

Electronic Nicotine Delivery Systems: A Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology

Thomas H. Brandon, Maciej L. Goniewicz, Nasser H. Hanna, Dorothy K. Hatsukami, Roy S. Herbst, Jennifer A. Hobin, Jamie S. Ostroff, Peter G. Shields, Benjamin A. Toll, Courtney A. Tyne, Kasisomayajula Viswanath, and Graham W. Warren

Thomas H. Brandon, Moffitt Cancer Center, Tampa, FL; Maciej L. Goniewicz, Roswell Park Cancer Center, Buffalo; Jamie S. Ostroff, Memorial Sloan-Kettering Cancer Center, New York, NY; Nasser H. Hanna, Indiana University Health Simon Cancer Center, Indianapolis, IN; Dorothy K. Hatsukami, Masonic Cancer Center, Minneapolis, MN; Roy S. Herbst and Benjamin A. Toll, Yale Comprehensive Cancer Center, New Haven, CT; Jennifer A. Hobin, American Association for Cancer Research, Philadelphia, PA; Peter G. Shields, Ohio State University Medical Center, Columbus, OH; Courtney A. Tyne, American Society of Clinical Oncology, Alexandria, VA; Kasisomayajula Viswanath, Dana-Farber Cancer Institute, Boston, MA; and Graham W. Warren, Medical University of South Carolina, Charleston, SC.

Published online ahead of print at www.jco.org on January 8, 2015.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Roy S. Herbst, MD, PhD, 333 Cedar St, WWW221, New Haven, CT 06520-8028; e-mail: roy.herbst@yale.edu.

© 2015 by American Association for Cancer Research and American Society of Clinical Oncology

0732-183X/15/3399-1/\$20.00

DOI: 10.1200/JCO.2014.59.4465

ABSTRACT

Combustible tobacco use remains the number-one preventable cause of disease, disability, and death in the United States. Electronic nicotine delivery systems (ENDS), which include electronic cigarettes, are devices capable of delivering nicotine in an aerosolized form. ENDS use by both adults and youth has increased rapidly, and some have advocated these products could serve as harm-reduction devices and smoking cessation aids. ENDS may be beneficial if they reduce smoking rates or prevent or reduce the known adverse health effects of smoking. However, ENDS may also be harmful, particularly to youth, if they increase the likelihood that nonsmokers or former smokers will use combustible tobacco products or if they discourage smokers from quitting. The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) recognize the potential ENDS have to alter patterns of tobacco use and affect the health of the public; however, definitive data are lacking. The AACR and ASCO recommend additional research on these devices, including assessing the health impacts of ENDS, understanding patterns of ENDS use, and determining what role ENDS have in cessation. Key policy recommendations include supporting federal, state, and local regulation of ENDS; requiring manufacturers to register with the US Food and Drug Administration and report all product ingredients, requiring childproof caps on ENDS liquids, and including warning labels on products and their advertisements; prohibiting youth-oriented marketing and sales; prohibiting child-friendly ENDS flavors; and prohibiting ENDS use in places where cigarette smoking is prohibited.

This policy statement was developed by a joint writing group composed of members from the Tobacco and Cancer Subcommittee of the American Association for Cancer Research (AACR) Science Policy and Government Affairs (SPGA) Committee and American Society of Clinical Oncology (ASCO) Tobacco Cessation and Control Subcommittee of the Cancer Prevention Committee (CaPC). The statement was reviewed by both parent committees (ie, the AACR SPGA Committee and the ASCO CaPC) and was approved by the AACR Boards of Directors on August 6, 2014, and the ASCO Executive Committee on September 18, 2014. This policy statement was published jointly by invitation and consent in both *Clinical Cancer Research* and *Journal of Clinical Oncology*. Copyright 2015 American Association for Cancer Research and American Society of Clinical Oncology. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or storage in any information storage and retrieval system, without written permission by the American Association for Cancer Research and the American Society of Clinical Oncology.

INTRODUCTION

Tobacco is the number-one preventable cause of disease, disability, and death in the United States. Combusted tobacco, which contains more than 7,000 chemicals, including hundreds of toxic compounds,¹ is particularly dangerous. The 2014 Surgeon General's Report reaffirmed the overwhelming adverse health effects of smoking, which has resulted

in 20,000,000 premature deaths since 1964.² An estimated 484,000 people in the United States die prematurely as a result of smoking-related illnesses each year; 5.6 million children alive today will die prematurely if current smoking trends continue.² Smoking causes 18 forms of cancer and accounts for 30% of all cancer deaths in the United States. It is also a known cause of numerous other diseases and conditions. The risk of lung cancer has increased in both

men and women over the past 50 years as a result of changes in the design and composition of cigarettes.² Moreover, continued smoking by patients with cancer and survivors reduces the effectiveness of cancer treatments and causes increased overall mortality, cancer-specific mortality, and risk for second primary cancer.^{2,3} Preventing tobacco use initiation and facilitating cessation are the best ways to combat the problems caused by smoking. Smokers who quit greatly reduce their risk for disease and premature death, and smoking cessation improves the outcomes of patients with cancer.² Clear evidence demonstrates that mass media campaigns and comprehensive community-based programs and statewide tobacco control programs reduce the prevalence of tobacco use among all age groups,² which has resulted in tobacco use becoming a less socially acceptable behavior over the last 50 years. Reductions in tobacco use are followed by subsequent reductions in chronic disease²; however, given the delayed time course needed to assess the adverse impacts of cigarette smoking and health benefits associated with cessation, evaluating the health effects of electronic nicotine delivery systems (ENDS) should be conducted in a more timely manner than was done with cigarettes.

There is agreement that eliminating the use of combustible tobacco products would improve public health substantially. However, there is less agreement as to whether ENDS should be used as a substitute for smoking among those who experience difficulty quitting or do not want to quit. ENDS, including electronic cigarettes (e-cigarettes), are battery-operated devices capable of delivering nicotine in an aerosolized form. ENDS do not combust tobacco or contain the same number or concentrations of carcinogens and toxicants found in cigarette smoke. They may, therefore, have value as harm-reduction devices and tobacco-cessation interventions.⁴ Indeed, many smokers report using ENDS to reduce and/or stop smoking.⁵ ENDS may be beneficial if they reduce smoking rates or prevent or reduce the known adverse health effects of smoking. However, ENDS may be harmful, particularly to youth, if they increase the likelihood that nonsmokers or former smokers will use combustible tobacco products or if they discourage smokers from quitting. Although ENDS are being marketed with health claims and smoking-cessation messages,⁶ there are insufficient data at this time on the long-term health consequences of ENDS to all segments of the population, their value as tobacco-cessation aids for current smokers, and their effects on the use of combustible tobacco products by nonsmokers and current smokers. Moreover, our understanding of ENDS is changing rapidly as use increases and products evolve, making it difficult to interpret the evidence, because conclusions based on studies conducted a few years ago may not apply to the marketplace today.

The American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) are leading professional societies for clinicians and researchers in the field of oncology, both with a focus that includes preventing and curing cancer through research, education, communication, and collaboration. As a new nicotine delivery technology with the unknown but potentially significant ability to alter patterns of tobacco use and its attendant public health consequences, ENDS are of particular interest to ASCO and the AACR. Our organizations convened an expert panel to develop a joint policy statement with the goals of:

- Educating policymakers, oncologists, and other health care providers, researchers, and the public on the major public health and policy issues relevant to ENDS.

- Outlining the clinical concerns oncologists and other health care providers face when encountering a patient who uses or expresses interest in ENDS.
- Identifying key research necessary to build a more complete evidence base for understanding the safety profile and public health impact of ENDS and for informing ENDS regulation and possible patient care.
- Providing recommendations to policymakers for regulating ENDS.

WHAT ARE ENDS?

ENDS are designed to deliver nicotine with fewer toxicants and carcinogens than traditional cigarettes by vaporizing a nicotine solution instead of combusting tobacco. In automatic ENDS models (Fig 1), when a user inhales from the device, airflow is detected by a sensor, which activates a heating element that aerosolizes a solution (ie, creates a fine mist of liquid droplets, often referred to as a vapor) typically containing nicotine that is stored in the mouthpiece cartridge. In manually operated models, a heating element is activated by pressing a button. Some models include a light-emitting diode that is activated during inhalation and simulates the glow of burning tobacco.

The first ENDS products appeared on the US market in the first decade of 2000 and were initially imported from China and distributed online by independent companies. These products have evolved rapidly in recent years, as the market has changed and products have become more available and more sophisticated.⁷ At the time of this publication, there are more than 460 ENDS brands, with more than 7,700 flavors available on the Internet. Rechargeable and disposable e-cigarettes are often referenced as first-generation ENDS, whereas

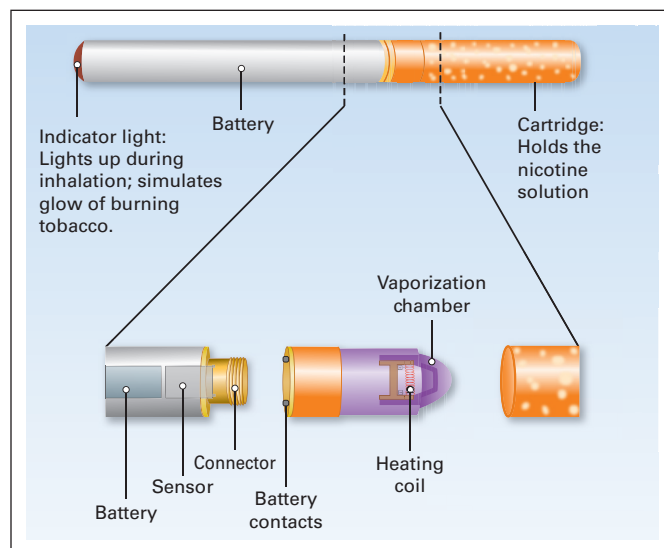


Fig 1. Basic components and operation of electronic nicotine delivery systems (ENDS). When a user inhales from the ENDS device, airflow is detected by a sensor. The sensor activates a heating element that pulls the e-liquid stored in the cartridge into the vaporization chamber where it is aerosolized (ie, turned from e-liquid into a fine mist of liquid droplets, often referred to as a vapor). The aerosolized e-liquid is then inhaled by the user. In some models, activation of the sensor also powers the indicator light, which simulates the glow of burning tobacco. In manually operated models, the heating element is activated by pressing a button.

tank systems and personal vaporizers are referred to as second- and third-generation products, respectively. First- and second-generation devices are typically distributed via convenience stores, pharmacies, and gas stations. There are a number of independent companies that sell only ENDS products (mostly second-generation tank systems), but major tobacco companies have begun to market their own ENDS brands as well, usually consisting of first-generation disposable or rechargeable products. Third-generation devices (personal vaporizers) are typically sold at local shops, commonly called vape shops or vape lounges. A fourth-generation digital delivery device became available nationally earlier this year.⁸ ENDS differ primarily in appearance, the nature and concentration of the nicotine solution, the capacity of the cartridge or reservoir (so-called tank) containing the solution, the nature of the heating element, and the size and type of battery (Fig 2). Propylene glycol and glycerin are the primary solvents for the nicotine. The solution may contain either or both solvents mixed with water. Various additives and flavorings are commonly added to the solution, including fruit and candy flavors, various sug-

ars, ethyl alcohol, non-nicotine pharmacologically active compounds, and stabilizers. The heating elements are usually thin wire made with various metals (nickel, chromium, copper coated with silver). These engineering features affect the chemical composition and potential toxicity of the ENDS aerosol.^{9,10}

Research reports on ENDS focus primarily on e-cigarettes and are largely limited by reports on self-selected groups of ENDS users. Long-term users report that they had started with cigarette-like ENDS products and progressed to more sophisticated devices. One study reported that novice users usually buy e-cigarette starter kits containing a basic model of the device, a battery charger, liquid refills, and instructions. Experienced users often seek products with a variety of batteries, atomizers, and liquids, which may not resemble traditional cigarettes and may include longer-lasting and higher-voltage batteries capable of vaporizing a larger amount of liquid and producing the so-called throat hit preferred by some users.¹¹ The numerous colors, artistic designs, carrying cases, and accessories for ENDS support a variety of individual styles.

ENDS type	Product characteristics
Disposable e-cigarette 	• For short time use • Cheap; widely available from gas stations or super markets • Convenient, as no refill solution or cartridge is needed • Might be a starting point for many users
Rechargeable e-cigarette 	• Various sizes from cigarette size to compact flashlight size • Various colors and styles • Requires battery with a charger • Requires replacing or refilling nicotine cartridges
Tank system e-cigarette 	• High capacity • Battery operated • Lasts longer than typical rechargeable models • Requires refilling the tank with nicotine solution • Often recommended for heavy smokers by retailers
Personal Vaporizer 	• Large size and heavy weight • Battery power output control allows the user to adjust the output of the voltage going to the heating element, which has a direct effect on the temperature of the heating element • Usually not recommended by retailers for beginning users
E-cigar 	• Looks like an authentic large cigar • Usually disposable

Fig 2. Overview of various types of electronic nicotine delivery systems (ENDS). This table lists and describes examples of ENDS on the market. ENDS and ENDS refill solutions are available in a wide variety of flavors, and the products are rapidly evolving.

Table 1. Major Provisions of FDA Proposal to Extend Its Regulatory Authority Over e-Cigarettes

Provision
Prohibit sale of e-cigarettes to individuals age < 18 years and require retailers to verify birth date of any purchaser age < 26 years by reviewing individual's photographic identification
Prohibit distribution of free samples of e-cigarettes
Prohibit sale of e-cigarettes through vending machines except in adults-only facilities
Require e-cigarette manufacturers to:
Register with FDA and report all product and ingredient listings, including harmful and potential harmful components
Only market new tobacco products after FDA review
Only make direct and implied claims of reduced risk if FDA confirms that scientific evidence supports claim and that reduced-risk product marketing will benefit public health as a whole
Include following health warning on e-cigarette packaging and advertising: "WARNING: This product contains nicotine. Nicotine is an addictive chemical."

NOTE. In April 2014, FDA released proposal to extend its regulatory authority over e-cigarettes using its authority under Family Smoking Prevention and Tobacco Control Act. If adopted, proposed rule would give FDA authority to regulate manufacturing, distribution, and marketing of these products. Proposed rule would not prohibit sale of flavored e-cigarettes; restrict advertising, marketing, or promotion of e-cigarettes; impose taxes on e-cigarettes; or impose restrictions on indoor e-cigarette use.

Abbreviation: FDA, US Food and Drug Administration.

Although definitive data are lacking, nicotine from ENDS is likely absorbed through the upper aerodigestive tract through mucosal surfaces or lung parenchyma that are in direct contact with ENDS aerosol. At this time, it remains unclear how effectively various ENDS deliver nicotine. Furthermore, some ENDS contain no nicotine or virtually no nicotine. There are at least four factors that affect the amount of nicotine from ENDS absorbed into the bloodstream and reaching the nicotinic receptors in the brain: 1) the nicotine content in a product; 2) how effectively the vaporization process transfers nicotine from the reservoir into the aerosol; 3) additives that may facilitate nicotine absorption; and 4) use habits (such as frequency and depth of inhalation) that may affect the bioavailability of nicotine. Some studies suggest large between-brand and within-brand differences in nicotine vaporization.¹²⁻¹⁴ The differences are likely to be a function of different types of heaters reacting differently to the spacing and frequency of puffs employed in the studies. Other factors affecting nicotine bioavailability are product characteristics such as cartridge size, battery strength, aerosol pH, and draw resistance. For example, some ENDS have cartridges that contain levels of nicotine similar to other brands, but the aerosol contains substantially lower levels.¹⁴ Early models tended to deliver relatively low doses of nicotine compared with cigarettes, but newer devices using high-nicotine concentration solutions might deliver nicotine at levels comparable to those derived from cigarettes.¹⁵⁻¹⁹ In addition to delivering nicotine, the aerosol may also provide a flavor and physical sensation sought by many smokers that are similar to those of inhaled combustible tobacco smoke.

CURRENT REGULATION OF ENDS

The policy environment for ENDS is rapidly changing, and regulation of these products varies widely around the world. At the time of this publication, ENDS containing nicotine derived from tobacco fall within the statutory definition of tobacco products within the United States so long as manufacturers do not make therapeutic claims that would qualify them as drugs or drug delivery devices. Unlike combustible cigarettes, however, ENDS are not yet regulated under the tobacco regulatory authority of the US Food and Drug Administration (FDA). As a result, there is a lack of mandatory manufacturing standards for ENDS, and few quality controls are in place.²⁰ The FDA

recently released a proposal²¹ to extend its regulatory authority over ENDS. If adopted, the rule would give the agency authority to: regulate the manufacturing, distribution, and marketing of these products, including requiring ENDS manufacturers to report product and ingredient listings; require public health warnings on products and advertisements; prohibit manufacturers from marketing new ENDS products before FDA review; and prohibit manufacturers from making direct and implied claims of reduced risk in the absence of scientific evidence supporting a public health benefit (Table 1). The FDA has also proposed prohibiting distribution of free samples of ENDS products, sales to youth, and sales through vending machines, except in adults-only facilities. Although the agency may choose to do so in the future, the proposal by the FDA does not impose restrictions on the advertising, marketing, or promotion of ENDS or impose ENDS products standards such as a ban on characterizing flavors (both of which apply to combustible cigarettes, although menthol-flavored cigarettes are permitted). In the absence of federal regulations, both advertising of ENDS^{6,22} and flavored ENDS⁷ have proliferated. At the time of publication, there are more than 7,700 e-cigarette flavors available,⁷ and youth and young adult exposure to e-cigarette advertising on television had increased by 257% and 321%, respectively, from 2011 to 2013.²³ The FDA does not have the authority to tax ENDS or restrict their use in public spaces, although states and local jurisdictions may do so. Indeed, many have already taken action to regulate ENDS, including imposing restrictions on the sale of ENDS to minors and prohibiting use of ENDS in public places.^{24,25} Currently, only one state, Minnesota, explicitly includes e-cigarettes in its tobacco tax regulation; this regulation equates to 95% of the wholesale cost of the product.²⁵ Comparatively, every state taxes cigarettes, with tax rates ranging from \$0.30 per pack in Virginia to \$4.35 per pack in New York.²⁶ Federal excise taxes for cigarettes are currently at \$1.01 per pack.²⁶

WHAT ARE THE PUBLIC HEALTH EFFECTS OF ENDS?

Toxicity

Of the relatively few research reports on the safety of ENDS, most involve e-cigarettes. Although e-cigarettes do not contain many of the toxic substances in cigarette smoke, a recent FDA review¹² reported that various chemical substances and ultrafine particles known to be

toxic or carcinogenic and/or to cause respiratory and heart distress have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions. Another study found the levels of the toxicants in e-cigarettes to be significantly lower than in cigarette smoke and, in many cases, comparable to the trace amounts found in a medicinal nicotine inhaler.²⁷ It is important to note that there is wide variation in product components and methodologies used in these studies, and methods for assessing toxicants in ENDS are not well validated.¹² Moreover, it remains unclear what effects these toxicants might have on ENDS users after chronic and frequent use of the devices, and there are several unanswered health questions, such as the pulmonary effects of propylene glycol, glycerin, and other constituents of ENDS.

Nicotine is the compound in tobacco that can cause addiction,²⁸ and like combustible cigarettes, many e-cigarettes deliver nicotine. The 2014 Surgeon General's Report concludes that nicotine activates multiple biologic pathways through which smoking increases risk for disease, that nicotine adversely affects maternal and fetal health during pregnancy, and that exposure to nicotine during fetal development has lasting adverse consequences for brain development.² Moreover, evidence suggests that nicotine exposure during adolescence may have lasting adverse consequences on the developing brain.

Nicotine is a known potentially lethal toxin, and poisoning related to ENDS can occur by ingestion, inhalation, or absorption through the skin or eyes. Concerns have been raised that ENDS can harm their users by delivering toxic nicotine levels. Nicotine levels can be assessed by measuring cotinine, a nicotine metabolite and validated biomarker of nicotine uptake.¹⁷ Two pilot studies measured saliva cotinine levels in samples collected from ENDS users and found high levels of cotinine, suggesting that experienced ENDS users are able to gain as much nicotine from ENDS as smokers do from cigarettes.^{17,29} The observed levels were similar to levels previously observed in smokers and higher than levels previously found in nicotine-replacement therapy (NRT) users.^{17,29} Other studies have shown that some ENDS users experience adverse effects such as mouth and throat irritation, which may be caused by exposure to nicotine itself, nicotine solvents, or toxicants found in the aerosol.^{30,31} However, given the relatively low doses of nicotine that ENDS deliver, and users' ability to titrate the desired dose by adjusting the frequency and topography of their puffs, serious overdose from ENDS aerosol inhalation is unlikely. In contrast, the concentrated nicotine in ENDS solutions can be toxic if it is inadvertently ingested or absorbed through the skin. Data from the Centers for Disease Control and Prevention showed a significant increase in e-cigarette-related calls to poison centers; the number of calls rose from one per month in September 2010 to 215 per month in February 2014, with more than half of the calls involving young children.³²

Exposure to secondhand smoke from combustible cigarettes is an established health risk.² There are no current data to suggest that secondhand exposure to ENDS has any health effects; however, secondhand exposure to ENDS vapor is possible. Although no side-stream aerosol is generated from ENDS between puffs, some of the aerosol is exhaled by the user, and e-cigarettes may expose nonusers to nicotine from secondhand exposure.^{33,34} It has also been reported that e-cigarettes emit ultrafine particles, trace amounts of carbonyls, volatile organic compounds, polyaromatic hydrocarbons, tobacco-specific nitrosamines, and glycols into the indoor air.^{35,36} However, other studies have found levels of dangerous substances that fall below Occupational Safety and Health Administration exposure limits.³⁷

The emissions of nicotine and toxicants from e-cigarettes were significantly lower than those of combustible cigarettes. It has been estimated that secondhand exposure to nicotine from e-cigarettes is on average 10× less than from tobacco smoke, but the level of exposure depends on the brand.³⁴

Thirdhand exposure occurs when nicotine and other chemicals from secondhand aerosol deposit on surfaces, exposing people via touch, ingestion, and inhalation.^{38,39} Nicotine is incredibly difficult to remove from surfaces, and although emissions of nicotine and toxicants from e-cigarettes are small compared with combustible cigarettes, they might still be a significant source of thirdhand exposure.^{34,35} There are no published studies evaluating thirdhand exposure to ENDS aerosol in indoor environments, although preliminary data suggest that nicotine from ENDS can stick to surfaces.⁴⁰

Assessments of the effects of secondhand ENDS use should consider not only the health effects of exposure to the aerosol, but also the effects it may have on an individual's desire to smoke. One study found that exposing young-adult daily smokers to e-cigarette use by others in an experimental setting increased their desire to smoke combustible and e-cigarettes.⁴¹

Abuse Liability

Nicotine is the primary addictive component of tobacco. Knowledge about the addictiveness or abuse liability of ENDS is important to determine the potential for continued and persistent use of these products, the extent to which they can substitute for cigarettes, and how difficult it will be for ENDS users to stop using these devices after initiation of regular use. Although some ENDS do not contain nicotine, surveys show that 97% of respondents who use e-cigarettes use products containing nicotine.⁴² However, research on the abuse liability of ENDS is complicated by variation among product composition and use patterns. In addition to variable nicotine delivery within and across brands,^{43,44} nicotine delivery varies by the user's level of experience with these products, with more experienced users obtaining levels of nicotine comparable to those achieved by cigarette smokers.^{17,19,45} However, the rate of absorption, an important factor contributing to the abuse liability of a drug, may be slower for e-cigarettes compared with conventional cigarettes,¹⁵ which may lessen the abuse potential of e-cigarettes compared with combustible cigarettes. The sensory aspects of ENDS use may also affect abuse liability. For example, Eissenberg⁴⁵ observed that despite the minimal increase in plasma nicotine from the e-cigarettes, there was a significant decrease in craving with the use of these products. Another study showed a reduction in self-reported stages of addiction whether or not the e-cigarettes contained nicotine.⁴⁶ To date, no study has been conducted that carefully investigated the effect of different nicotine doses of e-cigarettes to determine participant preference and effect. Furthermore, new generations of e-cigarettes are likely to improve nicotine delivery, and studies with these newer products are warranted.

WHO IS USING ENDS AND WHY?

When considering patterns of ENDS use, it is helpful to address adults and youth separately. Within either population, de novo use of ENDS by nonsmokers would present a public health concern, but this is a particular concern with respect to youth, especially if ENDS serve as a pathway to other tobacco products, including combustible cigarettes,

or renormalize cigarette smoking. With adults, the primary issue is the degree to which ENDS use by current smokers represents harm reduction (via smoking cessation or smoking reduction) versus harm escalation (by promoting greater nicotine intake through dual use and/or continued tobacco use). Current research to date cannot offer strong evidence with respect to these important public health issues, but it can provide context to identify future population-based changes in use and guide the design of more informative longitudinal research.

Youth ENDS Use

A 2011 study conducted with a national sample of adolescent males reported low use of e-cigarettes (< 1%). Approximately 18% of participants were willing to try e-cigarettes, and smokers were more willing to try them than nonsmokers.⁴⁷ National data on e-cigarette use by middle and high school students were gathered via the National Youth Tobacco Survey in 2011 and 2012.⁴⁸ Among middle and high school students, ever-use of e-cigarettes (tried at least once) increased from 3.3% to 6.8%, whereas current use (within the last 30 days) increased from 1.1% to 2.1%. Among high school students specifically, current use rose from 1.5% to 2.8%. However, of the ever-users in high school, 80.5% reported current use of combustible cigarettes in 2012, suggestive that e-cigarettes are primarily attractive to current smokers. Another analysis of National Youth Tobacco Survey data from the same time period confirmed that current e-cigarette users were much more likely to be current smokers.⁴⁹ Reasons for youth e-cigarette use are not well known at this time. Although absolute prevalence rates of e-cigarette use by youth are low, the proportional increase in current use is concerning.

Adult ENDS Use

The overall use of ENDS by adults is low, with less than 2% reporting using every day or some days in 2012 to 2013 compared with 18% who report using cigarettes.⁵⁰ Data on e-cigarette use by adults have been gathered primarily from Web-based surveys and convenience sampling, including regional samples, and from participants in online e-cigarette forums. Interpreting such data is difficult, but patterns suggest that e-cigarette prevalence is doubling annually and that the vast majority of e-cigarette users are smokers,⁵¹ with only approximately 1% lifetime prevalence among never-smokers.⁵² At least 20% to 35% of current smokers have tried e-cigarettes,⁵³⁻⁵⁵ with the proportion increasing rapidly. A recent review concluded that no consistent differences in prevalence have been found by sex, race/ethnicity, or age among adults, but low-income individuals seem more likely to have used e-cigarettes,⁵² a well-established pattern observed for cigarette use.² Adults primarily report use of e-cigarettes to quit or reduce smoking, because e-cigarettes are perceived to be safer than combustible cigarettes.⁵² Moreover, users tend to report high satisfaction with the product.⁵⁶

Overall, patterns suggest that e-cigarettes are used primarily by combustible cigarette smokers, but ever-use by never-smokers is higher among youth, raising concerns that this product may serve as an introduction to tobacco use among adolescents. Indeed, e-cigarette initiation by either youth or adult nonsmokers—including former smokers—is a cause for concern. Dual-use patterns seem to be common, and adults tend to report harm-reduction motivations for using e-cigarettes. However, existing data are rapidly evolving and are insufficient to clarify patterns of or motivations for ENDS use by youth or adults.

How Does ENDS Use Affect Smoking Cessation?

In the United States, the FDA has not approved ENDS as smoking cessation aids. To date, only a handful of studies have explored the efficacy of using ENDS for smoking cessation. The major studies are listed in Table 2. In general, these data suggest that ENDS might be as effective as NRT in helping smokers quit, and several studies have found ENDS use to be associated with withdrawal relief after smoking cessation. However, these studies are inconclusive to support or refute the use of ENDS as a potential smoking cessation aid. Although a few larger studies are reported here, most studies were observational. The clinical trials tended to be small and with limited or no assessment of nicotine delivery, ENDS product evaluation, or formal instructions on how to optimize product use. Furthermore, the types of products evaluated by these studies are no longer reflective of current products on the market.

Dual Use: Reducing Cigarette Use With ENDS

Dual use refers to the use of multiple tobacco products. Many ENDS users are dually using these products with combustible cigarettes, and studies find that ENDS use by cigarette smokers can reduce the number of cigarettes smoked.^{5,42,60,64} Although ENDS may deliver fewer toxic compounds compared with combustible cigarettes, the extent to which reducing exposure to these compounds would lead to meaningful reductions in adverse health effects is unknown. Prior studies show that reducing the number of cigarettes smoked by greater than 50% does not necessarily lead to health benefits.^{69,70} Although reducing smoking substantially may have health benefits, it may also be difficult to achieve. One study demonstrated that to achieve a 42% reduction in exposure to carcinogens, a reduction in cigarettes smoked of approximately 90% must occur.⁷¹ This result demonstrates that smokers trying to reduce the number of cigarettes they smoke tend to smoke each cigarette more intensely. The increased intensity occurred even when smokers were provided NRTs. Studies of e-cigarettes have shown that only 1% to 15% of those who continued to smoke reduced their usual brand smoking intake by approximately 90%.^{60,64} The health benefits or harms of dual use are as yet undefined. However, if dual use with reductions in smoking is a path toward abstinence from cigarette smoking, dual use could eventually lead to benefits in health.

Flavored ENDS

Flavored ENDS have proliferated, and there are now 7,764 unique flavors on the market.⁷ Research shows that flavored tobacco is particularly appealing to youth, and some flavored combustible products potentiate continued use and addiction.^{72,73} There is concern that flavored ENDS may have a similar effect on youth. Although it did not assess flavorants in general, a 2011 report from the Tobacco Products Scientific Advisory Committee concluded that there was sufficient evidence that the availability of menthol cigarettes likely increases experimentation and regular smoking and increases the likelihood of addiction and degree of addiction in youth.⁷² However, some experts believe that the availability of flavored ENDS may encourage adult smokers to switch from combustible products to ENDS, prevent youth from transitioning from ENDS to combustible products, and enhance the efficacy of ENDS as cessation aids. At present, the impact of flavored ENDS on patterns of use and smoking cessation is unknown.

Table 2. Major Studies on Use of ENDS for Smoking Cessation

Author	Study Type and Population	Sample Size	Results
Etter and Bullen ⁴²	Online survey of e-cigarette users recruited from Web sites who were current or former combustible cigarette smokers	3,567	92% of users who were current smokers reported e-cigarettes helped them to reduce smoking; 96% of former smokers reported product helped them to quit smoking; 79% used e-cigarettes to deal with craving; 67% used e-cigarettes to deal with tobacco withdrawal symptoms
Brown et al ⁵⁷	Survey of adults in United Kingdom who tried to quit smoking in last year	6,000	e-cigarette users had higher quit rate (20%) than those who used NRTs (10%) or no smoking cessation aids (15%)
Adkison et al ⁵	Four-country cross-sectional survey of current and/or former smokers	5,939	85% of current e-cigarette users reported using them to quit smoking; only 11% reported having quit, and there were no significant differences in quit rates between e-cigarette users and nonusers
Vickerman et al ⁵⁸	Survey of state telephone quit line participants registered for cessation services	2,758	e-cigarette users were less likely to quit smoking compared with never-users of e-cigarettes
Grana et al ⁵⁹	National sample of current US smokers recruited from Web-enabled panel	1,549	e-cigarette use at baseline did not predict smoking cessation 1 year later among smokers, regardless of whether they said they were using ENDS to quit or not
Polosa et al ^{60,61}	Observational study of smokers given access to e-cigarettes for 6 months	40	23% and 13% abstinence rates at 6 and 24 months, respectively; rates did not substantially differ from those found in similarly designed observational studies using NRT products ^{62,63}
Caponnetto et al ⁶⁴	Clinical trial of smokers assigned e-cigarettes with and without nicotine	300	No significant differences in abstinence rates were observed between smokers assigned e-cigarettes with and without nicotine; overall abstinence rates were similar to those found in trials where NRTs were provided for ≥ 6 months to reduce cigarette use ⁶⁵⁻⁶⁸
Bullen et al ⁴⁶	Clinical trial of adult smokers randomly assigned to nicotine-containing e-cigarettes, nicotine patches, or non-nicotine-containing patches	657	No difference in abstinence rates among groups at 6 months; quit rates were lower than expected for NRTs, but authors concluded that trial was not sufficiently powered to make conclusions on effectiveness of e-cigarettes

Abbreviations: ENDS, electronic nicotine delivery systems; NRT, nicotine replacement therapy.

WHAT ARE THE CLINICAL CONCERNS FOR ONCOLOGY?

The AACR and ASCO strongly encourage health care providers to provide or refer patients who use tobacco—including patients with cancer—to evidence-based cessation treatment and recommend the use of FDA-approved cessation methods.^{3,74,75} Providers treating patients with cancer should advise those who smoke that continued smoking can adversely affect their cancer treatment outcomes.^{2,3}

Given the overall lack of evidence supporting the use of ENDS as a proven cessation aid for smokers in general, and the absence of any data on the potential adverse effects of inhaling ENDS aerosol by patients with cancer undergoing treatment, oncologists would be wise to refrain from recommending ENDS to patients as a first-line therapy for smoking cessation. However, given the wide-scale marketing of ENDS, providers should expect that patients may ask questions such as: Are e-cigarettes safe for use? Are e-cigarettes effective in helping to quit smoking? Can I use e-cigarettes along with NRT to help me quit or cut down? In response to these queries, health care providers should commend their patients for their interest in quitting smoking and advise them that safe and effective cessation medications exist.⁷⁶ Providers should explain that ENDS are not currently approved for smoking cessation by the FDA and that there is wide variation in manufacturing and product design, as well as safety concerns for users and individuals exposed to ENDS aerosol. Currently, there is insufficient evidence to recommend ENDS to patients with cancer, and the potential benefits or harms of ENDS use by patients with cancer are unknown. A recent observational study of 1,074 patients with cancer seeking cessation treatment from 2012 to 2013 found increasingly high rates of e-cigarette use (38.5% of combustible cigarette smokers reported e-cigarette use in 2013 v 10.6% in 2012) and no evidence that

e-cigarette use was associated with superior cessation outcomes at follow-up.⁷⁷ No controlled trials have examined the efficacy and safety of ENDS in patients with cancer treated with surgery, chemotherapy, or radiotherapy. The potential interactions of ENDS with cytotoxic cancer therapeutics are also unknown, and there is in vitro evidence that nicotine stimulates proliferation, migration, invasion, and angiogenesis and decreases cancer cell death resulting from irradiation and chemotherapy, raising concern as to whether prolonged ENDS use might have similar effects in patients with cancer.⁷⁸ Moreover, scientists have found that human bronchial cells grown in a medium exposed to e-cigarette aerosol showed a similar pattern of gene expression to those grown in a medium exposed to tobacco smoke.⁷⁹

Whereas ENDS may have unknown adverse effects in patients with cancer, the adverse effects of smoking are not in question. Recognizing the importance of providing guidance to physicians, the International Association for the Study of Lung Cancer has published recommendations for discussing e-cigarette use with patients with cancer.⁸⁰ Oncologists should advise all smokers to quit smoking combustible cigarettes, encourage use of FDA-approved cessation medications, refer patients for smoking-cessation counseling, and provide education about the potential risks and lack of known benefits of long-term e-cigarette use.

RESEARCH CONSIDERATIONS FOR ENDS

The evidence regarding the risks and benefits of ENDS in different segments of the population such as current smokers and nonsmokers is difficult to interpret, because the marketplace of ENDS products is evolving rapidly, and data on the long-term consequences of ENDS use are not yet available. Additional studies are needed to inform

ENDS policy and regulation and to guide the decisions of consumers and health care providers related to ENDS use. Research in this field is complicated by the ever-changing and wide variability among and within products, a lack of standardized definitions of ENDS, variable user terminology, and a lack of established protocols for conducting ENDS research, including clinical trials. Despite the many challenges and gaps in our understanding, research on ENDS is progressing rapidly. The National Institutes of Health convened a workshop that resulted in a comprehensive research agenda for studying these products.⁸¹ The AACR and ASCO recommend research in the following areas, some of which were discussed at the National Institutes of Health workshop. Clinical studies should consider inclusion of healthy volunteers as well as vulnerable populations, such as children, pregnant women, patients with cancer and those with other acute or chronic medical conditions, and other underrepresented groups, where scientifically and ethically appropriate. Consistent with best practices, investigators should disclose potential conflicts of interest such as funding received from pharmaceutical, tobacco, and ENDS industry sources.

Analyzing ENDS products

What are the key design features of ENDS products? There are more than 460 ENDS brands, thousands of e-liquid alternatives on the market,⁷ and considerable variability in product design and performance.¹³ As a result, it is currently impossible draw firm conclusions about the health risks of these products as a whole. Research is needed to understand how different design features relate to potential abuse liability and toxicity, including if the compounds in ENDS are affected by heating, changes in chemical composition, or pH levels; if these compounds are absorbed into the bloodstream; and how e-liquid additives affect the bioavailability of these compounds, among other considerations. Research is also needed to understand whether potential health risks may be ameliorated by changes in product engineering.

How can ENDS product testing be standardized? Considering the wide variation in ENDS products and performance, a standardized system for testing ENDS would help define likely performance boundaries for different products, allow for comparison among products in regard to chemical composition and biologic and health effects, and enable longitudinal tracking of changes in product design.

Assessing the Health Impacts of ENDS

What are the health effects of acute and chronic ENDS product use, including second- and thirdhand exposure? In vitro, in vivo, and clinical studies are needed to develop biologic and clinical models of the physiologic effects of ENDS aerosol exposure. Studies should examine the efficacy and safety of ENDS in the general population and in patients with cancer treated with surgery, chemotherapy, and radiotherapy and how ENDS potentially interact with cytotoxic cancer therapies. The effect of ENDS use on treatment adverse effects, complications, response, and cancer recurrence also need to be examined. Relevant ENDS user outcomes should be examined relative to those individuals who continue to smoke, those who quit smoking, and those who use FDA-approved NRT products.

Does transition from smoking to ENDS confer a health benefit? The potential health benefits of using ENDS to eliminate or reduce the number of combustible cigarettes smoked should be exam-

ined in the general population and specific populations of interest, including patients with cancer.

What is the abuse potential of different types of ENDS? Although nicotine is a highly addictive drug, research is needed to determine the addictive potential of ENDS as related to nicotine content and product design. Studies should examine how variability in the nicotine concentration of ENDS liquid, the amount of nicotine vaporized, and ENDS topography affects delivery of nicotine to users and how this compares with nicotine delivered by combustible cigarettes and FDA-approved NRTs. Studies should also assess other factors that may contribute to potential abuse liability of ENDS, including non-nicotine additives and the sensory aspects of smoking.

Understanding the Perception and Patterns of ENDS Use

What are common patterns of ENDS use? Research is needed to understand reasons for, and patterns of, ENDS use among youth and adults, including how ENDS use affects use of combustible tobacco products. Research on ENDS use among patients with cancer and survivors is also warranted.

What are the effects of flavorants on the appeal and use of ENDS products, and what are their effects on smoking habits? Research is needed to understand how the addition of characterizing and noncharacterizing flavors to ENDS affects youth and adult ENDS initiation, long-term use, dual use with combustible products, the likelihood that users will transition to combustible tobacco products, and the use and utility of ENDS as cessation devices.

How does the marketing and availability of ENDS affect perception and use of ENDS as well as other tobacco products? Concerns have been raised that ENDS use may undermine the progress that has been made in tobacco control by renormalizing cigarette smoking.⁸² Studies are needed to understand how ENDS marketing and availability influences the perception and use of these and other tobacco products, particularly among youth.

How do tobacco control policies affect the pattern of ENDS use? The ultimate effect of ENDS on public health will likely depend on how they are regulated. In places where ENDS use is encouraged as an alternative to combustible cigarettes, it is likely that ENDS use will be more commonplace. The consequences of such policies are unknown and need to be studied.

Understanding the Potential Role of ENDS for Smoking Cessation

How do ENDS affect smoking reduction and cessation outcomes? Among smokers, controlled clinical trials are needed to determine whether ENDS facilitate or hinder short- and long-term smoking cessation as well as whether use of ENDS in addition to combustible cigarettes undermines cessation efforts or increases nicotine addiction/dependence. Studies should consider outcomes for smokers interested and not interested in quitting smoking. Currently, there is insufficient evidence regarding the potential benefits or harms of ENDS use among patients with cancer. Well-controlled trials examining the safety and efficacy of ENDS for treating tobacco dependence are needed to guide oncology practice guidelines.

Can ENDS be used effectively in combination with existing FDA-approved cessation medications? Patients who report polytobacco use or who use tobacco products in conjunction with NRT represent unique clinical challenges for appropriately managing acute nicotine

withdrawal and preventing nicotine toxicity, particularly in the medically vulnerable patient. Conversely, given the marked acceptability of ENDS among cigarette smokers interested in quitting, trials examining the safety and efficacy of combining ENDS with established FDA-approved cessation medications (standard care) should be considered.

How, if at all, should behavioral counseling be modified for ENDS cessation trials? Clinical practice guidelines currently recommend delivery of behavioral counseling and pharmacotherapy for optimal cessation outcomes. Research examining varied behavioral protocols in combination with ENDS is also warranted.

What effects does short- or long-term ENDS use have on smoking relapse among smokers who have quit using combustible cigarettes? The potential for abstinent smokers who sample ENDS to relapse to smoking as a result of nicotine or smoking cues triggered by ENDS should be evaluated, particularly in the context of stressful life events such as a cancer diagnosis and treatment.

POLICY RECOMMENDATIONS

There is a lack of data on the public health impact of ENDS on both individuals and the population as a whole, which makes it difficult to develop a comprehensive regulatory framework for these products at the current time. Nonetheless, it is prudent for policymakers to take steps to minimize the potential negative public health consequences of these products, particularly on youth, while taking care not to undermine their potential to reduce the harm caused by combustible cigarettes and other conventional tobacco products. The public health impact of cigarette smoking is devastating, and policy recommendations should consider reduction of the health hazards of smoking as paramount. With these goals in mind, the AACR and ASCO make the following policy recommendations:

1. The AACR and ASCO support regulation of all ENDS that meet the statutory definition of tobacco products, as well as their component parts, by the FDA Center for Tobacco Products, using its authority under the Family Smoking Prevention and Tobacco Control Act.^{8,3} The FDA Center for Tobacco Products should regulate both ENDS delivery systems and e-liquids containing tobacco-derived nicotine whether they are sold together or separately. The AACR and ASCO also support the major ENDS provisions in the regulation proposed by the FDA²¹ that are summarized in Table 1, and we encourage the FDA to release the final rule in a timely manner. ENDS products that do not meet the statutory definition of tobacco products (including those containing synthetic nicotine) should be regulated by the FDA through other appropriate authorities.
2. ENDS manufacturers should be required to register with the FDA and report all product and ingredient listings, including harmful and potential harmful components, as well as the nicotine concentration in the ENDS solution.
3. The AACR and ASCO encourage the FDA to exercise its regulatory authority to require health warning and safety labels in addition to its proposed nicotine

warning on e-cigarette packaging and advertising as appropriate to protect the public health.

4. To prevent youth from initiating use of ENDS products, the AACR and ASCO encourage the FDA to restrict youth-oriented marketing of ENDS, including prohibiting:
 - i) Self-service displays of ENDS in retail establishments;
 - ii) The provision of gifts and other giveaways with purchase of ENDS products;
 - iii) The sale and distribution of items such as hats or t-shirts with ENDS brand logos;
 - iv) Brand-name sponsorship of athletic, musical, or other social or cultural events or of any team in those events;
 - v) Youth-oriented advertising of tobacco products, including the use of cartoon characters in tobacco product advertising, promotion, packaging, or labeling.
5. The AACR and ASCO support applying federal regulations to ENDS that would require Internet and other mail-order sellers of ENDS products to check the age and identification of customers at the point of purchase and delivery; to comply with all laws in the purchaser's state or local jurisdiction; and pay all applicable federal, state, and local taxes.
6. The AACR and ASCO are concerned about the potential adverse health consequences of exposure to second- and thirdhand ENDS aerosol. To protect the health of nonusers, we support prohibiting the use of ENDS in places where combustible tobacco product use is prohibited by federal, state, or local law until the safety of second- and thirdhand aerosol exposure is established.
7. The AACR and ASCO fully support the FDA exercising its authority to require evidence-based changes to tobacco products and their constituents that are aimed at improving public health. Specifically, ASCO and the AACR support a product standard that would require all e-liquid refill bottles to be childproof, including childproof caps for eye-dropper refill bottles. Future research may point to the need for additional product changes for ENDS, including standards regulating design, constituents, nicotine levels, or other chemicals included in ENDS vapor.
8. Every effort should be made to prevent youth from using ENDS. Therefore, the AACR and ASCO recommend a prohibition on ENDS and ENDS liquid containing candy and other youth-friendly flavors unless there is evidence demonstrating that these products do not encourage youth uptake of ENDS. Flavors or flavor names that are brand and/or trademarked names for candy, cookies, soda, ice cream, and other nontobacco products that are especially attractive or recognizable to youth should also be prohibited. Every effort should be made to

prevent children from confusing ENDS and ENDS liquid with products designed for them or recognized as food. The AACR and ASCO recognize that flavored ENDS may be beneficial if they discourage the use of combustible products or facilitate cessation by appealing to the smoker who would use ENDS rather than cigarettes because of the flavoring. Today, there is no evidence for or against this, and the public health benefits of flavored ENDS are currently unknown. Therefore, priority should be placed on preventing youth from using these products.

9. The AACR and ASCO urge policymakers to support research on ENDS, including in the areas identified in the research recommendations section of this policy statement. This research should be used to guide future federal, state, and local regulatory and policy decisions with regard to taxation, indoor e-cigarette use, flavorings and other product standards, and e-cigarette marketing, among other issues. Funding generated through tobacco product taxes, including any potential taxes levied on ENDS, should be used to help support research on ENDS and other tobacco products, but should not preclude the allocation of federal funding for this research.
10. The AACR and ASCO recommend full public disclosure of all data related to ENDS composition, use, and health effects for dissemination and independent review as well as to enhance policy decisions for ENDS product regulation.
11. Particularly in the absence of federal ENDS regulation, the AACR and ASCO encourage state and local governments to implement ENDS regulations within their authorities that are appropriate for protecting the public health, including restricting the sale, distribution, marketing, and advertising of ENDS to youth.
12. Evidence shows that increasing taxes on cigarettes has been one of the most effective tobacco control strategies,² and differential taxation affects tobacco product use. The AACR and ASCO recommend taxing tobacco products proportionate to their harm. Therefore, at the present time, we recommend against taxing ENDS at equal or higher rates than combustible cigarettes.

13. The AACR and ASCO encourage international cooperation in developing standards for regulation of ENDS. Regulations should prioritize protection of the health of the public and draw on the best available scientific evidence whenever possible.

SUMMARY

Rapid elimination of combustible tobacco products would dramatically reduce the burden of tobacco-related death and disease. The AACR and ASCO support every effort to reduce the use of combustible tobacco, and we support careful consideration of ENDS as a potentially harmful, and a potentially beneficial, product in this regard. The benefits and harms must be evaluated with respect to the population as a whole and take into account the effect on youth, adults, nonsmokers, and smokers. There are currently too few data on the safety of ENDS and their efficacy as cessation products to recommend their use for the general population or for patients with chronic diseases such as cancer. The AACR and ASCO recommend strategic research on the composition, uptake, biologic effects, behavioral patterns, and health effects of ENDS use, including abuse liability of ENDS; research on how ENDS use affects other tobacco product use patterns; and research on how ENDS use affects treatment and outcomes for patients with cancer. The AACR and ASCO encourage policymakers to review the rapidly evolving literature regarding ENDS regularly and make public health decisions based on scientific evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Administrative support: Courtney A. Tyne

Data analysis and interpretation: Thomas H. Brandon, Maciej L. Goniewicz, Dorothy K. Hatsukami, Roy S. Herbst, Benjamin A. Toll, Kasisomayajula Viswanath, Graham W. Warren

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Centers for Disease Control and Prevention: Chemicals in Tobacco Smoke. http://www.cdc.gov/tobacco/data_statistics/sgr/2010/consumer_booklet/chemicals_smoke/
2. US Department of Health and Human Services: The Health Consequences of Smoking: 50 Years of Progress—A Report of the Surgeon General. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014

3. Toll BA, Brandon TH, Gritz ER, et al: Assessing tobacco use by cancer patients and facilitating cessation: An American Association for Cancer Research policy statement. *Clin Cancer Res* 19:1941-1948, 2013
4. Abrams DB: Promise and peril of e-cigarettes. *JAMA* 311:135-136, 2014
5. Adkison SE, O'Connor RJ, Bansal-Travers M, et al: Electronic nicotine delivery systems: International tobacco control four-country survey. *Am J Prev Med* 44:207-215, 2013
6. Grana RA, Ling PM: "Smoking revolution": A content analysis of electronic cigarette retail websites. *Am J Prev Med* 46:395-403, 2014
7. Zhu SH, Yun JY, Bonnevie E, et al: Four hundred and sixty brands of e-cigarettes and count-

ing: Implications for product regulation. *Tob Control* 23:iii3-iii9, 2014 (suppl 3)

8. iSmoke to launch new e-cigarette line: Electronics industry parent brings technology expertise to category. <http://www.cspnet.com/category-news/tobacco/articles/isoke-launch-new-e-cigarette-line>

9. Brown CJ, Cheng JM: Electronic cigarettes: Product characterisation and design considerations. *Tob Control* 23:ii4-ii10, 2014 (suppl 2)

10. Kosmider L, Sobczak A, Fik M, et al: Carbonyl compounds in electronic cigarette vapors-effects of nicotine solvent and battery output voltage. *Nicotine Tob Res* 16:1319-1326, 2014

11. McQueen A, Tower S, Sumner W: Interviews with "vapers": Implications for future research with

- electronic cigarettes. *Nicotine Tob Res* 13:860-867, 2011
12. Cheng T: Chemical evaluation of electronic cigarettes. *Tob Control* 23:ii11-ii17, 2014 (suppl 2)
13. Goniewicz ML, Kuma T, Gawron M, et al: Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 15:158-166, 2013
14. Goniewicz ML, Hajek P, McRobbie H: Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: Regulatory implications. *Addiction* 109:500-507, 2014
15. Farsalinos KE, Spyrou A, Tsimopoulou K, et al: Nicotine absorption from electronic cigarette use: Comparison between first and new-generation devices. *Sci Rep* 4:4133, 2014
16. Dawkins L, Corcoran O: Acute electronic cigarette use: Nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)* 231:401-407, 2014
17. Etter JF, Bullen C: Saliva cotinine levels in users of electronic cigarettes. *Eur Respir J* 38:1219-1220, 2011
18. Vansickel AR, Cobb CO, Weaver MF, et al: A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": Nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 19:1945-1953, 2010
19. Vansickel AR, Eissenberg T: Electronic cigarettes: Effective nicotine delivery after acute administration. *Nicotine Tob Res* 15:267-270, 2013
20. Benowitz NL, Goniewicz ML: Regulatory challenge of e-cigarettes. *JAMA* 310:685-686, 2013
21. Federal Register: Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act—Regulations on the sale and distribution of tobacco products and required warning statements for tobacco products. Proposed rule [79 FR 23141] 23:141-23207, 2014
22. Grana RA, Glantz SA, Ling PM: Electronic nicotine delivery systems in the hands of Hollywood. *Tob Control* 20:425-426, 2011
23. Duke JC, Lee YO, Kim AE, et al: Exposure to electronic cigarette television advertisements among youth and young adults. *Pediatrics* 134:e29-e36, 2014
24. American Nonsmokers' Rights Foundation: U.S. and Local Laws Regulating Use of Electronic Cigarettes. <http://www.no-smoke.org/pdf/ecigslaws.pdf>
25. National Conference of State Legislatures: Alternative Nicotine Products: Electronic Cigarettes. <http://www.ncsl.org/research/health/alternative-nicotine-products-e-cigarettes.aspx>
26. Campaign for Tobacco-Free Kids: State Cigarette Excise Tax Rates and Rankings. <http://www.tobaccofreekids.org/research/factsheets/pdf/0097.pdf>
27. Goniewicz ML, Knysak J, Gawron M, et al: Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 23:133-139, 2014
28. US Department of Health and Human Services: The Health Consequences of Smoking: Nicotine Addiction—A Report of the Surgeon General. Atlanta, GA, US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988
29. Etter JF: Levels of saliva cotinine in electronic cigarette users. *Addiction* 109:825-829, 2014
30. Bullen C, McRobbie H, Thornley S, et al: Effect of an electronic nicotine delivery device (e-cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: Randomised cross-over trial. *Tob Control* 19:98-103, 2010
31. Goniewicz ML, Lingas EO, Hajek P: Patterns of electronic cigarette use and user beliefs about their safety and benefits: An internet survey. *Drug Alcohol Rev* 32:133-140, 2013
32. Chatham-Stephens K, Law R, Taylor E, et al: Notes from the field: Calls to poison centers for exposures to electronic cigarettes—United States, September 2010-February 2014. *MMWR Morb Mortal Wkly Rep* 63:292-293, 2014
33. Flouris AD, Chorti MS, Poulitani KP, et al: Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol* 25:91-101, 2013
34. Czogala J, Goniewicz ML, Fidelus B, et al: Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res* 16:655-662, 2014
35. Schripp T, Markewitz D, Uhde E, et al: Does e-cigarette consumption cause passing vaping? *Indoor Air* 23:25-31, 2013
36. McAuley TR, Hopke PK, Zhao J, et al: Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol* 24:850-857, 2012
37. Rabinowitz JD, Leischow SJ: Electronic cigarettes that produce nicotine aerosols substantially devoid of known toxic impurities. Presented at the 20th Annual Meeting of the Society for Research on Nicotine and Tobacco, Seattle, WA, February 5-8, 2014
38. Protano C, Vitali M: The new danger of third-hand smoke: Why passive smoking does not stop at secondhand smoke. *Environ Health Perspect* 119:A422, 2011
39. Sleiman M, Gundel LA, Pankow JF, et al: Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci U S A* 107:6576-6581, 2010
40. Goniewicz ML, Lee L: Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine Tob Res* [epub ahead of print on August 30, 2014]
41. King AC, Smith LJ, McNamara PJ, et al: Passive exposure to electronic cigarette (e-cigarette) use increases desire for combustible and e-cigarettes in young adult smokers. *Tob Control* [epub ahead of print on May 21, 2014]
42. Etter JF, Bullen C: Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. *Addiction* 106:2017-2028, 2011
43. Williams M, Talbot P: Variability among electronic cigarettes in the pressure drop, airflow rate, and aerosol production. *Nicotine Tob Res* 13:1276-1283, 2011
44. Trtchounian A, Williams M, Talbot P: Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine Tob Res* 12:905-912, 2010
45. Eissenberg T: Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 19:87-88, 2010
46. Bullen C, Howe C, Laugesen M, et al: Electronic cigarettes for smoking cessation: A randomised controlled trial. *Lancet* 382:1629-1637, 2013
47. Pepper JK, Reiter PL, McRee AL, et al: Adolescent males' awareness of and willingness to try electronic cigarettes. *J Adolesc Health* 52:144-150, 2013
48. Centers for Disease Control and Prevention: Notes from the field: Electronic cigarette use among middle and high school students—United States, 2011-2012. *MMWR Morb Mortal Wkly Rep* 62:729-730, 2013
49. Dutra LM, Glantz SA: Electronic cigarettes and conventional cigarette use among US adolescents: A cross-sectional study. *JAMA Pediatr* 168:610-617, 2014
50. Agaku IT, King BA, Husten CG, et al: Tobacco product use among adults: United States, 2012-2013. *MMWR Morb Mortal Wkly Rep* 63:542-547, 2014
51. Grana R, Benowitz N, Glantz SA: Background paper on e-cigarettes (electronic nicotine delivery systems). <http://escholarship.org/uc/item/13p2b72n>
52. Carroll Chapman SL, Wu LT: E-cigarette prevalence and correlates of use among adolescents versus adults: A review and comparison. *J Psychiatr Res* 54:43-54, 2014
53. Czoli CD, Hammond D, White CM: Electronic cigarettes in Canada: Prevalence of use and perceptions among youth and young adults. *Can J Public Health* 105:e97-e102, 2014
54. Popova L, Ling PM: Alternative tobacco product use and smoking cessation: A national study. *Am J Public Health* 103:923-930, 2013
55. Regan AK, Promoff G, Dube SR, et al: Electronic nicotine delivery systems: Adult use and awareness of the "e-cigarette" in the USA. *Tob Control* 22:19-23, 2013
56. Pepper JK, Brewer NT: Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: A systematic review. *Tob Control* 23:375-384, 2014
57. Brown J, Beard E, Kotz D, et al: Real-world effectiveness of e-cigarettes when used to aid smoking cessation: A cross-sectional population study. *Addiction* 109:1531-1540, 2014
58. Vickerman KA, Carpenter KM, Altman T, et al: Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res* 15:1787-1791, 2013
59. Grana RA, Popova L, Ling PM: A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Intern Med* 174:812-813, 2014
60. Polosa R, Morjaria JB, Caponnetto P, et al: Effectiveness and tolerability of electronic cigarette in real-life: A 24-month prospective observational study. *Intern Emerg Med* 9:537-546, 2013
61. Polosa R, Caponnetto P, Morjaria JB, et al: Effect of an electronic nicotine delivery device (e-cigarette) on smoking reduction and cessation: A prospective 6-month pilot study. *BMC Public Health* 11:786, 2011
62. Carpenter MJ, Hughes JR, Gray KM, et al: Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: A randomized clinical trial. *Arch Intern Med* 171:1901-1907, 2011
63. Jolicoeur DG, Richter KP, Ahluwalia JS, et al: Smoking cessation, smoking reduction, and delayed quitting among smokers given nicotine patches and a self-help pamphlet. *Subst Abuse* 24:101-106, 2003
64. Caponnetto P, Campagna D, Cibella F, et al: Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. *PLoS One* 8:e66317, 2013
65. Wennike P, Danielsson T, Landfeldt B, et al: Smoking reduction promotes smoking cessation: Results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction* 98:1395-1402, 2003

66. Bolliger CT, Zellweger JP, Danielsson T, et al: Smoking reduction with oral nicotine inhalers: Double blind, randomised clinical trial of efficacy and safety. *BMJ* 321:329-333, 2000
67. Batra A, Klingler K, Landfeldt B, et al: Smoking reduction treatment with 4-mg nicotine gum: A double-blind, randomized, placebo-controlled study. *J Clin Pharm Ther* 78:689-696, 2005
68. Etter JF, Laszlo E, Zellweger JP, et al: Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: A randomized trial. *J Clin Psychopharmacol* 22:487-495, 2002
69. Stead LF, Lancaster T: Interventions to reduce harm from continued tobacco use. *Cochrane Database Syst Rev* 3:CD005231, 2007
70. Hughes JR, Carpenter MJ: Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res* 8:739-749, 2006
71. Hecht SS, Murphy SE, Carmella SG, et al: Effects of reduced cigarette smoking on uptake of a tobacco-specific lung carcinogen. *J Natl Cancer Inst* 96:107-115, 2004
72. Tobacco Products Scientific Advisory Committee: Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf>
73. Minaker LM, Ahmed R, Hammond D, et al: Flavored tobacco use among Canadian students in grades 9 through 12: Prevalence and patterns from the 2010-2011 youth smoking survey. *Prev Chronic Dis* 11:E102, 2014
74. Hanna N, Mulshine J, Wollins DS, et al: Tobacco cessation and control a decade later: American Society of Clinical Oncology policy statement update. *J Clin Oncol* 31:3147-3157, 2013
75. Viswanath K, Herbst RS, Land SR, et al: Tobacco and cancer: An American Association for Cancer Research policy statement. *Cancer Res* 70:3419-3430, 2010
76. Fiore MC, Jaen C, Baker T, et al (eds): Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD, US Department of Health and Human Services, 2008
77. Borderud SP, Li Y, Burkhalter JE, et al: Electronic cigarette use among patients with cancer: Characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer* 120:3527-3535, 2014
78. Warren GW, Singh AK: Nicotine and lung cancer. *J Carcinog* 12:1, 2013
79. Park SJ, Walser TC, Perdomo C, et al: The effect of e-cigarette exposure on airway epithelia cell gene expression and transformation. *Clin Cancer Res* 20, 2014 (suppl; abstr B16)
80. Cummings KM, Dresler CM, Field JK, et al: E-cigarettes and cancer patients. *J Thorac Oncol* 9:438-441, 2014
81. Walton KM, Abrams DB, Bailey WC, et al: NIH electronic cigarette workshop: Developing a research agenda. *Nicotine Tob Res* [epub ahead of print on October 21, 2014]
82. Fairchild AL, Bayer R, Colgrove J: The renormalizing of smoking? E-cigarettes and the tobacco endgame. *N Engl J Med* 370:293-295, 2014
83. Pub Law 111-31. Family Smoking Prevention and Tobacco Control Act 2009. <http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/html/PLAW-111publ31.htm>



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Electronic Nicotine Delivery Systems: A Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Thomas H. Brandon

Consulting or Advisory Role: Voxiva

Research Funding: Pfizer

Maciej L. Goniewicz

No relationship to disclose

Nasser H. Hanna

No relationship to disclose

Dorothy K. Hatsukami

No relationship to disclose

Roy S. Herbst

Honoraria: Eli Lilly, Merck, Boehringer Ingelheim, Celgene, Pfizer, NovaRX

Consulting or Advisory Role: Koltan Pharmaceuticals, DiaTech Oncology, n of 1, Biothera

Research Funding: Genentech/Roche

Jennifer A. Hobin

No relationship to disclose

Jamie S. Ostroff

Research Funding: Pfizer

Peter G. Shields

No relationship to disclose

Benjamin A. Toll

No relationship to disclose

Courtney A. Tyne

No relationship to disclose

Kasisomayajula Viswanath

No relationship to disclose

Graham W. Warren

No relationship to disclose

Acknowledgment

The joint writing group thanks Drs Neal Benowitz, K. Michael Cummings, Stephen Hecht, and Marina Picciotto and Micah Berman for providing insightful comments on the statement.