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EDITORIAL

Hope in Wisdom Past and for Future Clinical Trials

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"Hope springs eternal in the human breast."

The famous quote from Alexander Pope's poem "An Essay on Man"[1] is oft-quipped today, although penned nearly 3 centuries ago. The aphorism has been truncated to "hope springs eternal," dropping hope's purported origin. In remarkable brevity, Pope opines the essential, even eternal, nature of hope to humanity.

Building on growing literature regarding the construct of hope, the present study by Corn et al challenges the characteristics of hope asserted by Pope and the subsequent generations repeating his pithy phrase. First, the study asserts that hope is not "eternal," or rather, not impervious to human circumstances and conditions. The investigators purport hope as "both a dependent and independent variable." Accordingly, hope is subject to the influence of other factors, such as disruption of the brain "hope center" by radiation therapy, even as it exerts influence on other facets of patient experience, most notably, quality of life (QOL). Second, this investigation hypothesizes that hope has a specific, localizable pathway within the human brain, a central component of which is the hippocampus. This contrasts with the origin declared by Pope. Subsequent lines in his poem reveal hope's origin—"the human breast"—is a metaphor for the human soul.

The investigators embark on their empirical inquiry of hope with remarkable tools at their disposal. NRG-CC003 offers a robust sample size of 393 patients with small cell lung cancer who were prospectively followed with validated scales assessing hope (Adult Hope Scale [AHS]) and QOL (European Organization for Research and Treatment of Cancer to assess Quality of Life in Cancer patients [EORTC-QLQ-C30]), together with assessments of potential confounding factors, including depression, religious affiliation, and study stratification factors (eg, concurrent memantine). The putative "hope center" in the hippocampus was inadvertently tested within the NRG-CC003 study schema. Patients were randomized to prophylactic cranial irradiation (PCI) with or without hippocampal avoidance (HA), with primary endpoints being 12-month intracranial relapse and 6-month Hopkins Verbal Learning Test-Revised Delayed Recall failure. Based on an initial report of outcomes,[2] intracranial relapse was noninferior in the HA-PCI group at 12 months; Hopkins Verbal Learning Test-Revised Delayed Recall deterioration was also not statistically different. However, the secondary cognitive function outcome, any neurocognitive failure, did demonstrate greater failure in the group not receiving HA-PCI.

Baseline hope scores as assessed by the AHS were not different between the randomization groups. Contrary to the study hypothesis, there were no differences in changes in hope scores from baseline to 6 months comparing the HA-PCI and PCI arms. More specifically, changes in the 2 AHS hope subscales were examined: (1) agency—perceptions of personal energy and will to reach goals—and (2) pathway—perceptions of avenues by which a person can attain goals. The authors also examined the relationship of the hope subscales to changes in QOL scores (EORTC-QLQ-C30). Notably, both hope-agency and hope-pathway change scores

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were significantly correlated with changes in QOL, prospectively establishing hope as a correlate of patient QOL.

The authors summarize these findings as follows: (1) hope plays a significant role in patient QOL and (2) the "hope center remains elusive." The first conclusion dovetails with the larger literature regarding hope and QOL. Multiple studies from varied populations of patients from diverse settings—including the United States, the Netherlands, China, and Iran—have shown positive cross-sectional associations between measures of hope and QOL.[3-6] The present study prospectively demonstrates positive associations between hope and QOL among patients with cancer, providing greater support for the central role that hope plays in QOL. However, hope did not appear to be modified by treatment arm. Although the null findings do not obviate the possibility that the hippocampus is part of a "hope center" in the brain, the findings at the least suggest that treatment arm-resultant differences in hippocampal function, as demonstrated by differential neurocognitive failure between groups, did not result in discernable differences in hope. Importantly, the authors note that the measure used—the AHS − [7]—may not be optimal given it emphasizes the more stable "trait" aspects of hope. In contrast, "state" hope is the more affective, dynamic aspect of hope thought to be more sensitive to change. Other validated hope scales, such as the State Hope Scale,[8] have greater emphasis on affective aspects of hope and could be considered for future trials where hope is being assessed as a dependent variable.

The findings of this study are in and of themselves weighty as they further an understanding of hope as a component of QOL and lay early groundwork toward a neural-anatomic map of hope. However, there is arguably an additional, important contribution made—the choice to include an investigation of hope within the study methodology of a biomedical intervention. This decision, and the thoughtfulness surrounding its attendant methods, demonstrates a deepening commitment to a holistic approach to human well-being within therapeutic clinical trials. The standard inclusion of quality-of-life measures in clinical trials has been a critical first step in this regard. Further steps are needed to more fully embrace a person-centered, holistic bio-psychosocial-spiritual model of health.[9] Key additional domains of holistic well-being include hope, and a related construct, spirituality. Hope and spirituality are interconnected domains, with measures of spirituality, such as spiritual coping, associated with hopefulness in patients.[10,11] Furthermore, spiritual care intervention studies, such as meaning-centered psychotherapy, demonstrate improvements in hope among patients with cancer.[12,13] These studies suggest that spirituality is providing an important foundation for hope. Given spirituality encompasses sources of meaning, purpose, value, and connection that transcend the material realities of the human condition,[14] it may foster a resilient grounding for hope, particularly when confronting life-threatening illness. Interestingly, Pope's aforementioned aphorism names hope's origin as the human soul, or the spirituality of the person.

Echoing the foundational role of spirituality to hope, the authors note in this present study that religious affiliation was associated with greater hopefulness, particularly the pathway hope subdomain. It is important to note that religious affiliation is a narrower construct than spirituality—spirituality includes traditional and nontraditional forms (eg, experiencing the sacred in nature), and individual as well as communal experiences and practices of spirituality. Religious affiliation captures the communal practices surrounding a spirituality but can miss personal aspects that may be present with or without a religion. Furthermore, having a religious affiliation does not necessarily translate to an active spirituality; it is not uncommon for individuals to have loose cultural connections to a religious identity that do not permeate personal experiences or practices. Ideally measures of spirituality include both personal assessments, such as the Functional Assessment of Chronic Illness Therapy-Spiritual Well-being Scale,[15] as well as measures of communal involvement, such as religious identification and participation (eg, Duke University Religious Index).[16]

Regardless of these points of improvement for future trials, the present study is an example of an opportunity to refine not only our biomedical understanding and technical tools to improve the care of patients with cancer, but to also broaden our conception of, and ability to intervene on, the holistic patient experience to improve well-being. Such an endeavor requires a team approach with a broad variety of expertise, as illustrated by the author list of the present trial. The more our biomedical inquiries are integrated with psychosocial-spiritual questions and approaches, the more we within medicine will grow in our ability to overcome the siloing of knowledge that can be a source of dehumanization to our patients, their families, and ourselves. Although this fragmentation has seemed necessary to meet the sheer complexity of human disease, it is ultimately an error we must recognize on a path to truly holistic medical care. Once again, Pope's sage words provide prescient guidance and conclusion, "To err is human, to forgive is divine."[17] We must first recognize our error, and then—as seen in the present study—our collective commitment to a spirit of care enables "forgiveness," or what overcomes that error.

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