Electronic Nicotine Delivery Systems: An Updated Policy Statement from the American Association for Cancer Research and the American Society of Clinical Oncology

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ABSTRACT

Combustible tobacco use has reached historic lows, demonstrating the importance of proven strategies to reduce smoking since publication of the 1964 Surgeon General's report. In contrast, the use of electronic nicotine delivery systems (ENDS), specifically e-cigarettes, has grown to alarming rates and threatens to hinder progress against tobacco use. A major concern is ENDS use by youth and adults who never previously used tobacco. While ENDS emit fewer carcinogens than combustible tobacco, preliminary evidence links ENDS use to DNA damage and inflammation, key steps in cancer development. Furthermore, high levels of nicotine can also increase addiction, raise blood pressure, interfere with brain development, and suppress the immune system. The magnitude of long-term health risks will remain unknown until longitudinal studies are completed. ENDS have been billed as a promising tool for combustible tobacco cessation, but further evidence is needed to assess their potential efficacy for adults who smoke. Of concern, epidemiological studies estimate that approximately 15% to 42% of adults who use ENDS have never used another tobacco product, and another 36% to 54% "dual use" both ENDS and combustible tobacco. This policy statement details advances in science related to ENDS and calls for urgent action to end predatory practices of the tobacco industry and protect public health. Importantly, we call for an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine to reduce ENDS use by youth and adults who never previously used tobacco. Concurrently, evidence-based treatments to promote smoking cessation and prevent smoking relapse to reduce cancer incidence and improve public health remain top priorities for our organizations. We also recognize there is an urgent need for research to understand the relationship between ENDS and tobacco-related disparities.

Introduction

In 2015, the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) published a joint policy statement describing a rapidly growing epidemic of electronic nicotine delivery systems (ENDS), including e-cigarettes, and policies to address this trend (1). The 2015 statement sought to balance curtailing youth use while remaining optimistic that ENDS could be a less harmful alternative to combustible tobacco cigarettes for adult smokers. As detailed in the following sections, youth ENDS use has further increased since the 2015 statement while evidence remains insufficient to show ENDS are more effective than current smoking cessation strategies. Additionally, several major health authorities have determined that the current evidence base is lacking in supporting ENDS as tobacco cessation aids, including the U.S. Surgeon General (2); the National Academies of Science, Engineering, and Medicine (NASEM; ref. 3); the U.S. Preventive Services Task Force (USPSTF; ref. 4); and the National Comprehensive Cancer Network, a coalition of 31 leading cancer centers (5). At the time of this writing, no ENDS manufacturer has applied to the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) for an Investigational New Drug (IND) application, a prerequisite to run a

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tobacco cessation clinical trial. The AACR and ASCO are publishing the present statement to detail advances in scientific understanding of the ENDS epidemic, strengthen recommendations to protect public health, promote evidence-based tobacco cessation across all groups, and highlight areas where more research is needed.

Carcinogens from combustible tobacco products are very harmful to health, contributing to nearly half a million deaths each year in the United States and more than 8 million deaths per year globally (6, 7). The process of burning creates a large amount of carcinogens, such as benzo[a]pyrene, that are inhaled in smoke from traditional cigarettes (8). The first ENDS were introduced to the U.S. market in 2006 as a way to deliver nicotine to users without burning tobacco (9). Instead of burning tobacco, ENDS use electricity to power a heating element that aerosolizes an e-liquid, containing a solvent (e.g., propylene glycol or glycerin); nicotine; flavors; and other additives. Some ENDS products can result in rapid delivery of a similar amount of nicotine as modern American cigarettes, which contribute to high addiction potentials (10, 11).

Tobacco would likely not be the top public health issue without the highly addictive properties of nicotine when delivered rapidly. Every time someone consumes nicotine, the brain releases the neurotransmitter dopamine, which provides a sense of pleasure or satisfaction (12). Primarily due to the pharmacology of nicotine, over time, tobacco users become dependent on nicotine to feel pleasure and stave off withdrawal symptoms (13). This rewiring of brain circuitry is especially of concern for the developing brains of youth (14). Nicotine can also harm health by raising blood pressure (15) and suppressing immune function (16). Strong evidence from clinical trials examining very low nicotine cigarettes demonstrates that reducing nicotine to less addictive levels could effectively decrease smoking rates by reducing initiation and increasing cessation of cigarette use (17–21). In 2018, the FDA issued a proposed rule to lower the level of nicotine in cigarettes to nonaddictive or minimally addictive levels (22), but at the time of writing this rule has not advanced. While the present statement focuses on policies related to ENDS, additional regulations to reduce the addictiveness and appeal of combustible tobacco are also highly important.

The following sections outline updates since our previous statement related to the evidence of biological effects from ENDS that can contribute to cancer risk, use trends, effective tobacco cessation efforts, and ENDS regulations. The data support strong, urgent action to reduce ENDS use among youth and adults who never previously used tobacco. Because of the wide use of non-tobacco-flavored ENDS among these groups, we recommend an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine. However, if non-tobacco-flavored ENDS are reviewed and approved by FDA CDER to increase cessation efficacy, the AACR and ASCO would welcome these as cessation therapies at that time. At the same time, new tobacco regulations should be structured to avoid any increases in combustible tobacco use, including smoking initiation and relapse. The following sections describe the evidence by which we based our recommendations.

ENDS Linked to Key Steps in Cancer Development

ENDS expose users to carcinogens

The cancer-causing potential of ENDS is inferred from the currently available studies investigating the presence of carcinogens, human biomarkers of carcinogenesis, and animal and cell culture experiments. Carcinogens in ENDS can include four classes of chemicals, namely tobacco-specific nitrosamines; metals; volatile organic compounds; and polycyclic aromatic hydrocarbons. **Table 1** highlights several recent reports comparing carcinogens and metabolites in urine or saliva samples from ENDS users and those who never used tobacco. The data show that at least 12 carcinogens are significantly elevated in ENDS users compared with nontobacco users, but that their levels were generally lower than the levels of carcinogens seen in smokers and dual users (**Table 1**; refs. 23–26). Unfortunately, the data are limited by a small number of studies that compared ENDS users with nonusers, and each study reported a different set of carcinogens. Separate studies further characterized carcinogens in ENDS aerosols and found that the power and temperature of devices greatly influences the amount of toxic metals and volatile organic compounds emitted (27–30). Therefore, additional studies are needed for a more thorough and comprehensive understanding of the carcinogen load experienced by ENDS users. Nevertheless, the results of ENDS use investigated to date clearly indicate that vaping exposes the user to carcinogens and therefore likely increases long-term cancer risk, but for most carcinogens at levels far lower than from smoking combustible tobacco cigarettes.

ENDS linked to DNA damage

Several reports have found that ENDS vapor or extracts cause DNA damage in cell culture either by directly changing the chemical structure of DNA or indirectly by increasing highly reactive oxygen-containing molecules (32–36). One of those reports found that potent antioxidant molecules prevented DNA damage in cell culture, confirming the contribution of reactive oxygen species (32). A limitation of some studies is that they use higher concentrations of ENDS vapor than experienced by ENDS users, but DNA damage was also found in studies that used lower concentrations. Chemical modification of DNA by ENDS extracts leads to broken DNA strands (35, 37), which must be repaired by cells, or they will die. Repairing broken DNA strands can cause mutations that predispose cells to become cancerous, depending on how the damage is repaired (38).

Furthermore, nicotine itself and ENDS extracts can inhibit DNA repair processes in cell cultures. The DNA Checkpoint is a critical cellular system that senses damage and prevents cells from making new DNA in order to prevent further damage and initiate DNA repair. Nishioka and colleagues found that nicotine overrides the DNA Checkpoint and allows cells to make DNA even when there is DNA damage (39). Base Excision Repair (BER) is a key repair mechanism for DNA that has been chemically altered; two studies found that ENDS extracts reduce the abundance of BER proteins, thus limiting the ability of cells to repair damage caused by ENDS (33, 34). It is possible inhibition of DNA repair from ENDS use could exacerbate DNA damage and related DNA mutations caused by smoking in people who dual use.

ENDS linked to inflammation and cellular replication

In addition to DNA damage, ENDS vapor could also lead to cancer by promoting inflammation and cellular replication that expands mutations caused by prior carcinogen exposure. A core hallmark of cancer is uncontrolled cellular replication (40). Several constituents in ENDS vapor can cause inflammation, as demonstrated by increased pro-inflammatory cytokines such as IL6 and CXCL8 (41–46). Wang and colleagues found that nicotine signaling in mouse lungs was a significant contributor to inflammation, and that deleting the nicotine

Table 1. Carcinogens significantly increased in ENDS users compared with nonusers.

Class of carcinogen	Name of carcinogen	Metabolite analyzed	Increase compared with nonusers			Sample size	Ref
			ENDS Users	Dual users	Smokers		
Tobacco-specific nitrosamines	4-(N-Nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	431%	28,412%	21,996%	5097	23
	4-(N-Nitrosomethylamino)-a-(3-pyridyl)-1-butanone	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	75%	N/A	3,100%	57	26
	N'-Nitrosonornicotine	N/A	80%	513%	514%	4985	23
	N'-Nitrosonornicotine (saliva)	N/A	5,740%	N/A	37,700%	59	26
Metals	Cadmium	N/A	30%	88%	86%	5091	23
	Lead	N/A	23%	42%	36%	5105	23
Polycyclic aromatic hydrocarbons	2-Naphthylamine	N/A	29%	N/A	N/A	23	24
Volatile organic compounds	Acrylonitrile	N-Acetyl-S-(2-cyanoethyl)-L-cysteine	201%	11,018%	9,322%	4,877	23
	Acrylonitrile	N-Acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine	30%	1,242%	1,066%	4,877	23
	N,N-Dimethylformamide	N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine	46%	424%	359%	4,844	23
	Acrylamide	N-Acetyl-S-(2-carbamoylethyl)-L-cysteine	95%	583%	N/A	103	25
	Propylene oxide	2-Hydroxy-Propyl Methacrylate	89%	94%	N/A	103	25
	Crotonaldehyde	N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine	48%	85%	N/A	103	25
	Acrolein	3-hydroxypropyl mercapturic acid	32%	128%	N/A	103	25
	ortho-Toluidine	N/A	133%	N/A	N/A	22	24

Note: The table lists carcinogens identified by Goniewicz and colleagues (23), Fuller and colleagues (24), Rubinstein and colleagues (25), and Bustamante an colleagues (26), to be elevated in the urine (or saliva where noted) of adults who use ENDS products compared with adults who do not use any tobacco products. All listed carcinogens are rated "Possibly Carcinogenic" (Group 2B) to "Carcinogenic to Humans" (Group 1) by the International Agency for Research on Cancer (31). "ENDS Users" refers to exclusive ENDS use. "Smokers" refers to exclusive combustible cigarette use. "Dual Users" refers to people who use both ENDS and combustible cigarettes.

receptor in lung cells reduced inflammation, confirming nicotine directly causes inflammation (44). However, even use of ENDS that only contained propylene glycol and vegetable glycerin had moderate pro-inflammatory effects in human lungs (43). An additional study found that ENDS users had significantly elevated levels of IL6 and CXCL8 in the blood compared with never smokers (45). IL6 is well documented to induce cell signaling pathways that promote cellular replication and transform precancerous cells into cancerous cells (47–49). Singh and colleagues also found that ENDS users had elevated levels of growth signaling molecules commonly implicated in cancer progression compared with never tobacco users, including epidermal growth factor, vascular endothelial growth factor, and hepatocyte growth factor (45). These findings suggest that ENDS vapor can promote replication of precancerous cells and therefore promote cancer-predisposing DNA mutations.

Summary

A growing body of evidence points toward a biologically plausible role for ENDS use in contributing to human carcinogenesis, based on the presence of carcinogens in ENDS aerosols; metabolites of carcinogens in human urine samples; inflammation markers in human lung swabs and blood samples; and cell culture and mouse experiments exhibiting DNA damage and inflammation. It is important to note that the evidence from biomarker studies tends to show lower carcinogen exposures in ENDS users compared with dual users and exclusive smokers of combustible tobacco, likely due to the absence of combustion-related carcinogens. Additionally, the lack of well-designed epidemiologic studies is a critical hurdle to definitively characterizing cancer risk. ENDS remain relatively new products, so it may take decades for enough exposure to occur that would enable studies with sufficient follow-up to fully characterize the associations between ENDS use and cancer. Even less is known about the harms of second-hand exposure to ENDS vapor. In contrast, the scientific evidence very clearly demonstrates smoking combustible tobacco increases the risk of being diagnosed with lung cancer by approximately 25-fold compared with never smoking (6), and is an established cause of at least 17 other human cancers (6, 50).

Patterns of ENDS Use Support a Ban on ENDS Flavors

While youth and adult use of combustible tobacco has decreased to historic lows (2), the epidemic of youth ENDS use threatens to diminish progress against nicotine addiction. The AACR and ASCO published our first ENDS statement in 2015 due to concerns regarding the almost 400% rise between 2012 and 2014 in ENDS use among U.S. high school students, according to the 2014 National Youth Tobacco Use Survey (NYTS; **Fig. 1**; ref. 51). The number of high school students who had used ENDS in the past 30 days increased by an additional 46% in 2020 compared with 2014 levels, to a total of 3.6 million youth (52). A separate national survey,

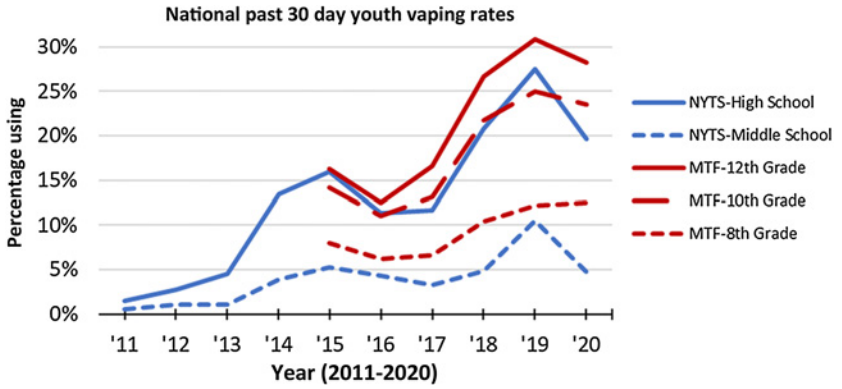

Figure 1.
Percentage of various school age groups who vaped in the past 30 days. Blue lines indicate data from the NYTS (51, 52, 54–60), and red lines indicate data from the MTF survey (53). MTF, Monitoring the Future; NYTS, National Youth Tobacco Use Survey.

Monitoring the Future (MTF), also found a dramatic 73% increase between 2015 and 2020 among 12th grade students who had vaped in the past 30 days (**Fig. 1**; ref. 53). This continued increase in the youth ENDS epidemic underscores the need for urgent action to save a generation of youth from life-long nicotine addiction.

Numerous studies have clearly demonstrated that appealing flavors are key drivers of youth initiation of ENDS use, with the pharmacology of nicotine as the key driver of addiction to ENDS (61–68). The 2020 NYTS found that 82.9% of youth ENDS users used flavored products. Among high school ENDS users, 73% reported vaping fruit-flavored ENDS, 55.8% vaped mint, and 37% vaped menthol (percentages add to greater than 100 % due to use of multiple flavors by one person) (52). In comparison, the 2020 MTF found that only 2.9% of youth ENDS users vaped tobacco-flavored products (69). Youth who are offered fruit flavored ENDS by peers are 6.49-fold more likely to try ENDS compared with tobacco-flavored ENDS (61). In contrast, adults are 21-fold more likely to exclusively use tobacco-flavored ENDS compared with youth (63). Flavored ENDS follow a long history of the tobacco industry using flavors to attract youth towards nicotine by disguising the otherwise unpleasant taste of tobacco and purposefully altering perceptions of risk (61).

In February 2020, the FDA implemented restrictions on pod- or cartridge-based ENDS product flavors, except for menthol and tobacco flavors (70). The policy lacked definitions of "mint" or "menthol," thus allowing manufacturers to simply relabel products to avoid the flavor restriction (71). Open tank and single-use ENDS were also exempted from any flavor restrictions, which left thousands of appealing flavors on the market. Consequently, youth switched to exempted products. The 2020 NYTS found that disposable products were used by 2.4% of high school ENDS users in 2019 (52), but this increased 11-fold to 26.5% in 2020. The prevalence of flavored disposable ENDS also increased among middle schoolers, with a 5-fold increase in disposable product use between 2019 and 2020 (3.0% vs. 15.2%). Flavoring chemicals and other additives of ENDS have not been studied to determine the health risks associated with inhalation. The ability to mix flavors at the point of sale also increases the difficulty of regulators to gain a complete understanding of the health impact of these chemicals in real-world use.

The use of ENDS among adults has also increased in recent years, particularly among young adults. According to the Behavioral Risk Factor Surveillance System (BRFSS, $N = 1{,}156{,}411$), the prevalence of ENDS use increased among U.S. adults from 4.5% in 2016 to 5.4% in 2018 (72), and was 15.0% among adults under the age of 24 years. These data correspond to almost 14 million adults using ENDS in 2018. A second study analyzed data from the Population Assessment of Tobacco and Health (PATH) study ($N = 30{,}191$), which is also representative of the population of U.S. adults, and found that 6.5% of U.S. residents used ENDS in 2018 (73). Concerningly, the BRFSS study found that 42% of adult ENDS users had never previously used another tobacco product (72), and the PATH study found 15% of adult ENDS users had never used another type of tobacco product (73). While the high variability between analyses necessitates further study, the data suggest ENDS are being used by millions of adults who never previously used tobacco. In addition, approximately 36% of ENDS users in the BRFSS study and 52% in the PATH study "dual use" ENDS and combustible tobacco. A separate nation-wide survey ($N = 5{,}989$) found that 27.7% of adults who smoked also dual used ENDS in 2018 (74). Notably, dual use rates were higher in adults who wanted to quit smoking within 6 months (33.1%), compared with 18.7% of those who did not plan to quit smoking. Similar to the general population, adult patients with cancer and survivors who use ENDS are more likely to be under the age of 50 years (75, 76), but patients with cancer who use ENDS are far more likely to be current or former smokers than never smokers. As presented in **Table 1**, dual users continue to be exposed to similarly high levels of carcinogens as exclusive users of combustible tobacco and the current evidence of the efficacy of dual using ENDS to help quit smoking remains unclear. The evidence is clear that any combustible smoking, even one cigarette per day, has significant negative health impacts (77).

As stated in the introduction, major U.S. public health authorities have found insufficient evidence to conclude ENDS effectively help smokers quit combustible tobacco (2–5). In contrast, there is evidence that demonstrates ENDS significantly increase the likelihood youth and young adults start smoking combustible tobacco. A 2021 meta-analysis analyzed nine studies (combined baseline $N = 32{,}286$), which compared the likelihood of smoking initiation between youth ENDS users and never users (78); youth who used ENDS were 4-fold more likely to ever smoke a combustible cigarette than never users, even after accounting for potentially confounding factors. Similarly, a 2020 meta-analysis analyzed 17 studies (combined baseline $N = 57{,}514$), which compared the likelihood of smoking initiation between young adult ENDS users and never users; young adults who used ENDS were approximately three-fold more likely to ever smoke a combustible cigarette compared with never users (79). On the other hand, the nation-wide increased rates of e-cigarette use among youth is accompanied by a substantial decrease in past month smoking rates (53, 80), and the extent to which ENDS use leads to established or regular smoking to date appears to be low (81). Nonetheless, the well-documented ability of ENDS to roughly triple smoking initiation by youth and young

adults is of concern and overshadows the more limited evidence suggesting the efficacy of ENDS for smoking cessation (82). As stated above, flavors are a key driver of youth initiation of ENDS, with the pharmacology of nicotine leading to addiction and continued, repetitive use. Therefore, to limit youth nicotine dependence, we recommend an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine, unless an ENDS product is approved by FDA CDER as a smoking cessation therapy.

Advertising Contributes to Youth ENDS Initiation

Advertising has a powerful effect on youth tobacco initiation, including for ENDS. Many studies have found that advertisements from social media influencers, television, radio, print, and in retail stores significantly increases the probability that youth will start using ENDS (83–90). Additionally, a national survey ($N = 4{,}604$) found that high exposure to tobacco use during television shows more than doubled the likelihood of initiating ENDS use among youth and young adults (91). These findings demonstrate a strong link between ENDS advertising or imagery exposure and subsequent initiation. Therefore, in addition to a ban on flavors, we support efforts to prevent all forms of advertisement for nicotine products from reaching youth.

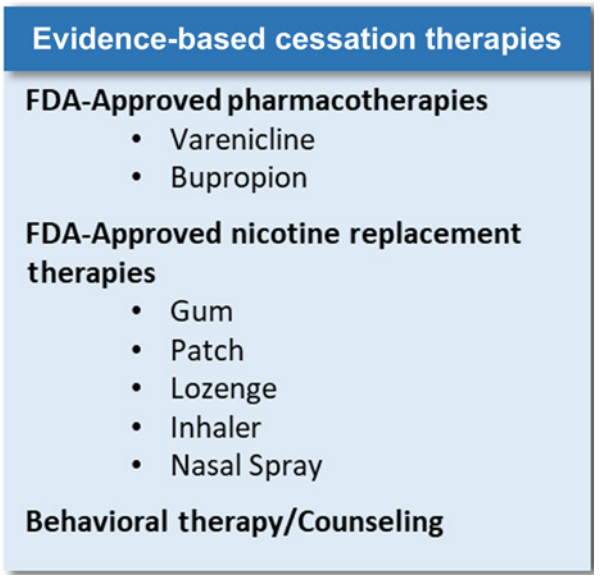

Figure 2.
Evidence-based cessation therapies. FDA, U.S. Food and Drug Administration.

Leveraging Evidence-Based Smoking and ENDS Cessation Therapies and Awareness Campaigns

There are currently no evidence-based pharmacologic therapies to help ENDS users quit vaping (92). However, it is reasonable to conclude that lessons learned from smoking cessation could aid in treating nicotine dependence from ENDS. The 2021 USPSTF tobacco cessation recommendation concluded that the most effective treatment for tobacco use includes both FDA-approved pharmacotherapies and behavioral counseling (**Fig. 2**; ref.4). Additional research is critically needed to identify effective cessation therapies specifically for ENDS users. A major hurdle to assessing tobacco use in clinical research studies is the lack of standardized definitions for terms describing tobacco use history, such as "current smoking," "current ENDS use," "former smoking," etc. Evidence-based definitions provided by the FDA or National Cancer Institute will be helpful to further advance tobacco research.

Little is known about the interaction of smoking and ENDS use and subsequent impact on different anticancer treatments or on cancer prognoses. In the context of cancer treatment, smoking by patients with cancer and survivors increases the risk of overall or cancer related mortality by roughly 50% to 60%, increases risk for a second primary cancer, and has strong associations with increased cancer treatment toxicity (6). Consequently, it is important to consider the biologic and clinical effects of smoking when considering the effects of ENDS use by patients with cancer. Quitting smoking after a cancer diagnosis is associated with a median 45% improvement in survival (2). Therefore, evidence-based smoking cessation is considered a critical component of cancer care by AACR, ASCO, and other major oncology organizations (93). However, large surveys demonstrate that few oncology providers regularly assist patients with quitting (94, 95). Compared with the general adult population, the data are even less clear on whether ENDS aid cessation efforts by patients with cancer, or whether ENDS will have a positive or negative effect on cancer treatment. This is further complicated by frequent transitions between smoking and ENDS. However, smoking cessation confers significant benefits by reducing cancer risk, improving cancer treatment outcomes, and improving several other health outcomes beyond cancer (2). Given the clear and strong evidence for the adverse effects of smoking on cancer treatment outcomes, quitting smoking should remain the top priority for patients with cancer and providers, with emphasis on the importance of quitting smoking to improve cancer treatment outcomes. When considering these important data and findings, it is critical that patients with cancer who are using ENDS currently not return to cigarette smoking.

A significant hurdle to evidence-based cessation therapies is inconsistent insurance coverage. This is most pronounced among uninsured smokers, who are 33% less likely than the general population to use evidence-based therapies (96). After Massachusetts implemented comprehensive Medicaid smoking cessation coverage in 2006, the smoking rate of beneficiaries dropped by 26% in two years (97); every dollar spent on cessation coverage saved $3.12 in U.S. dollars (USD) in spending on tobacco-related illnesses (98). Unfortunately, most state Medicaid plans do not cover all FDA-approved medications, and coverage of behavioral therapy is inconsistent (99). Additional barriers such as extreme shortages of healthcare workers, demanding physician schedules, medical preauthorizations, co-payments, and limits on quit attempts per year also reduce success rates (100–102). Nonphysician certified tobacco cessation specialists are also often not reimbursed by insurance plans. Payment reform for cessation specialists, FDA-approved therapies, and addressing other barriers to cessation could be powerful cost-saving interventions to increase quit rates by making it as easy as possible to receive evidence-based help. An improved coverage and reimbursement environment for tobacco cessation services and medications will benefit population health; this would even apply should an ENDS product ever become an FDA-approved cessation device.

A number of awareness campaigns and free cessation resources (**Fig. 2**) have emerged over the past decade to prevent initiation and help tobacco users quit, some of which could be used or repurposed in the context of ENDS cessation. The "This is Quitting" campaign by the Truth Initiative increased seven-month quit rates among young adult ENDS users to 24.1% compared with 18.6% among participants who did not participate in the campaign (103). The FDA's "The Real Cost of Vaping" advertising campaign helped prevent an estimated 380,000–587,000 youth from starting ENDS use between 2013 and 2016 (104). The CDC's "Tips from Former Smokers" campaign saved an estimated $11 billion (USD) in tobacco-related healthcare spending over 6 years at a cost of $490 million (USD) (105) and helped more than 1 million smokers permanently quit (106). Among smokers who visited the free cessation services website, SmokeFree.gov (107), as part of a randomized clinical trial, 26% successfully quit one year later (108). Finally, Quitline counseling services increased quit rates by 60% (109). Increasing resources for these excellent evidence-based tobacco treatment services could help significantly to expand their reach and quality of service.

Evidence needed to determine if ENDS can help smokers quit smoking

To our knowledge, to date, there is a lack of sufficient evidence for the use of ENDS as tobacco cessation therapies (2–5). This is because very few randomized clinical trials have directly compared the efficacy of ENDS to standard cessation therapies; the failure of ENDS manufacturers to submit an IND application is the primary reason for a lack of ENDS clinical trials in the United States. However, a 2021 systematic review found that preliminary evidence suggests ENDS could be more effective for smoking cessation than nicotine-replacement therapy alone (82), although the authors caution that the small number of studies and variations in study design limit the strength of their conclusions. The moderate strength conclusion of the review was primarily based on two clinical trials that investigated the efficacy of ENDS to help with smoking cessation. The first trial ($N = 886$), from the United Kingdom, found ENDS helped smokers quit at statistically significantly higher rates than nicotine patches (110); the trial found 18% of participants who used ENDS plus behavioral therapy had quit smoking by one year, compared with 9.9% of participants who used nicotine patches plus behavioral therapy. The second trial ($N = 1{,}124$), from New Zealand, found that 18% of those randomly assigned to patches plus a nicotine e-cigarette quit smoking, compared with 10% randomized to a nicotine-free e-cigarette plus patches and 8% randomized to patches alone (111). It is noteworthy in both trials that a large proportion of participants continued using ENDS at the long-term follow-up visit in these studies. Moreover, all groups in the above studies experienced slightly lower but comparable rates of successful cessation as found for 6-month follow-up when using FDA-approved nicotine patches alone (22%; ref. 112). Therefore, we recommend that ENDS manufacturers apply for IND applications to facilitate randomized clinical trials to definitively assess the cessation efficacy of their products compared with FDA-approved cessation therapies.

Regulation of ENDS Needs Improvement

During the last 15 years, the FDA has attempted to regulate ENDS products with limited success. In 2009, Congress passed the Family Smoking Prevention and Tobacco Control Act (TCA; ref. 113), which granted the FDA the authority to regulate tobacco products. In May 2016, the FDA "deemed" ENDS as tobacco products under the TCA (114). This ruling required ENDS manufacturers to submit a premarket tobacco product application (PMTA) to prove that the product is "appropriate for the protection of public health" (112). In 2017, the FDA elected to delay the PMTA deadlines for ENDS from 2018 to 2022. During this time, many users believed that ENDS were safe and did not contain nicotine (61, 69, 115). As described in the epidemiology section, perceptions of safety contributed to alarming increases in ENDS use among those who never previously used tobacco.

In 2019, U.S. District Judge Paul W. Grimm ruled that the FDA had acted improperly by delaying ENDS regulations (116). Citing a "clear public health emergency," Judge Grimm required PMTA applications for ENDS to be submitted by May 2020, but this was delayed to September 2020 due to the COVID-19 pandemic. By September 2020, more than 6 million PMTAs for ENDS products were submitted for FDA review (117). The FDA has denied marketing orders for more than 98% of those products, which requires those products to be removed from the market (118). However, the FDA is still reviewing PMTAs for ENDS products from manufacturers with the largest market shares and permitting those products to remain on the market in the meantime.

Two additional policies have also had a major impact on the use of ENDS products: age restrictions and taxation. In 2015, Hawaii became the first state to raise the minimum legal age to purchase tobacco products to 21 years (119), based on a NASEM report that estimated nearly 250,000 premature deaths could be prevented over 30 years (120). Following Hawaii's lead, 18 additional states and Washington D.C. also raised the minimum age to 21 years between 2016 and 2019. As part of the federal fiscal year 2020 appropriations package, Congress raised the minimum legal age to purchase tobacco products to 21 years in the entire United States (121). Separately, for every 1% increase in the price of tobacco products, consumption decreases by 0.4% on average (122). While the federal government does not yet tax ENDS, 24 states have passed ENDS taxes (123). Due to the powerful disincentivizing effect of taxes on tobacco use, the AACR and ASCO support imposing a federal excise tax on all products that contain natural or synthetic nicotine in a manner that promotes public health benefit (124, 125). Additional policy recommendations are included in **Table 2**.

Conclusion

ENDS emit fewer carcinogens than combustible tobacco primarily due to the absence of combustion products, and for some ENDS, the absence of some tobacco-specific nitrosamines, but it is clear that they still pose health risks. Additionally, e-cigarettes have addicted a new generation of youth and young adults to nicotine and threaten to hinder progress against tobacco-related illnesses. For these reasons, the AACR and ASCO call for urgent action by Congress, state legislatures, and regulatory agencies to implement the various legislative, regulatory, and research recommendations outlined in this report, including calling for an immediate ban on all non-tobacco-flavored ENDS products that contain natural or synthetic nicotine with the goal of reducing ENDS use by youth and adults who never previously used tobacco. The top tobacco control priorities for the AACR and ASCO continue to be preventing initiation of tobacco use, including ENDS, preventing smoking relapse, and promotion of evidence-based tobacco cessation treatment for all groups.

Table 2. AACR and ASCO recommendations.

Legislative Recommendations
Ban all non-tobacco-flavored products that contain natural or synthetic nicotine; flavors may only be used for research purposes or FDA-approved tobacco cessation therapies.
Tax all products that contain natural or synthetic nicotine in a manner that reduces tobacco use and promotes public health.
Increase funding for evidence-based tobacco control programs and campaigns such as the CDC's Office on Smoking and Health, state tobacco control programs, and Quit Lines.
Prohibit the use of ENDS in places where combustible tobacco use is prohibited by federal, state, or local laws. All tobacco use should be prohibited at medical facilities.
Limit the sale of tobacco products to stores or areas within stores that require age verification upon entrance.
Require health insurance plans, including Medicare/Medicaid, to cover all FDA-approved cessation therapies, expand coverage limits, and reimburse healthcare providers, including cessation specialists, for time helping patients quit smoking and vaping.
Regulatory Recommendations
Regulate predatory tobacco advertising practices including packaging, product designs, and labeling appealing to youth; misleading statements about cessation efficacy; athletic, musical, social, or cultural event sponsorship; giveaways when buying tobacco products; branded clothing; social media, digital, and print advertising; and tobacco use in movies and television.
The FDA should enforce removal of ENDS products from the market that have not received a marketing order, publish PMTAs with confidential information redacted, and update PMTA review progress with a publicly available database.
The FDA should develop product standards for tobacco products to improve public health, including but not limited to minimizing appeal to youth; capping the amount of nicotine delivery to minimize addictiveness; eliminating or substantially reducing human exposure to known carcinogens (e.g., heavy metals) and other toxicants (e.g., additives, contaminants, and manufacturing residues); and regulating the power and operating temperature of ENDS products.
PMTAs should require information regarding: composition of ENDS and e-liquid components; appeal to people who have never used tobacco products; impacts on health; geotracking or biometric capabilities; and steps taken to protect consumer privacy.
Require health warning and safety labels on ENDS packaging and advertising; these labels should contain ENDS/e-liquid composition information from PMTAs.
The FDA and/or NCI should provide evidence-based, non-stigmatizing definitions for categories of tobacco use for human studies, for example no tobacco history; no smoking history; no ENDS history; currently smoking; currently using ENDS; former smoking history. The FDA and/or NCI should provide guidance on best practices for measuring tobacco use data in human studies. The FDA should require all oncology clinical trials to assess tobacco use and report findings.
The FDA should increase enforcement of the minimum age to legally purchase tobacco products
Additional Research Needs
Research is needed to determine effective ENDS cessation therapies for youth, young adults, and adults, as well as cessation therapies for youth combustible tobacco users.
Large prospective epidemiological studies are needed to investigate the long-term health impacts of ENDS use and disparities in tobacco-related illness.
Additional research is needed for a comprehensive understanding of the acute and long-term biologic effects of ENDS use, carcinogen exposures, and the use of ENDS in the context of smoke exposure.
Additional research is needed on how patients diagnosed with cancer use tobacco products, their reasons for use, perceptions of health impacts, impact of cessation on cancer-related outcomes, and interactions with anticancer therapies.
Randomized clinical trials are needed to investigate the cessation efficacy of ENDS compared to FDA-approved cessation therapies. Investigational New Drug applications are necessary to facilitate such trials.
Research is needed to monitor the impacts of federal, state, and local tobacco policies on youth and adult use patterns, as well as the use of evidence-based approaches to develop policy.

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ENDS, electronic nicotine delivery systems; FDA, US Food and Drug Administration; NCI, National Cancer Institute; PMTA, premarket tobacco product application.

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