therapies in Integrative Oncology

Integrative oncology incorporates the best therapies, conventional and/or nonconventional (these subdomains are represented within the Intervention Domain), when addressing various health-related issues. During the active phase of cancer treatment, this often includes the most common conventional oncological therapies: surgery, chemotherapy, and radiation therapy. A variety of therapies can be used during this phase to help ameliorate the side effects of treatment, psychoemotional symptoms, and/or symptoms from the cancer itself. In lieu of, or in addition to, conventional pharmacological therapies, integrative oncology providers may recommend evidence-based nonconventional therapies (ie, acupuncture, yoga, massage, meditation, guided imagery,

etc) during and after the active phase of cancer treatment for treating many of these symptoms. Nonpharmacological interventions may be preferable to pharmacological agents as they often have no untoward side effects, and there is no risk of drug–drug interactions with other pharmacological therapies.

These therapies (conventional and nonconventional) affect many domains within the IOSM and may interact with parameters in multiple domains (ie, both acupuncture and chemotherapy may cause changes within the Inflammatory Response Domain, Nervous System Domain, and Endocrine Domain, etc).

Because of the complex and dynamic interactions among the effects of treatments on the body and mind, deciding which therapies to recommend is among the more difficult challenges in integrative oncology. We expect BSM to be a useful tool for helping providers and patients simulate the effects of implementing different therapies at different stages of the cancer cycle (ie, cancer prevention, during/after cancer diagnosis/treatment).

IOSM in Practice: A Patient Case

The IOSM can be used as a visual aid to demonstrate to patients and providers how an individual's behaviors, lifestyle, biology, genetics, external stressors, and therapeutic/screening interventions might impact various domains and parameters throughout the model.

Example Case (Mary)

Mary is a 67-year-old female with a new diagnosis of invasive breast cancer. A suspicious, 1.8-cm spiculated lesion was detected by her annual screening mammogram, which led to additional mammographic and ultrasound studies and a stereotactic core biopsy. The pathology demonstrated invasive ductal carcinoma, moderately differentiated, associated with high-grade ductal carcinoma-in-situ; estrogen and progesterone receptors were strongly positive, and HER-2 neu was not overexpressed. A week later, the hospital's multidisciplinary tumor board reviewed the details of her presentation, physical exam, past medical history, family medical history, social history, pathology, and radiographic studies.

The tumor board recommended that Mary should be offered either breast-conserving surgery (lumpectomy and sentinel lymph node biopsy) or a modified radical mastectomy. Upfront chemotherapy (neoadjuvant) was also discussed as an option to assess the response of her tumor to chemotherapy. The following therapeutic management options were discussed and would be selected based on the pathological findings from her surgery:

- completion axillary lymph node dissection (if the intraoperative frozen-tissue evaluation of the

sentinel lymph node identified metastatic cancer; a more extensive dissection of axillary lymph nodes would be done during the same operation);

- adjuvant radiation therapy (if she underwent lumpectomy, she would be offered postoperative adjuvant breast +/- regional lymphatic irradiation; if she underwent mastectomy and had a positive surgical margin or positive axillary lymph node, she would be offered postoperative adjuvant chest wall +/- regional lymphatic irradiation);
- adjuvant chemotherapy (if she had any positive lymph nodes, she would be offered adjuvant chemotherapy; chemotherapy regimen would depend on the choice of the medical oncologist);
- adjuvant aromatase inhibitor (AI; because her estrogen receptors were strongly positive, she would be offered a 5-year course of adjuvant AI therapy.)

She opted for lumpectomy and sentinel lymph node biopsy. Intraoperative frozen-tissue analysis of the sentinel lymph node identified 1 out of 2 involved lymph nodes with metastatic breast cancer; therefore, a completion axillary lymph node dissection was performed (0 out of 8 additional axillary lymph nodes were involved with cancer.) The final pathology demonstrated a 2.1-cm moderately differentiated invasive ductal carcinoma associated with 1.5-cm of high-grade ductal carcinoma-in-situ; all margins were negative. The stage was a 2B, pT2N1aM0 (CT scans of the chest, abdomen, and pelvis did not identify any evidence of metastatic disease).

Her case was re-presented at the tumor board, and they recommended adjuvant chemotherapy (4 cycles of adriamycin and cytoxan) to be followed by adjuvant breast (and supraclavicular nodal) radiation therapy. At the completion of radiation therapy, she would begin a 5-year course of an AI.

Mary's surgeon referred her to a medical oncologist who reviewed with her the recommendations of the tumor board. During this visit, her medical oncologist opened up a computerized version of the IOSM that walked both of them through various parameters and domains that pertained to Mary. The IOSM software prompted her to answer multiple questions regarding her cancer details (ie, stage, type, etc), treatments (ie, surgery type, extent of lymph node surgery, chemotherapy type/regimen, radiation therapy type/regimen/breast +/- regional lymphatics, etc), and assessment of stressors/lifestyle/behaviors and physical factors (ie, body mass index, comorbidities, performance status, etc). Based on her answers, the IOSM calculated survival and recurrence percentages (not dissimilar to what can be calculated using online calculators, such as Adjuvant Online). The unique aspect of the IOSM is that it demonstrates to the user how following various recommendations may affect multiple outcomes (ie, displaying

up or down arrows, hazard ratios, percentage changes, etc). For example,

- Achieve a healthy body mass index (ie, 20-25)
 - may reduce breast cancer recurrence
 - may improve survival
 - may reduce the risk of dying from or exacerbating noncancer comorbidities (ie, cardiovascular disease, diabetes, etc)
 - may reduce plasma estrogen, insulin and IGF-1, proinflammatory cytokines, and so on
- Increase physical activity levels (ie, walk 30-45 minutes per day, 5 days per week)
 - may reduce breast cancer recurrence
 - may improve survival
 - may reduce the risk of dying from or exacerbating noncancer comorbidities (ie, cardiovascular disease, diabetes, etc)
 - improves overall quality of life
 - improves cardiovascular performance
 - improves flexibility
 - helps maintain/build muscle mass and bone density
- Learning/practicing methods to reduce stress
 - may improve overall quality of life
 - reduces pain, anxiety, depression, sleeping difficulties, and fatigue
 - may reduce the risk of breast cancer recurrence and death
- Limit alcohol consumption (0-2 drinks per day)
 - may decrease the risk of breast cancer recurrence and death
- Continuing to undergo yearly diagnostic mammograms after treatment
 - may identify an in-breast recurrence at an early stage, which increases the success cure rate of salvage mastectomy
- Increasing dietary intake of vegetables, fruits, and nuts and decreasing intake of saturated fats and simple sugars
 - may reduce the risk of breast cancer recurrence
 - may reduce the risk of exacerbating noncancer comorbidities (ie, cardiovascular disease, diabetes, etc)
- Increase consumption of foods that are high in omega 3 fatty acids and low in omega 6 fatty acids
 - omega 3 fatty acids may reduce system inflammation and oxidation (both of which have been associated with anticancer physiological effects)
 - omega 6 fatty acids may increase systemic inflammation and oxidation (both of which have been associated with physiological effects that may lead to cancer development and progression)

- Supplement diet with adequate levels of vitamin D3 and calcium
 - may reduce the risk of osteoporosis (particularly in postmenopausal women, patients on AIs or androgen deprivation therapy, etc)
 - vitamin D3 may reduce the risk of cancer progression, recurrence, or development
- Undergo posttreatment assessments for identifying lymphedema
 - early identification and treatment of lymphedema has been shown to lead to increased treatment success rates

Future versions of the IOSM will eventually be able to demonstrate the complex interactions that occur throughout the model as individual parameters are modulated. This will help the user better understand the relative importance of following specific recommendations.

Discussion

It is important to note that the IOSM is a hypothetical construct based on evidence of varying degrees of quality and strength. This model is at the first stage of Delphi consensus. As future iterations of the IOSM mature, the evolving construct will gain sophistication and begin to account for specific tumor types and staging; tissue microenvironment parameters; immune, endocrine, and inflammatory factors; age; gender; genetic markers; psychosocial and behavioral factors; comorbidities, and so on. Eventually, this model(s) will incorporate parameters that are unique to the patients' disease timeframe (ie, before, during, or after cancer treatment) because these periods are often associated with distinctly different values for any one parameter (eg, nutritional state, performance status, etc). The inclusion of new data and studies will not be limited to randomized controlled trials but instead will incorporate the highest quality research available at the time (as assessed by the Delphi panel experts.)

The model also allows for weighting levels of evidence, adding/subtracting/rearranging the parameters and interrelationships, adding referenced data at any scalable level of the system, and defining interrelationships with other systems in the human body. In addition, SysML includes other views of the system that could potentially be leveraged to represent other complex physiological, psychological, and anatomical relationships. Live models can be updated with as many additional parameters as desired, and investigators will be able to select a parameter of interest or cross-parameter relationship to examine the supporting references, study details, and underlying equations. Future models will be scalable to examine effects/relationships at the parameter level (eg, study *x* reported that a defined increase in salivary

cortisol level causes a defined increase in vascular endothelial growth factor production, whereas increases in norepinephrine had no effect on vascular endothelial growth factor production). This type of scalable model will enable researchers to focus in or out at any level of the system to get a big picture or detailed view of any aspect of the biological system and help them identify potential areas of intervention using the principles of integrative oncology.

Although the integrative oncology literature looks promising in the ability of different interventions to improve behaviors and influence various biological systems subdomains, it is not clear which intervention (or combinations of interventions) are effective for improving cancer-specific outcomes. Furthermore, we do not know which interventions work on which patients and have modulating effects on which tumor types. These questions, among many others, will need to be studied in a methodical and systematic manner. To that end, implementing a BSM approach to the study of this complex topic is highly encouraged. Without a standardized methodology and common language to help investigators and clinicians collect, synthesize, and process data, it will be a monumental task to understand the relationships among all the unique parameters that may be involved.

The wide-reaching effects of integrative oncology interventions will become more clearly understood within the framework of an integrative whole-body-systems biology model. The IOSM will also help identify gaps to be filled by further research studies and analysis. Further investigation includes patient profiling and individualization of interventions. Future studies need to focus on defining the relative values of various packages of techniques tailored for individual patients and the timing of delivery within their cancer trajectory. This will require routine psychological profiling as well as a detailed history on lifestyle attributes such as exercise and nutrition. More sophisticated investigations, such as genomic, proteomic and biochemical status, will become important for individualization. To date, the majority of studies have been conducted on individuals with breast cancer, so more data are necessary to determine effectiveness of interventions for other tumor types. Future investigations should focus on the effects of each domain and their combined interactions as well as on their impact when combined with different personality traits, genetic parameters, and environmental factors.

Many organizations have already established clinical pathways for a wide range of topics: the National Comprehensive Cancer Network published recommended guidelines on the management of “cancer-related fatigue”⁴⁸; the Institute of Medicine published a report, in 2004, on “Meeting Psychosocial Needs of Women With Breast Cancer.”⁴⁹ The primary objective of these panels is to give best practices

recommendations that are safe and effective. Patients and clinicians do not need to wait until all questions have been answered before a therapy is offered.

The cancer survivorship period is a time in which behavioral and lifestyle changes may improve not only cancer-specific and quality-of-life outcomes but also improve the global health state. Systems models can be a useful educational tool to demonstrate how specific interventions and behaviors might be able to both reduce the risks of cancer recurrence and new cancer development and also reduce the risks of developing or exacerbating other medical problems. Eventually, as more data become available, systems models can be developed to study how multiple medical conditions are thought to be interconnected and how modifying specific parameters affects outcomes throughout the model. For example, systems models for diabetes, cardiovascular disease, and other health problems can all be linked together to demonstrate how behavioral changes (ie, dietary and physical activity behavioral/lifestyle modifications/interventions) that lead to a healthy body mass index may reduce the risk of developing or exacerbating these medical conditions.

Furthermore, systems models can be developed for individuals prior to any cancer diagnosis to help inform them of the factors that may be placing them at an increased risk for developing specific cancers. Systems models for cancer prevention may help our patients determine both the value of behavioral changes and what specific things they can do that might decrease these risks.

In the future, the IOSM will allow simulation to evaluate the cost effectiveness of programs (represented within the Economic Domain). Assuming the hypothesis that psychosocial stress is associated with cancer development and recurrence is valid, it is likely that providing stress-reducing interventions and behavior modification to at-risk individuals would be significantly less expensive than the costs of diagnosing and treating new or recurrent cancers. In terms of cost and benefits, Andersen et al³¹ reported that a 4-month intervention to reduce stress and improve mood and health behaviors in patients with a history of breast cancer significantly improved rates of cancer-specific survival, reduced recurrence, and improved overall survival. In 2002, Medicare paid approximately \$40K, \$41K, \$21K, and \$18K for just the initial care to treat each patient with lung cancer, colorectal cancer, breast cancer, and prostate cancer, respectively.⁵⁰ In one economic model, the annual productivity cost (based on estimated lost income) from cancer mortality was \$115.8 billion in 2000 and is projected to be \$147.6 billion in 2020. The authors found that a mere 1% annual reduction in lung, colorectal, breast, leukemia, pancreatic, and brain cancer mortality lowered productivity losses by \$814 million per year. Including the imputed earnings lost as a result of caregiving and household activity

increased the total productivity loss to \$232.4 billion in 2000 and to \$308 billion in 2020.⁵¹ Based on these figures, even if integrative oncology interventions only improve overall survival to a small degree, it is likely that the costs of their implementation would be worth the investment. As emphasized at the recently convened Institute of Medicine Summit on Integrative Medicine and the Health of the Public, modest changes in human behavior and lifestyle can lead to dramatic improvements in health outcomes (eg, cancer, cardiovascular disease, etc).⁵²

Future Directions

The next phase in developing and testing the IOSM will be for our group to examine how well it holds up against published data for the involved parameters. In the early stages, the IOSM will continue to evolve based on nonquantitative and reductionist hypothetical relationships between the included parameters.

One possible approach to testing the IOSM is to create a Web-based questionnaire that asks research participants (with or without a history of cancer) to provide answers to a wide range of questions (ie, demographics, lifestyle factors, stress level, diagnosis of cancer/type, treatments, outcomes, etc) that can be compiled in a database for future qualitative and quantitative modeling. The questions would be designed to explore the parameters and relationships within evolving iterations of the IOSM. Ideally, the research participants would be followed over time to collect additional data from them because they (and the model) are in a dynamic and evolving state.

Predicting complexity among parameters and relationships is the eventual goal of the IOSM; however, its clinical utility does not need to wait until it has been validated before it can be offered as a helpful educational tool for patients and providers. Although the entirety of the IOSM is not validated as a whole, limited components of the model can be used to visually/graphically demonstrate factual relationships as they pertain to important (albeit reductionist) aspects of integrative oncology. For example, we have proposed converting aspects of the IOSM into Web-based educational tools, such as risk calculators, to provide valuable predictive information based on data from published studies (ie, relative risk of breast cancer development/recurrence in relationship to physical activity level or body mass index.)

In our practice of integrative oncology, we recognize that a new approach to the evaluation of complexity will help us more clearly define the parameters by which specific modalities will be effective in bringing about important overall changes. Future research needs to be designed within the parameters of a whole-systems model that can restore the reductionist elements back into the pragmatic

realities of health care and provide the opportunity for measuring outcomes resulting from systematically defined input data.

Appendix

IOSM Detailed Contents

Intervention Domain (contains subdomains for conventional and nonconventional approaches for treating cancer and/or mitigating the untoward effects of cancer and/or treatment, behavioral counseling, and diagnostic screening to identify precancerous/cancerous conditions)

- Intervention Subdomains
 - Conventional Treatment Factors
 - Radiation Treatment Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Hormonal Treatment Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Chemotherapy Treatment Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Immune Treatment Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Surgery Treatment Domain (examples of parameters evaluated: type of intervention, extent of resection, when initiated, cost)
 - Nonconventional Treatment Factors
 - Acupuncture Treatment Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Spiritual Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Psychosocial Treatment and Counseling Domain (examples of parameters evaluated: type of intervention, frequency, duration, dose, when initiated, cost)
 - Diagnostic Screening Domain (examples of parameters evaluated: type of screening/test, frequency, when initiated, cost, sensitivity/specificity)

(continued)

Appendix (continued)

External Psychosocial Domain (represents various parameters that introduce external stressors that may influence parameters within the “Biological Systems Domain,” “Intervention Domain,” and “Behavioral Domain.”)

- (examples of parameters evaluated: personal income, health care access, social support level, other stress contributors)

Economic Domain (represents various financial parameters, which subsequently impact domains across the IOSM.)

- (examples of parameters evaluated: personal income, cost of treatment)

Overall Effectiveness Domain (represents various outcome parameters that demonstrate the effectiveness of modulating the value of any “downstream” parameter)

- (examples of parameters evaluated: economic impact, impact on caregivers, cancer recurrence, cancer specific survival, quality of life, overall survival)

Biological Systems Domain (contains subdomains for organ-specific physiology/pathophysiology and cancer biology)

- Biological Systems Subdomains:
 - Cancer Biology Subdomain
 - Cancer Development Domain (examples of parameters evaluated: histological type, nutritional status, physical activity level, alcohol consumption, smoking, genome factors, gastrointestinal motility, carcinogenic exposures, DNA repair capacity, DNA damage extent, antioxidant status, etc)
 - Cancer Progression Domain (examples of parameters evaluated: angiogenesis mechanisms, tumor invasion mechanisms, tumor proliferation rate, apoptosis rate, tumor cell adhesion mechanisms, growth factor receptor response, chemotherapy resistance mechanisms, etc)
 - Organ Specific Subdomain
 - Reproductive System Domain (examples of parameters evaluated: sex, age, menopausal status, pregnancy history, testosterone/estrogen levels, sex hormone-binding globulin levels, etc)
 - Adiposity Domain (examples of parameters evaluated: body mass index, central obesity, etc)

- Metabolic Domain (examples of parameters evaluated: physical activity level, metabolic homeostasis demand, etc)
- Gastrointestinal Domain (examples of parameters evaluated: GI motility rate, nutritional absorption capacity, calorie intake, etc)
- Endocrine System Domain (examples of parameters evaluated: insulin level, melatonin level, growth hormone level, cortisol level, central/peripheral nervous system response level, etc)
- Nervous System Domain (example of parameters evaluated: pain level, circadian regulation, neuropathy, proprioception, cognition, memory, mood, anxiety, motivation level, sleep, fatigue, personality traits, etc)
- Immune Response Domain (examples of parameters evaluated: natural killer cell activity, white blood cell count, macrophage activity, etc)
- Inflammatory Response Domain (examples of parameters evaluated: anti-inflammatory cytokine levels, pro-inflammatory cytokine levels, antibody levels, etc)
- Hematopoietic Domain (examples of parameters evaluated: red blood cell count, platelet count, erythropoietin level, etc)
- Genitourinary Domain (examples of parameters evaluated: erythropoietin production capacity, blood urea nitrogen level, creatinine level, glomerular filtration rate, protein absorption capacity, etc)
- Coagulation Domain (examples of parameters evaluated: PT, PTT, INR, bleeding time, etc)
- Skeletal Domain (example of parameters evaluated: bone density, bone fracture, etc)
- Integumentary Domain (examples of parameters evaluated: lymphedema, fibrosis, etc)
- Muscle/Tendon/Ligament Domain (examples of parameters evaluated: muscle endurance, muscle strength, flexibility, etc)
- Respiratory Domain (examples of parameters evaluated: physical activity level, smoking level, pulmonary function level, pneumonia, pneumonitis, pulmonary embolism, pulmonary fibrosis, etc)
- Cardiovascular Domain (examples of parameters evaluated: cardiac ejection fraction, physical activity level, cardiovascular fitness level, peripheral vascular disease, red blood cell count, etc)

Behavioral Domain (contains subdomains for specific behaviors that may affect or be affected by factors within the “Biological Systems Domain” and “External Psychosocial Domain” and lead to the development/progression of cancer and other outcomes)

- Nutrition Subdomain
 - Phytochemical Domain (examples of parameters evaluated: type of phytochemical consumed, frequency, duration, dose, when initiated, etc)
 - Fats Domain (not indicated on current model diagram)
 - Protein Domain (not indicated on current model diagram)
 - Carbohydrates Domain (not indicated on current model diagram)
 - Micronutrient Domain (not indicated on current model diagram)
- Alcohol Consumption Domain (examples of parameters evaluated: type, frequency, duration, dose, when initiated, etc)
- Physical Activity Domain (examples of parameters evaluated: type of activity, fractionation, volume, when initiated, motor performance levels, cardiovascular fitness level, etc)
- Smoking Domain (examples of parameters evaluated: type, frequency, duration, dose, when initiated, etc)

Authors' Note

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