As the premier scholarly publication of the osteopathic medical profession, JAOA—The Journal of the American Osteopathic Association encourages osteopathic physicians, faculty members and students at colleges of osteopathic medicine, and others within the healthcare professions to submit comments related to articles published in the JAOA and the mission of the osteopathic medical profession. The JAOA’s editors are particularly interested in letters that discuss recently published original research.

Letters to the editor are considered for publication in the JAOA with the understanding that they have not been published elsewhere and that they are not simultaneously under consideration by any other publication.

All accepted letters to the editor are subject to editing and abridgment. Letter writers may be asked to provide JAOA staff with photocopies of referenced material so that the references themselves and statements cited may be verified.

Letters are encouraged to prepare letters electronically in Microsoft Word (.doc) or in plain (.txt) or rich text (.rtf) format. The JAOA prefers that readers e-mail letters to jaoa@osteopathic.org. Mailed letters should be addressed to Gilbert E. D’Alonzo, Jr, DO, Editor in Chief, American Osteopathic Association, 142 E Ontario St, Chicago, IL 60611-2864.

Letter writers must include their full professional titles and affiliations, complete preferred mailing address, day and evening telephone numbers, fax numbers, and e-mail address. In addition, writers are responsible for disclosing financial associations and other conflicts of interest.

Although the JAOA cannot acknowledge the receipt of letters, a JAOA staff member will notify writers whose letters have been accepted for publication. Mailed submissions and supporting materials will not be returned unless letter writers provide self-addressed, stamped envelopes with their submissions.

All osteopathic physicians who have letters published in the JAOA receive continuing medical education (CME) credit for their contributions. Writers of original letters receive 5 AOA Category 1-B CME credits. Authors of published articles who respond to letters about their research receive 3 Category 1-B CME credits for their responses.

Although the JAOA welcomes letters to the editor, readers should be aware that these contributions have a lower publication priority than other submissions. As a consequence, letters are published only when space allows.

Graduating Osteopathic Medical Students’ Perceptions and Recommendations on the Decision to Take the USMLE

To the Editor:
As an osteopathic physician who took the United States Medical Licensing Examination (USMLE) and an associate program director of one of the nation’s largest allopathic internal medicine residency programs, I read the medical education article by Robert T. Hasty, DO, and colleagues in the February issue with great interest. On the basis of a survey of graduating osteopathic medical students, Hasty et al attempted to evaluate students’ perceptions related to the USMLE. As the primary reason for taking the USMLE, 46% of the respondents cited keeping their options open, and 35.5% cited enhancing their chances of getting into an allopathic residency.1

It is important to point out that graduating osteopathic medical students need not take the USMLE to better their chances of being accepted into an allopathic residency—with rare exceptions. These exceptions include training programs in highly competitive fields, such as neurosurgery, ophthalmology, dermatology, and orthopedic surgery. The fact is that most allopathic residency program directors know nothing about the Comprehensive Osteopathic Medical Licensing Examination-USA (COMLEX-USA). They do not know about the general validity of COMLEX-USA, and they do not know what information is tested or how to accurately compare this test’s scores to those of the more familiar USMLE. Thus, allopathic residency program directors typically make baseless, assumed, and subjective comparisons between the 2 examinations.

Osteopathic medical students who score higher on COMLEX-USA than the USMLE will foster a belief that the former is not as rigorous as the latter. As a result, some allopathic residency program directors may direct students to take the USMLE in order to be considered for residency training. The motivation for this recommendation is a lack of knowledge about COMLEX-USA, an unwillingness to accept osteopathic medical students (by using the test as an obstacle to overcome), or a lack of trust in the scores of COMLEX-USA.

I disagree with the contention of Hasty et al that “the present study represents the first reasonably objective findings specific to this issue that might aid faculty in their ability to counsel osteopathic medical students on this topic.” If their study described a survey of allopathic residency program directors—as they suggest be done in the future—then this statement could be valid. However, a survey of osteopathic medical students who have no role in making allopathic residency acceptance deci-

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1 Hasty RT, Akers KO, Burt JS, et al. Graduating osteopathic medical students’ perceptions and recommendations on the decision to take the USMLE. J Am Osteopath Assoc 2012;112:479-88.
The American Osteopathic Association (AOA) should take a proactive role in ensuring that allopathic residency program directors understand the nuances of COMLEX-USA and that this test cannot be compared directly to the USMLE. The AOA should also work to ensure that osteopathic medical students not be disadvantaged if they do not take the USMLE. However, the AOA must accept the fact that a majority of osteopathic medical students seek allopathic residency training. 2,3 Between 2007 and 2011, the percentage of graduating osteopathic medical students who applied to the National Resident Matching Program varied between 52.4% (in 2011) and 56.3% (in 2010). 2,3 During that period, the number of osteopathic medical students who applied to the National Resident Matching Program increased from 1652 in 2007 to 2178 in 2011. 2,3

Graduating osteopathic medical students want the best postgraduate training—regardless of whether it is osteopathic or allopathic. The osteopathic medical profession should attempt to understand why osteopathic medical students do not choose our own institutions for training, rather than continue to keep allopathic training programs in the dark about COMLEX-USA and its usefulness in our own institutions for training, as reported in our study. 1

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References

Response
Thank you for the opportunity to respond to the letter to the editor by Joshua D. Lenchus, DO, RPh, regarding the JAOA article I authored, “Graduating Osteopathic Medical Students’ Perceptions and Recommendations on the Decision to Take the United States Medical Licensing Examination.” I agree with most of the comments made by Dr Lenchus, particularly with his assertion that “graduating osteopathic medical students need not take the USMLE [United States Medical Licensing Examination].” In addition, I agree that most osteopathic medical students are served well by their Comprehensive Osteopathic Medical Licensing Examination-USA (COMLEX-USA) scores as credentials for entry into residency programs accredited by either the Accreditation Council for Graduate Medical Education (ACGME) or the American Osteopathic Association (AOA). The COMLEX-USA scores are also essential credentials for licensure in all 50 states. 2,4

Furthermore, Dr Lenchus brings an important perspective and his personal observations regarding the current practices of ACGME program directors. This perspective serves as an important contrast to the opinions of graduating osteopathic medical students, as reported in our study. 1

I would like to point out that the AOA and the National Board of Osteopathic Medical Examiners (NBOME) are actively working together on educating residency program directors regarding COMLEX-USA. 5 The NBOME has made 6 major presentations on COMLEX-USA at national or regional meetings of residency program directors during the past year. The NBOME also includes a COMLEX-USA informational handout as part of the new residency program directors’ orientation program. This handout was made available at the recent ACGME Annual Meeting, in March 2012, and can be obtained from the NBOME Web site 6 and in various graduate medical education newsletters. Since 2010, all ACGME residency program directors receive the NBOME Annual Report, and representatives from graduate medical education (eg, ACGME, Association of Osteopathic Directors and Medical Educators, Organization
of Program Directors Associations [of the Council of Medical Specialty Societies] participate in a number of NBOME committees and activities, including NBOME’s Liaison Committee. Upon the request of the NBOME, the AOA has added communicating with residency program directors about COMLEX-USA to its 2011-2013 Strategic Plan.7

I would further add that the discrepancies between the perceptions of graduating osteopathic medical students reported in our article1 and the observations of Dr Lenchus articulate a need to better educate osteopathic medical students on these important issues.

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Editor’s Note: Dr Hasty is Vice Coordinator for Advanced Items, Chair of the Innovations in Testing Advisory Committee, and an item writer for the National Board of Osteopathic Medical Examiners.

The Failed Theratope Vaccine: 10 Years Later

To the Editor:

The year was 2002. There was excitement in the air. Immunology and oncology were finally coming together in what appeared to be the most novel agent in the field of breast cancer treatment since the revolutionary introduction of trastuzumab. A vaccine had been shown to stimulate antibody- and cell-mediated immune responses against tumor-associated antigens.1 Phase I and II studies provided convincing evidence that this highly touted therapeutic breast cancer vaccine, dubbed Theratope (synthetic O-linked disaccharide, sialyl-Tn-keyhole limpet hemocyanin [STn-KLH]; Biomira Inc, Edmonton, Alberta, Canada), was the next big idea in the field.1 Hundreds of researchers around the world were eager to see the results of phase III clinical trials of this promising agent.

One of the first studies describing the use of Theratope in clinical practice had been published in 1996 by MacLean and colleagues.2 They described how Theratope produced clinically significant antibody titers and a marked increase in survival in patients with breast cancer.3 Vaccine activity was also associated with expression of CD69+ lymphocytes and CA27.29 (MUC-1), a high-molecular-weight glycoprotein rich in serine and threonine residues.3 Two phase II trials compared the use of low-dose cyclophosphamide with and without Theratope and found that there was a statistically significant increase in survival among patients treated with the STn-KLH vaccine (overall median survival, 19.1 months; n=50), compared with those patients not treated with the vaccine (overall median survival, 9.2 months; n=104).4,5 The trials reported minimal toxic effects with mild injection-site reactions and flulike symptoms.4,5 Sandmaier et al tested Theratope in vitro in 33 high-risk patients with breast cancer after stem cell transplantation. The researchers reported in 1999 that they observed STn antigen-specific T-cell proliferation and peripheral blood lymphocyte lytic activity.6,7

The stage was set for mid-2003. Numerous in vitro and phase II studies had delivered encouraging results for Theratope. There was a wave of optimism in the air. One June day in 2003, however, there was breaking news8:

Biomira Inc. (Nasdaq: BIOM) (TSX:BRA) and Merck KGaA of Darmstadt, Germany, announced today that the results from a large pivotal Phase III trial of Theratope(R) vaccine for women with metastatic breast cancer did not meet the two pre-determined statistical endpoints of time to disease progression and overall survival. However, one pre-stratified subset of patients in the treatment group, women on hormonal treatment following chemotherapy, appeared to show a favourable trend to improvement in survival. ... The Phase III randomized, double-blind trial was designed and powered primarily as a survival study. Enrolment [sic] in the trial totaled 1,030 women at more than 120 sites in 10 countries and, to date, is believed to be the largest trial of a therapeutic vaccine conducted in women with metastatic breast cancer.

In the study referred to in this June 2003 news report—the final results of which were published in 20119—week-12 antibody testing revealed high specific immunoglobulin G titers in the group treated with Theratope and no detectable anti-mucin antibodies in the control group.
However, median survival time between the treatment and control groups (23.1 months vs 22.3 months, respectively) was not significantly different.\(^5\)

Researchers were shocked by the initial phase III results reported in 2003.\(^6,7\) The idea that vaccines could be given to stimulate antibody- and cell-mediated immune responses against tumor-associated antigens made so much sense at the cellular level, and results of phase I and II clinical trials were so promising! Patients treated with the Theratope vaccine produced clinically significant antibody titers, but—for some reason—this result was not translating into increased survival for the patients. What had gone wrong? Researchers went back to the drawing board to elucidate a clear mechanism describing the efficacy of the vaccine.

Although interest and hope waned, further research was conducted during the next few years. Epidemiologic studies showed that STn expression was highly restricted in normal tissue and was seen in approximately 25% to 30% of breast cancer cases.\(^10\) In 2005, Braun et al.\(^10\) reported that tumor cells treated in vitro with an aromatase inhibitor exhibited increased sensitivity to monocye-mediated, antibody-dependent cellular toxicity. Gilewski and colleagues\(^11\) found that the combination of 2 vaccines—STn-KLH and the immunologic adjuvant QS-21—produced clinically significant antibody titers in high-risk patients with breast cancer, with little or no resulting toxicity.

Today, almost 10 years after the disappointing report on the pivotal phase III clinical trial of Theratope,\(^8,9\) therapeutic vaccines for metastatic breast cancer no longer hold the same promise as they once did. Multiple vaccines have failed to show any meaningful benefits. Despite encouraging recent results for the use of combination vaccines in the treatment of hormone-sensitive patients,\(^11\) these findings need to be verified in large randomized controlled trials. Meanwhile, vaccines have shown some success with other types of cancer, such as prostate cancer (sipuleucel-T)\(^12\) and melanoma (ipilimumab).\(^13\)

Only time will tell whether vaccines will ever have a permanent role in treating patients with breast cancer. However, the Theratope vaccine story has ultimately become a tale of caution in the field of breast oncology.

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References