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Integrative Oncology's 30-Year Anniversary: What Have We Achieved? A North American Naturopathic Oncology Perspective

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Abstract

In 1991 the U.S. Congress mandated that the National Institutes of Health (NIH) form the Office of Alternative Medicine to study alternative medical therapies, especially in oncology care. Shortly after, the National Cancer Institute (NCI) created its own division of complementary and alternative medicine (Office of Complementary and Alternative Medicine). At the genesis of the field 30 years ago, what were we hoping to see accomplished by now? In this article we take a look back at milestones, shortfalls and future directions. Exciting opportunities exist to direct our established subspeciality's future directions and we have made valuable advances the field of integrative oncology over the last 30 years: 1, IV high dose ascorbate has clinical research-based applications when used concurrently with some chemotherapeutic agents. 2. Whole body, extracorporeal and locoregional hyperthermia are being applied in treating solid tumors, including brain tumors. 3. PDL-1 tumor microenvironment testing and PDL-1 inhibitor immunotherapies have surprisingly excellent outcomes in a subgroup of cancer patients. 4. Tumor DNA sequencing (resected tumor and circulating tumor DNA in blood) has led to personalized precision targeted treatments. 5. Glucose metabolism's role in cancer progression is better understood and better therapies are available (e.g., intermittent fasting, metformin). 6. Medical cannabis has a larger role in treating chemotherapy-related side effects and shows promise for anti-proliferative effects. 8. Greater understanding has been gained of the interdependence and mutual regulation of processes in psychoneuroendocrinoimmunology (PNEI). The burgeoning field of PNEI has exponentially expanded the discussion of tumorigenesis, apoptosis, and introduced to the field the investigation of more holistic approaches to immune regulation and cancer care. 8. Psychedelic-assisted psychotherapy is gaining traction especially for cancer patients facing demoralization, existential and spiritual distress, anxiety, depression and trauma related to the diagnosis and treatment of their cancer. 9. Spiritual health of cancer patients is more commonly addressed and measurable with an NIH validated scale. 10. Mind-Body therapies are efficacious for reducing cancer-related distress and are included in many cancer care programs.

Keywords

integrative oncology, naturopathic oncology, circulating tumor DNA, psychedelic therapy, psychoneuroendocrine immunology, prospective cancer outcomes study, cannabis, hyperthermia

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Introduction

The editors of Integrative Cancer Therapies (ICT) have asked for reflections on how integrative oncology in the U.S. has progressed since its origins. Many clinicians and researchers in the field mark 1991 as its beginning, codified by Congressional mandate for specific research oversight

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within integrative oncology. In 1990 to 1991 Congress, led by Iowa Congressman Berkley Bedell, mandated the National Institutes of Health (NIH) to form the Office of Alternative Medicine (OAM) in order to study alternative medicine, especially cancer therapies. The NIH OAM was established as an office independent of the NIH's National Cancer Institute (NCI). A few years after, in 1998, the NCI created its own division of complementary and alternative medicine (Office of Complementary and Alternative Medicine). Also, in 1998, the National Center for Complementary and Alternative Medicine (NCCAM) was established by Congress, elevating the NIH Office of Alternative Medicine (OAM) to the status of center. NCCAM changed its name to National Center for Complementary and Integrative Health (NCCIH) in 2014. These name changes over the decades reflect how the focus of the research mandate has changed, and perhaps softened, since its inception in 1992. Thirty years later, in what ways has the field undertaken Congressman Bedell's task for rigorous examination of "alternative" cancer therapies? How has clinical care in integrative oncology evolved as a result?

The lead author was present at the first meetings of the nascent NIH Office of Alternative Medicine in Bethesda, D.C. and Chantilly (LJS). As a career-long clinician and researcher in integrative oncology, this is a prime moment to reflect on and articulate both the challenges and achievements in integrative oncology over the past 30 years. Indicated in this manuscript are areas in which significant progress has been made to the clinical and basic science research, and clinical practice, of integrative oncology. Identified throughout the manuscript are also areas of growth for the field. These authors are hopeful that with optimistic imagination and academic rigor, the next 30 years may bear an increasingly cohesive system of delivery for evidence-based integrative oncologic care in North America. To that end, reflected here are also gaps that remain to be elucidated, researched and developed into clinical practice.

Disappointments

Advancements in Therapeutics

Before delving into accomplishments, we would first like to recognize where our field fell short. Thirty years ago, clinicians and researchers in naturopathic and integrative oncology envisioned a well-funded NIH program to collect clinical outcomes data from the thousands of daily experiments being conducted in integrative oncology clinics all over the world. We envisioned significant advances in botanical and fungal immunotherapy clinical research. We envisioned the interesting principles of homeopathy being translated into cancer nanomedicine and applied in the clinic. We imagined that the multiple and diverse radiofrequency, electromagnetic field, and hyperthermia therapies that are available to and utilized by cancer patients would be evaluated, discarded or improved upon for clinic application. We foresaw major advancements in allogenic and autogenic dendritic immunotherapy. We thought the field would understand by now why cancer recurs after years of quiescence, and how to safely prevent such relapses. However, only limited improvements have been demonstrated as to the integration of research efforts, or gaining consensus on the role of plant medicine, the paradigm of homeopathy, or clinical utility of other noninvasive integrative therapies to oncology care. We have yet to clarify the variables that accurately describe and prognose the natural history of an individual's cancer and importantly how to monitor and interrupt risk factors for recurrence.

Access to Integrative Therapies

As integratively minded clinicians and researchers, we also envisioned advancements and modernization in the availability of effective therapeutics, such as botanical and fungal traditional cancer therapies carrying FDA approval and coverage by third party payors. We had hoped that parenteral nutrition and phytomedicine therapy for cancer would be more thoroughly researched and accessible. Instead, only 3 botanical medicines have received FDA approval to date: sinecatechins in 2006, crofelemer in 2013, and cannabidiol oral solution in 2018. We never imagined that in the 21st century the FDA would increase restrictions on compounding pharmacies—resources that have been at the core of advanced botanical and nutritional oncologic medicine and that have proven crucial for the appropriate study of these therapeutics by integrative clinician-researchers.

The impact of these restrictions is not small. Parenteral liposomal curcumin holds great promise in the treatment of some adenocarcinomas and sarcoma, as well as glioblastoma multiforme (GBM) brain cancer.[1-5] However, with no FDA-approved parenteral curcumin available, we must depend on high quality compounding pharmacies to prepare these sterile medications for our patients. A 6-week course of IV curcumin twice a week can cost up to $40 000 out-of-pocket for the patient. Restricted access to these compounds inhibits their appropriate study. The absence of coordinated research efforts on a national level adds import to the presence of compounding pharmacies as crucial allies and resources for the investigation of therapeutic efficacy by integrative clinical-researchers, such as these authors.

Integrated Academics and Education

Clinicians in naturopathic and integrative oncology care imagined a larger academic presence, impact and practice. Thirty years ago, we hoped for widespread hospital-based integrative oncology (IO) residency programs representing all major academic cancer centers with naturopathic

oncologists fully embedded in most mainstream health systems. We envisioned a larger role for naturopathic medicine in oncology, specifically, and in the nation's health care system, generally. Instead, CTCA (Cancer Treatment Centers of America), pioneers in the instruction of naturopathic oncology with NDs embedded in its U.S. treatment hospitals, dissolved its naturopathic oncology residency program. Residencies for naturopathic doctors (NDs) proceed in isolation, resulting in few conventional medical and radiation oncologists understanding the utility of NDs in the management of their patients.

Clinical Research

We imagined the profound impact of NCI's initiative to independently review retrospective results of cancer patients treated with unconventional therapies. Instead, the "best case series" has yet to produce significant early results from clinical experiments being conducted all over the world in integrative oncology clinics. The national NIH-based Prospective Outcomes Monitoring System proposed in 1992 at the first meeting of the NIH OAM has yet to come to fruition.

Cancer clinical centers lag behind breakthroughs in IO treatment. Too often their delivery of integrative oncology reflects only its softer and less controversial face: massage, nutrition counseling, yoga, meditation, herbal medicine and acupuncture (but rarely full traditional Chinese medicine). Thirty years after the first NIH Scientific meeting on alternative medicine, a 2021 paper, coauthored by Wayne Jonas, reported improved survival outcomes compared with those treated exclusively with conventional programs.[6] Instead, we await the results of well-powered studies to guide future directions in cancer therapies.

Advances in Screening and Surveillance

Finally, when the first biotechnology companies began to develop in vitro chemosensitivity assays, we anticipated this technology would be validated and in widespread use by 2021. Instead, few medical oncologists were willing to act on assays available to adventurous and resourced cancer patients through commercial chemosensitivity assay companies.

Accomplishments

Collaborative Research

So, what has naturopathic and integrative oncology achieved in the last 30 years? In 2004 a group of NDs who were working with cancer patients formed the American Board of Naturopathic Oncology, which was charged with defining the training and experience and board exam requirements in order to be named a Fellow of the American Board of Naturopathic Oncology (FABNO). Board certified ND FABNOs currently provide adjunctive oncology care in most states per the Oncologic Association of Naturopathic Physicians (OncANP). In 1992, the POMS concept led to the collaboration of researchers at Bastyr University in Kenmore, WA and Fred Hutchinson Cancer Research Center in Seattle, WA. Their efforts resulted in the development of methodology for controlled prospective outcomes monitoring in cancer patients who receive naturopathic oncology care. Between 2009 and 2015 a match-controlled longitudinal outcomes study of 750 women with breast cancer was conducted, and later published.[7]

Then, in 2015 two naturopathic medical colleges, the Canadian College of Naturopathic Medicine and Bastyr University, partnered to develop a naturopathic oncology clinical research site consortium consisting of 12 North American clinics that provide cutting edge naturopathic oncology, typically adjuvant to standard conventional therapies to treat patients with advanced cancer. The Canadian /U.S. Integrative Oncology Study (CUSIOS) began enrolling and following 398 advanced cancer patients receiving care in North American advanced naturopathic oncology clinics. The goal of this study was to obtain 3-year survival data on patients receiving advanced naturopathic oncology treatments and compare to U.S. SEER survival outcomes (ClinicalTrials.gov Identifier: NCT02494037).

Advancements in Understanding of Cancer Etiology and Novel Therapeutics

In retrospect there have been 10 areas of growth in integrative oncology. Some of these developments were not predicted.

1. IV high dose ascorbate has clinical research-based applications when used concurrently with some chemotherapeutic agents.
2. Whole body, extracorporeal and locoregional hyperthermia are being applied in treating solid tumors, including brain tumors.
3. PDL-1 tumor microenvironment testing and PDL-1 inhibitor immunotherapies have surprisingly excellent outcomes in a subgroup of cancer patients.
4. Tumor DNA sequencing (resected tumor and circulating tumor DNA in blood) has led to personalized precision targeted treatments.
5. The role of glucose metabolism in cancer progression is better understood and better therapies are available (e.g., intermittent fasting, metformin).
6. Medical cannabis has a larger role in treating chemotherapy-related side effects and shows promise for anti-proliferative effects.

a. Greater understanding has been gained of the interdependence and mutual regulation of processes in psychoneuroendocrinoimmunology (PNEI). The burgeoning field of PNEI has exponentially expanded the discussion of tumorigenesis and apoptosis, and introduced to the field the investigation of more holistic approaches to immune regulation and cancer care.

7. Psychedelic-assisted psychotherapy is gaining traction especially for cancer patients facing demoralization, existential and spiritual distress, anxiety, depression and trauma related to the diagnosis and treatment of their cancer.
8. Spiritual health of cancer patients is more commonly addressed and measurable with an NIH validated scale.
9. Mind-Body therapies are efficacious for reducing cancer-related distress and are included in many cancer care programs.

Intravenous vitamin C with chemotherapy. Since 2002 there have been 38 peer-reviewed papers on the clinical use of parenteral high dose ascorbate in cancer patients including multiple phase II studies. The published literature indicates that high dose I.V. vitamin C, when administered concurrently with some chemotherapy drugs, improves quality of life.[7-9] There is early evidence that intravenous vitamin C improves disease-free survival in ovarian cancer patients.[10,11] That said, parenteral vitamin C is still considered experimental and is a non-covered expense.

Advances in hyperthermia. Induction of an artificial fever has long been a naturopathic approach to both infection and malignancy. Non-invasive locoregional hyperthermia has been successfully used in treating glioblastoma blastoma (GBM) brain cancer by naturopathic oncologists in Germany and Canada. Parmar et al (manuscript in review) has reported on median overall survival in 58 consecutive GBM patients who received locoregional electro hyperthermia treatment (13.56 MHz with 18 cm penetration that heats skin 20 degrees C and tumor 40 degrees C). These patients had a median overall survival of 21 months, which compares favorably to median overall survival for adjuvant temozolomide plus radiotherapy of 12 months.[12]

The PDL-1 ligand and immunotherapies. The strides in the basic science of cancer cell biology and epigenetics have generated productive therapeutic hypotheses, some of which have led to treatment breakthroughs such as immune checkpoint inhibitors, and the monoclonal immunotherapies that followed. Perhaps the most significant development in cancer medicine in the last 30 years has been the development of immunotherapies. The goal of immunotherapy is to activate the patient's immune system to attack cancer cells. The old naturopathic adage that "the only cure for cancer is the immune system" now has a scientific and practical basis. Clinical research throughout Asia and in the U.S. has led to widespread use of the immunologically active mushroom species named *Trametes versicolor* by both integrative oncologists and patients.[13-15]

Ipilimumab was the first checkpoint inhibitor approved by the FDA, in 2011. This monoclonal antibody binds to the T lymphocyte-associated protein 4 (CTLA-4), leading to an inhibition of cancer cell activity. The binding of ipilimumab to CTLA-4 turns off one of the inhibitory pathways that blocks the immune system's antitumor response and has led to some enduring remissions of stage 4 melanoma.[16]

Another class of immune checkpoint inhibitors targets the programed cell death protein 1 (PD-1) and its ligand PD-L1, leading to a separate inhibitory pathway.[17] Blocking PD-1 or PD-L1 can enhance the anti-tumor T cell response. Immune checkpoint inhibitors are now approved for several types of solid tumors including non-small cell lung, kidney, breast and glioblastoma multiforme.

The enhancement of T cell function in some patients treated with immune checkpoint inhibitors leads to autoimmune disease, including thyroiditis and meningitis. Interestingly, the efficacy of immunotherapy may be modulated by the gastrointestinal microbiome. Microbiota diversity and the presence of *Akkermansia muciniphila* in the gut predicts better response to immunotherapy.[18] Integrative oncology may have a role in enhancing the microbiome and managing the inflammatory side effects of immunotherapy.

Tumor DNA sequencing. The complete sequencing of the entire human genome in 2003 revolutionized cancer research. This powerful and unique technology allowed for characterization of the somatic and germline defects that lead to cancer cell genesis and proliferation. Greater emphasis is now placed on tumor genetics rather than on the anatomical site of the primary cancer. For example, we have discovered that 8% of pancreatic cancer patients carry a *BRCA* gene mutation, previously thought to be more associated with breast and ovarian cancers.[19] We now know oncogenic *BRAF* mutations occur in 100% of hairy cell leukemias, ~50% of melanomas, ~50% of papillary thyroid cancers, ~10% of brain tumors, ~10% of colorectal cancers and less frequently in a variety of other cancer types.[20]

Genomic profiling is now used to identify targetable alterations, mutational load, microsatellite instability complex mutation signatures, tumor-specific antigens and utilize targeted therapies.[21] While solid tumor DNA sequencing has been employed in conventional oncology for over 2 decades, liquid biopsies only gained traction in 2016, when FDA approved the first "liquid biopsy" test.[22] Integrative

oncologists were early adopters of this gene sequencing technology. Many of these circulating tumor DNA sequencing tests are now commercially available and most are FDA approved.

Evaluation of circulating tumor DNA (ctDNA) dynamics in advanced cancer patients is a real-time, precise, non-invasive method to assess treatment response and disease progression.[23] It is now possible to assess the efficacy of a new cancer treatment in as early as 4 weeks. This tool has revamped integrative oncology clinical research. Treatment response can now be assessed more rapidly and more frequently than the few and far between interval scans. Some tumor markers—CA19-9, CA27.29, CA125, PSA, CEA among others—have a long half-life and may not accurately reflect tumor growth or tumor burden.[24]

Genomic profiling has found utility in conventional oncology and beyond. Naturopathic physicians board certified in naturopathic oncology and other integrative oncology providers now utilize tumor and ctDNA to identify potential therapeutic targets for a variety of nutraceuticals and phytomedicines. For example, the PI3K/AKT/mTOR pathway is an actionable target for the flavonoids quercetin and curcumin, an extract of turmeric root.[25,26] The EGFR mutation is an actionable target for resveratrol and the ID1 is an actionable target for the phytocannabinoid cannabidiol.[27,28] Targeted therapy is becoming the preferred treatment in integrative and conventional oncology alike.

Massive clinical and tumor genetic data sets are now available thanks to next generation CRISPR tumor gene sequencing, artificial intelligence and big data. These can be harnessed by pharmaceutical companies to develop new targeted therapies. Data driven precision medicine is in rapid development. Tempus in Chicago is an example of a gene sequencing data company, which collects resected tumor DNA and circulating tumor DNA data from cancer patients and correlates it with clinical data.

Clinical research in advanced integrative oncology (e.g., IV phytomedicines, EMF devices, off-label use of FDA approved drugs) is made more efficient and less costly because of ctDNA assays. This type of research is very expensive and botanical drug approval is an arduous path for chemistry, manufacturing and controls required to make a clinical grade standardized medicine. It is unlikely that a pharmaceutical company will take on these 10 to 20 year projects. Integrative oncology research that involves botanical medicines, EMF devices, or hyperthermia, will likely depend on federal (e.g., NIH) and private grant funding.

Glucose metabolism and cancer progression. Cancer cells exhibit metabolic dysregulation to survive; these cells multiply under compromised conditions of the tumor microenvironment. Cancer cells rely on a constant supply of energy to support rapid proliferation. There have been increased efforts devoted to finding therapeutic modalities which target the increased uptake of glucose and production of lactate by cancer cells, known as the Warburg effect, present in about 90% of all cancers.[29] Intermittent fasting is now widely recommended in integrative oncology as clinical data has demonstrated that prolonged overnight fasting reduces glycemic markers and in turn has been shown to reduce recurrence risk in breast cancer.[30]

Probably most well-known among informed cancer patients and their integrative oncologists is the metabolic cancer therapy utilizing off-label FDA drugs that modulate cancer cell metabolism.[31] These metabolic protocols are designed to reduce overall availability of glucose and low-density lipoproteins.[32] Combination therapy commonly consists of a statin, metformin, doxycycline, and mebendazole. Metformin is the most studied out of the 4; retrospective and observational studies have associated metformin use with better survival statistics for locally advanced pancreatic cancer, kidney cancer, liver cancer, endometrial cancer, lung cancer, colorectal cancer.[33-38] Gastrointestinal distress is not uncommon with metformin but berberine, a nutraceutical, offers a reliable alternative. Berberine not only improves blood glucose regulation and lowers HbA1c; it has also been shown to inhibit cancer cell cycle proliferation, invasion and metastasis.[39]

Cannabinoids in oncology. Few of us in integrative cancer care anticipated the rise of interest in cannabis therapy among patients and their oncologists. For many decades, cannabinoids fell under the domain of palliative medicine as delta-9 tetrahydrocannabinol was initially authorized for the treatment of nausea in 1985 and became FDA approved for cachexia in 1992.[40] However, it has become widely accepted that the therapeutic potential of cannabinoids spans beyond palliative care. Cannabinoids might have a place in oncotherapeutics as early pre-clinical and early clinical data has documented antiproliferative and anti-inflammatory actions.[41] Cannabinoids as adjunctive oncotherapeutics have been reported in glioblastoma multiforme (GBM). Specifically, cannabinoids in ratios of 1:1 CBD:THC were found to improve quality of life, functional capacity and sleep in patients with high-grade gliomas.[42] In a 2017 placebo-controlled phase II clinical trial temozolomide was administered alongside nabiximols, a cannabinoid extract spray, versus temozolomide alone in 21 patients with GBM. Patients who were randomized to the nabiximols group had an 83% 1-year survival rate compared to 44% in the temozolomide only group.[41,43,44]

To date, the FDA has approved formulations of one cannabis-derived drug product of cannabidiol for seizure treatment, and 3 synthetic dronabinol drug products approved for cancer-related side effects. Alongside the FDA approved cannabinoids, there has been significant growth in the over-the-counter (OTC) medical cannabis market. In 2020, the global cannabis market was valued at 22 billion dollars and

is expected to reach 197 billion by 2028. Patients are now able to purchase cannabinoid formulations over the counter in many states, and can thus use them to independently manage cancer-related side effects: insomnia, pain, anxiety, depression, low appetite, nausea. CBD is successfully utilized for the treatment of Dravet syndrome, a severe form of epilepsy.[45] This piqued the public's interest in the application of medical cannabis and has led to increased anecdotal evidence. However, the lack of standardized dosing guidelines hinders clinical application. Standardized dosing and the use of cannabinoid integrative medicine in both palliative and oncologic care promises improvements in overall health related quality of life and provision of further relief from both physical and existential distress.[46]

As stewards of phytomedicine, naturopathic academic institutions have an opportunity to lead the way in cannabinoid research. As naturopathic and allopathic physicians at AIMS Institute, we have begun collecting data to establish dosing and administration guidelines. Cannabis is not legalized at the federal level and therefore it is up to state regulatory bodies to determine how cannabis should be recommended, produced and dispensed. This lack of cohesion creates a barrier for standardization of care with both patients and physicians. In order to promote more clinical research, de-scheduling cannabis at the federal level will be critical.

Psychoneuroendocrinoimmunology (PNEI) and oncology. The 2003 publication in *Brain, Behavior and Immunity* of the supplement *Biological Mechanisms of Psychosocial Effects on Diseases* catalyzed a discussion of psychosocial and neuro-endocrine features of both healthy immunological "terrain" and tumorigenicity in cancer.[47] From these roots of psychoneuroendocrinoimmunology, concepts of a tumor's microenvironment, psychosocial risk factors for cancer and cancer survivorship have developed, as has the crucial role of the central nervous system in health, quality of life, and disease.

We now know that the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system regulate key features of the tumor microenvironment. This includes inflammation, angiogenesis, and cell survival, as well as the initiation of molecular signaling pathways coordinating DNA repair, invasion, or metastasis. Catecholamines (epinephrine, norepinephrine and dopamine) influence leukocyte gene expression, and can lead to antibody and cytokine production as well as the development of resistance to anti-cancer therapies. Importantly, the influence connecting nervous system and immune system functions is mutual: the presence of cytokines and local inflammation stimulates afferent branches of the CNS and can result in "sickness behaviors" and treatment-related fatigue, depression, sleep disturbance, anxiety and cognitive dysfunction.[48]

Psychological distress and cancer. This growing understanding of a multi-scale, multi-system and multi-factorial etiology of cancer has been accompanied by the exploration of similarly encompassing and integrated approaches to treatment. The investigation of mental health among cancer patients has broadened and deepened accordingly.

Depression has been shown to be a salient psychological feature predictive of shortened survival time in cancer patients. Affective and existential mental health complaints are thought to affect cancer outcome through several mechanisms, including the biomedical changes noted above (i.e., heightened inflammatory state) and psychosocial or behavioral differences.[49,50] Common variables among poor cancer outcomes and mental health disorders could explain the correlation, including deficiency of social support, low resilience, or interference in treatment adherence.

ACEs and cancer risk. In 1998, the landmark "ACE" study was published revealing the correlation between Adverse Childhood Experiences (ACEs) and the risk of disease and mortality in adulthood.[51] In the 2 decades since then, the scientific community has amassed evidence linking childhood adversity and traumatic exposure to many chronic health conditions plaguing adult populations, including cancer.[52] Since 1998, issues previously considered purely sociological in nature—that is, exposure to violence as a child, substance misuse in the household, and other adverse experiences have gained recognition and understanding for their medical implications. ACEs are of particular interest to the fields of preventive and integrative medicine including integrative oncology.

With updates to our understanding of the role of HPA-axis and nervous system in tumorigenesis, it is perhaps unsurprising that adverse psychological experiences and exposures during developmental years have been correlated with lifetime risk of cancer.[53] Recent analyses have focused on explaining the mechanisms behind this correlation to guide earlier intervention and prevention of cancer. The risk of developing any type of cancer is increased among those who have experienced childhood physical abuse (OR = 1.26), childhood sexual abuse (OR = 1.23), witnessing intimate partner violence in the home (OR = 1.26) or family financial challenges (OR = 1.16).[52] Studies have varied on which traumatic exposures qualify as an ACE. Regardless, systematic reviews suggest that a higher discrete number of any ACE is associated with a greater number of well-established modifiable cancer risk factors.[54] Greater than 4 ACEs of ACEs in 2 to 3 different categories increases the risk of cancer (OR = 2.17 and OR = 1.35, respectively).[52] Namely, the use of alcohol or tobacco and poor immunity including chronic inflammation, chronic infections, or immunosuppression are particularly predictive of cancer diagnosis.[54] In fact, having just one ACE, which 67% of the US population does, puts an

individual at risk for lower levels of interleukin-2 and thus lower T-regulatory lymphocyte counts, and is associated with poorer survival among oncology patients.[55]

Cancer is a leading cause of death in the United States, and ACEs are common with two-thirds of the US population experiencing at least one ACE and an eighth (12-13%) experiencing greater than 4 ACEs.[51] The field of integrative oncology is called to further investigate the biologic mechanisms by which challenges during childhood and sustaining physiological and psychological changes ultimately correlate to exposures to cancer risk factors. This line of inquiry, including the social context in our understanding of PNEI tumorigenesis, holds promise for important new treatment avenues. Preventing adverse childhood experiences will continue to require integrative public health policies and practices. This highlights how imperative multidisciplinary thinking and action is in integrative health delivery. Ultimately we anticipate and hope for increased incorporation of mind-body and PNEI theory in our implementation of public health strategies.

Advances in psychedelic medicine. The existential distress experienced by patients with life threatening diagnoses is rarely relieved by conventional pharmaceutical approaches to anxiety or depression.[49,50] Some evidence suggests antidepressants may exert anti-inflammatory action which could account for some of their efficacy from a PNEI perspective.[56,57] In most cases it is overly reductive to attribute mental distress in terminal illness to mere deficiencies in neurotransmitters, explaining why this complaint in this population is not adequately or efficiently relieved by targeting serotonin or dopamine levels, for example. This calls us to consider the tremendous psycho-spiritual effect of cancer on a person's sense of self, their outlook on the world, their spirituality, and other elements composing our psyche. The integrative mental health care of cancer patients must consider both the possibility of changes in their psychiatric composition, and the almost-certain changes in psychological state.

The field of psychedelic-assisted psychotherapy has offered an integrated (psychiatric and psychological) approach to the unique mental health crises faced by cancer patients. The goals of reducing suffering for patients facing a life-threatening disease, the existential quandary of a poor prognosis, adapting to unprecedented stressors or loss of function, and promoting quality of life have made way for powerful potential psychological and psychiatric avenues for care. Regardless of the direct or indirect etiology, addressing psychological distress in cancer patients is, and should be, a priority in integrative oncology care. In assessing and appropriately treating psychological distress, we can relieve more suffering, and perhaps address a contributing factor to both immunological disease and mental distress.

Ayahuasca. Ayahuasca is an ancient South American traditional psychoactive plant medicine with a possible immunologic mechanism of action and great promise in the realm of cancer therapy. Ayahuasca is brewed with at least 2 plants: the Chacruna plant (*Psychotria viridis*) containing the serotonergic agonist monoamine dimethyltryptamine (DMT), and the Ayahuasca vine (*Banisteriopsis caapi*) containing beta carbolines acting as MAOIs. The synergy between the MAOIs and the dimethyltryptamine is an important feature of this ancient plant medicine, as the MAOIs facilitate the passage of DMT across the blood-brain barrier, where it then may exhibit its psychoactive effects. Recent evidence demonstrates that immunologic T cells with serotonin receptor sites can be modulated by serotonergic agonists such as ayahuasca.[58] Dimethyltryptamine is also known to bind sigma-1 receptors, which are correlated with antiproliferative and anticancer activity.[59] Plant alkaloids abundant in the brew have been shown to have an antiproliferative effect in pancreatic cancer cell lines.[60] In 2013, nine case reports were examined where ayahuasca had been used for cancer treatment, with several cases noting improvement in condition.[58]

AIMS Institute in Seattle is striving to both improve cancer survival and facilitate effective palliative care at the end of life. To this end we have observed that spiritual ease can be facilitated by proper access to entheogenic plants. *Banisteriopsis caapi* and *Psychotria viridis*, the 2 most commonly used sacred plants present in Ayahuasca tea, are powerful means to achieve this. These plants are deeply sacred to many indigenous Amazonian rain forest communities in South America where Ayahuasca has been used for thousands of years to cure both physical and spiritual ailments. Practicing integrative and whole-systems health care necessitates the protection of precious ecosystems.

Ketamine. Ketamine's multiple effects on the neurologic system suggests its roles in cancer treatment and recovery. Broadly, ketamine has been shown to exhibit neuroplastic and neuroregenerative potential that can be useful in CNS cancers before and after conventional treatment. Pain secondary to cancer and conventional cancer treatment can also be ameliorated with the use of ketamine due to its inherent analgesic properties, specifically when opioid treatment is not indicated or has lost efficacy due to tolerance.[61]

Ketamine in the form of ketamine-assisted psychotherapy (KAP) has promising implications for addressing anxious and depressive symptoms secondary to a cancer diagnosis and treatment.[62] KAP utilizes ketamine at sub-anesthetic doses to facilitate psychological insights including a more positive view of self, positive changes in life values, and spiritual development. At sub-anesthetic doses ketamine has also been shown to produce robust, rapid and transient antidepressant and anti-suicidal effect, critical in patients with end of life demoralization and sorrow.[63]

Ketamine's mechanism of action has been linked to transient enhancement of structural plasticity induced by a glutamate burst occurring in the frontal, hippocampal and mesencephalic dopaminergic neurons during ketamine treatment.[64] Patients with a cancer diagnosis undergoing KAP may be able to process medical trauma related to their diagnosis and treatment, the adverse events of childhood that may have increased their risk of cancer, and reduce anxious and depressive symptoms by finding harmony by exploring their own life values and spiritual development. Ketamine is an important multi-modal tool to address several areas of suffering for cancer patients, and specifically offers a biomedical alternative to antidepressants and, at psycholytic or psychedelic doses, an effective adjunct to psychotherapy.[65]

Psilocybin. The first modern design clinical trial of psilocybin, a psychoactive molecule present in the *Psilocybe* mushroom genus, was conducted with cancer patients at the end-of-life.[66] Psilocybin has been shown to alleviate anxious and depressive symptoms correlated with a cancer diagnosis. A randomized double-blind placebo-controlled trial involving 51 cancer patients given placebo and high-dose psilocybin showed that high-dose psilocybin administration resulted in lower depressive and anxious mood symptoms measured by clinicians and patients themselves. Increases in optimism, quality of life, and decreases in death anxiety were observed. All of these measures were observed beyond 6 months after the trial took place, with participants crediting these changes with the mystical experience facilitated by psilocybin.[66] Similarly rapid and robust anxiolytic and anti-depressants effects have also been demonstrated with the use of psilocybin in cancer patients with cancer-related psychological distress.[67] The Aquilino Cancer Center in Maryland has reported antidepressant effectiveness in cancer patients receiving 20 mg psilocybin orally. Our group in Seattle is planning to conduct a Phase II trial of psilocybin in hospice patients and hope to be piloting the first group psilocybin therapy study in hospice patients with their close family members.

The state of Oregon recently approved the use of psilocybin therapy and other states will soon follow with decriminalization of Psilocybe mushrooms or the legalization and regulation of psilocybin therapy practice. Many cancer patients are already seeking out psilocybin therapy. Psychedelic therapy is certain to play a large role in cancer medicine in the next decades.

Spiritual health in cancer patients. Naturopathic medical schools teach the mind/body/spirit view of human health, yet at the first NIH OAM meeting that marked the beginning of the field of integrative oncology, the words spiritual or spirituality were not mentioned, per the recollections of the first author of this paper. However, this omission has not persisted in oncology and other medical fields, with much of the change spurred by the increasing recognition of palliative care as a critical need in the care of cancer patients.

Palliative care is a multidisciplinary medical specialty—often involving nursing, social work and spiritual care—that is concerned with impeccable symptom management and supportive care for patients and their families facing life-limiting illness. It focuses on the amelioration of physical, emotional, psychological, and *spiritual* suffering. Hospice and palliative care medicine has advanced in prominence in medicine in the last 30 years, with one milestone being its recognition as a specialty board certification in the US starting in 2006. However, palliative care is not strictly reserved for practice by palliative care specialists; non–palliative care treating specialists such as integrative oncologists can and should be trained to provide what is called "primary palliative care" such as basic pain management and supporting facilitation of clinical discussions with patients and families about disease prognosis and advanced care planning.

One confusion related to spiritual health care has stemmed from the question of how to define spirituality. Spirituality is deeply subjective, yet there are several recognized universal definitions by health authorities. To inform spiritual assessments in healthcare, in 2009 the National Consensus Project in the U.S. developed a robust, broadly applicable definition of spirituality using a Delphic approach drawing on experts from the field of palliative care. They defined spirituality as

> '. . .the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred.'[68]

This definition goes beyond solely religious concerns to include philosophical and existential concerns around connection, meaning, purpose, and the search for the significant or the sacred. In 1983, the World Health Organization (WHO) first adopted policies recognizing the implicit spiritual dimension in the concept of health.[63] In January 1998, the WHO Executive Board adopted resolution EB 10 1.R2 recommending "spiritual" be added to the definition of health, as follows: "Health is a dynamic state of complete physical, mental, spiritual and social well-being and not merely the absence of disease or infirmity."[69]

Two recent developments are helping further bring spirituality in medical care to the forefront. Firstly, scientists have validated new tools to measure spiritual health. Healing Experience of All Life Stressors (NIH-HEALS) was developed by the NIH Clinical Center Pain and Palliative Care Service as a psycho-social-spiritual measure of healing that assesses positive transformation in response to challenging life events.[70] It is a self-report,

35-item questionnaire developed by the observation that some patients with life-threatening and/or severe chronic illness report positive psychological, social, and spiritual change during the diagnosis or treatment of their illness, even in the face of unfavorable prognosis. The creators of the instrument feel that identifying the factors that contribute to or detract from the positive transformation known as "healing," has far reaching implications for interventions aimed at improving quality of life, mind, body, and spiritual wellness in the face of life's challenges. We foresee the periodic use of such instruments will bring greater clarity to the question of how to address the core health-related needs of cancer patients.

The second recent development that is bringing spiritual health in oncologic care to the forefront is the wave of research discussed earlier known as the "psychedelic renaissance" that is highlighting the unmet needs of demoralization and existential and spiritual distress in cancer patients. Many practitioners of psychedelic medicine refer to the spiritual domain in a time when the materialist ontology of the 20th century is being replaced by greater acceptance of all things spiritual.

Mind-body therapies in the oncology setting. Mind-body therapies such as acupuncture, meditation and mindfulness have been more widely accepted within conventional care models, probably because they are viewed as low-risk, potentially helpful, and do not interfere with the mechanisms of "standard of care" treatments. Whereas access to acupuncture, guided meditation or mindfulness was limited 30 years ago to those who knew to look for it in an outpatient setting, today cancer patients can benefit from these modalities within integrative treatment wings of several major conventional oncology care centers in the United States.[71-75]

Acupuncture. Acupuncture offers an individualized approach to common complaints among patients with cancer such as fatigue or treatment-related adverse effects. A 2015 analysis of systematic reviews investigating acupuncture for cancer patients indicated improvement in cancer-related fatigue, nausea, vomiting, and leukopenia.[76] Acupuncture has also been shown to significantly improve sleep quality in patients with cancer and to reduce cancer-related pain.[77,78]

Mindfulness and meditation. Research over the past 3 decades has elucidated the importance of emotional expression and regulation in cancer outcomes and quality of life.[79] A 2022 study of psychoemotional traits in a cancer cohort found that greater resilience and lesser emotional control are protective, whereas the *control* of emotions is correlated with worse mental health status.[80] We now have a validated instrument for assessing levels of emotional suppression (Courtauld Emotional Control Scale (CECS)), which positively correlate with psychological distress at the time of cancer diagnosis and throughout treatment.[81,82]

Meditation and mindfulness are well-established methods of acknowledging, engaging with, regulating and moving through psycho-emotional distress. Yunlin et al concluded in a 2020 meta-analysis of mindfulness interventions for oncology patients that mindfulness-based art therapy (MBAT) most significantly reduced levels of anxiety and depression, followed by mindfulness-based stress reduction (MBSR) and mindfulness-based care recovery (MBCR) programs.[83] Even when performed 3 months after concluding conventional breast cancer-treatment, MBSR and facilitated emotional expression was found to maintain telomere length, compared to shortened telomeres in cancer survivors who did not use MBSR in the early months of their recovery.[84] We now have evidence for considering cancer survivorship and recovery a whole-person and lifelong process.

Conclusions After 30 Years

This is an exciting time for naturopathic and integrative oncology because the field has been early to apply new cancer molecular biology and genetics advances, as well as early application of developments in psychoneuroendocrinoimmunology and botanical medicine. Naturopathic oncology researchers have developed better research methodologies to evaluate the impact of integrative oncology on disease free and overall survival as well as quality of life and spiritual health.

1. Clinical research has emerged for the use of IV high dose ascorbate concurrently with some chemotherapeutic agents, with good outcomes for disease-free survival and quality of life.
2. Locoregional hyperthermia shows great promise in treating some solid tumors, including malignant brain cancer.
3. PDL-1 tumor microenvironment testing and PDL-1 inhibitor immunotherapies are important new conventional oncology options for cancer patients.
4. Tumor DNA sequencing (resected tumor and circulating tumor DNA in blood) has led to personalized precision targeted treatments. Genomic profiling allows clinicians and researchers to reliably assess tumor make-up, identify targetable alterations, and implement and evaluate the effectiveness of treatment on monthly intervals.
5. Glucose metabolism's role in cancer progression is better understood and better therapies are available (e.g., intermittent fasting, metformin). Metabolic therapy for cancer is a promising area. There are preliminary data to support 13 to 14-hour intermittent fasting as a way to prevent cancer recurrence. But

the safety and efficacy of other aspects of metabolic therapy (statins, glucose modulating drugs, antifungal and antibiotic therapy) await rigorous trials.
6. Access to medical cannabis has increased and the understanding of cannabinoid applications in integrative oncology has expanded.
7. The field of psychoneuroendocrinoimmunology has matured and is being applied to both clinical research and cancer patient care among naturopathic oncology clinics.
8. Psychedelic-assisted psychotherapy is gaining traction especially for cancer patients facing demoralization, existential and spiritual distress, anxiety, depression and trauma related to the diagnosis and treatment of their cancer. The current "psychedelic remembrance" is addressing the role of Adverse Childhood Experiences in cancer risk.
9. Spiritual health of cancer patients is more commonly addressed and now the NIH has developed a validated scale to measure it, both in clinical trials and in clinical care.
10. Oncology patients benefit from the integration of mind-body therapies within and following their cancer care programs, including acupuncture, mindfulness and meditation.

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