Since the first Early Lung Cancer Action Program lung cancer (LC) screening trials led by Henschke et al., smoking cessation has been included. The reason for this is obvious. The overwhelming most participants in screening trials are still smoking. Although most LC screening computed tomography (CT) scan results will be negative for cancer, screening is an excellent time for a "teachable moment" to encourage those using tobacco to stop. Cessation after LC screening leads to a decrease in all-cause mortality because smoking causes many more serious illnesses than just LC. Using this teachable moment at the time of LC screening to help individuals to stop smoking has the potential to decrease the morbidity and mortality from cardiovascular and respiratory diseases, in addition to LC.

Despite the huge potential value of integrating smoking cessation into a LC screening program, the uptake, even in the United States, has been extremely poor. Although there are numerous implementation challenges to overcome, one problem is that integrating smoking cessation into a low-dose CT screening program adds expense to an already resource-intensive undertaking, which can be challenging on a population basis in higher income countries and largely impossible in low- and middle-income countries. If the smoking cessation initiative adds significantly to the cost burden, it may impede implementation in publicly funded health care systems and preclude individual participation in a private pay system.

At present, smoking cessation is not systematically offered in low-dose CT screening programs even though counseling and pharmacologic support could substantially increase quit rates and increase life expectancy, even in patients with LC.

In this issue of the *Journal of Thoracic Oncology*, Pastorino et al. report on the Screening and Multiple Intervention on Lung Epidemics (SMILE) trial, an ongoing, single-center, randomized, controlled trial conducted at the Istituto Nazionale dei Tumori in Milan, Italy. The SMILE trial provides evidence that a less expensive smoking cessation intervention—cytisine—is effective and safe as a smoking cessation aid in the context of LC screening. The SMILE trial was designed to recruit 2000 individuals, but owing to the coronavirus disease 2019 (COVID-19) pandemic, only 1114 volunteers were recruited before the trial being temporarily closed in March 2020. Eligible participants were current tobacco users aged 50 to 75 years with more than or equal to 30 pack-year smoking history or people with a similar smoking history but who had stopped within the previous 10 years. Furthermore, 78% of the recruits to the trial were people who were still smoking. The trial participants were randomized to one of four different groups with stratification by smoking history, sex, and age. The four groups were the following: (A) cytisine plus counseling plus CardioASA; (B) cytisine plus counseling; (C) CardioASA plus counseling; and (D) counseling alone. For the current analysis, groups A and B were combined, as were groups C and D, and only people who were currently smoking were included (n = 750). The intervention arm underwent a further randomization to a standard schedule of cytisine of 40 days or a more prolonged schedule of 84 days. The primary end point was continuous abstinence from smoking at 12 months, confirmed by exhaled carbon monoxide monitoring. The secondary end point was the 7-day point prevalence of abstinence.

The overall quit rate was significantly higher in the combined (A + B) intervention arms (31%) versus 3% in the arms (C + D) receiving only counseling with an adjusted OR of 7.2 (95% confidence interval [CI]: 4.6–11.2). The 7-day point prevalence for abstinence was 37.5% versus 12.3% with a corresponding OR of 4.3 (95% CI: 3.0–6.1). Among those who failed to quit, there was a greater reduction in the number of cigarettes smoked in the cytisine arms compared...
with the counseling only group. An adjusted OR of 7 between an intervention and a control is unheard of for a smoking cessation drug. The fact that cytisine also has an excellent safety profile adds to its attractiveness. The most frequent side effects were sleep disorders (12.1%), nausea and vomiting (8.5%), and increased appetite and weight gain (4.0%). Only 41 individuals (8.7%) discontinued cytisine owing to adverse events.

Relapse after cessation remains a challenge, and an 18% relapse rate was observed in SMILE. The rate of relapse and time to relapse may have been confounded by COVID-19 restrictions (lockdown) and August summer holidays in Italy. The SMILE randomized controlled trial intended to compare a 40-day schedule to a more prolonged schedule of 84 days (similar to varenicline), but the study failed to reach a sample size adequate to prove significant benefit. Nevertheless, the adjusted OR of continuous abstinence for 12 months between standard and prolonged treatments favored the prolonged administration (OR = 1.5, 95% CI: 1.0–2.3) Because cessation is frequently accompanied by relapses back to smoking, a more prolonged intervention with an effective cessation agent that is safe would make sense, especially if the medication is inexpensive and has an acceptable adverse event profile.

Cytisine is a plant-based alkaloid derived from the Cytisus laburnum plant that binds with high affinity to the a4 β2 nicotinic acetylcholine receptor, which is responsible for the central effects of nicotine. This natural product inspired the development of varenicline, and similar to varenicline, it can reduce the craving to smoke during the prequit period and the withdrawal discomfort of quitting. Cytisine has clearly been found to be an effective smoking cessation aid in multiple studies. A systematic review and meta-analysis of eight randomized controlled trials of 4020 users of tobacco reported a 59% (p < 0.00001) higher abstinence rate from smoking while taking cytisine versus placebo. An open-label randomized trial comparing cytisine with nicotine replacement therapy (NRT) in people who smoked every day revealed a self-reported cessation rate at 1 month of 40% in those taking cytisine versus 31% for NRT (p < 0.001). The 6-month self-reported cessation rate was also higher with cytisine (22% versus 15%, p = 0.002). A randomized clinical trial, undertaken in 1452 Australian adults who smoked every day, compared a 25-day course of cytisine with a standard 84-day course of varenicline to determine whether cytisine was at least as effective as varenicline. The 6-month continuous abstinence confirmed by carbon monoxide testing was 12% in the cytisine group and 13% in the varenicline group. Self-reported adverse events were reported less frequently in the cytisine group.

Varenicline has a longer half-life than cytisine (17 h versus 4.8 h) making for an easier administration schedule but also a longer course of therapy (12 wk versus 3.5 wk). One drawback to the use of cytisine is that the administration schedule is more complex than that of varenicline. In the SMILE trial, participants on the 40-day schedule received 165 tablets of 1.5 mg. A cytisine dosing schedule typically involves taking six capsules daily (every 2 h) in the first 3 days and then gradually reducing in the 25-day course. Current trials are evaluating a different dose (3 mg) and a three-times-per-day administration.

As the authors point out, cytisine is inexpensive and has been used for decades in eastern Europe and Russia. Canada approved it for cessation in 2017 as a natural health product, and as a consequence, it is available without prescription from select pharmacies, health shops, and directly online from the manufacturer. Cytisine costs approximately $56 for a 25-day treatment course compared with NRT ($360–$449), bupropion ($215), and varenicline ($340), in Canada. Nevertheless, most of the world does not have access to the product. Achieve Life Sciences, a pharmaceutical company, has been conducting the required studies, to obtain approval from the Food and Drug Administration. One can only hope that the U.S. Food and Drug Administration does not require the product to be a prescription drug, as it will dramatically decrease its usefulness for public health. In addition, we can hope that Achieve makes the product available as an inexpensive drug to help people quit, as many who continue to smoke in developed countries are from marginalized communities, have lower socioeconomic status and lower educational attainment, and hence have fewer resources to purchase an expensive smoking cessation aid.

As more and better tobacco control policies are put in place globally, it is critical that, simultaneously, there be good and sufficient cessation resources available. Article 14 of the Framework Convention on Tobacco Control calls for cessation and that the requisite guidelines for countries are available. Nevertheless, very few countries actually fund cessation interventions adequately. The cost of the behavioral and pharmacotherapy needed to treat this chronic, relapsing addiction is undoubtedly one of the reasons so few cessation resources are available in any country—low, middle, or high income.

Therefore, the authors are to be commended for designing this trial with an inexpensive smoking cessation aid and creatively working to continue the trial during the global COVID-19 pandemic. Even more so, they are to be congratulated on their stellar results that should get every LC screening program implementing
cessation—and demanding that their country’s government get cytisine approved.

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Carolyn M. Dresler, William K. Evans: Conceptualization, Methodology, Writing—original draft, Final review and approval of the manuscript.

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