

Cost-effectiveness of Colorectal Cancer Screening

To the Editor: Dr Frazier and colleagues¹ estimate that providing patients aged 50 years and older at average risk for colorectal cancer with screening colonoscopy every 10 years will reduce colorectal cancer mortality by 64%. These results are similar to those reported by Sonnenberg et al.² The standard evidence given in support of this dramatic mortality benefit, which is substantially greater than has been demonstrated for any screening test, is the National Polyp Study.³ This study was not a randomized trial of the effect of colonoscopy on colorectal cancer mortality but a cohort study of selected patients undergoing colonoscopy. Because the National Polyp Study was not a randomized trial, the comparability of the case and control groups (3 historical cohorts) is open to question. Furthermore, the study's end point was the incidence of colorectal cancer, not mortality. This would not matter if every incident cancer resulted in death, but that was not the case. To the extent there is heterogeneity in the growth rate of colon cancers, screening will miss the fastest growing (and deadliest) cancers. This selection effect means that the remaining incident cases have a disproportionate impact on mortality.

Before clinicians recommend the most invasive, complex, and resource-intensive cancer screening program yet proposed, a randomized trial of colonoscopy is needed. If screening colonoscopy is as effective as asserted, an extremely large study would not be required. Until randomized trials confirm its effectiveness, discussions of the cost-effectiveness of colorectal cancer screening are premature.

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To the Editor: Dr Frazier and colleagues¹ present a timely cost-effectiveness analysis of methods for screening the general population to decrease mortality from colorectal cancer. Although colonoscopy, the most sensitive test, is currently the most expensive, costs could decrease dramatically if the procedure were performed by trained, nonphysician technicians under the supervision of a gastroenterologist. The gastroenterologist could supervise a number of technicians simultaneously while per-

sonally visualizing suspicious lesions and performing biopsies when appropriate.

Frazier et al quote data from the 1997 Behavioral Risk Factor Surveillance System² in which only 20% of respondents reported having had fecal occult blood testing (FOBT) during the preceding year, and only 30% reported having had a proctoscopy or sigmoidoscopy in the preceding 5 years. While patient recall of proctoscopy or sigmoidoscopy is likely to be fairly accurate given the invasiveness of these procedures, recall of FOBT may be poor, as has been shown regarding accuracy of patients' recall of Papanicolaou tests and cholesterol screening.³ While recall of FOBT may underestimate the true rate of screening, it is likely that FOBT still remains underutilized, as are many other preventive screening measures.⁴ Health care organizations and the media need to play a greater role in publicizing the usefulness of screening for early detection of colorectal carcinoma, which can prompt curative treatment of this major killer.

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1. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA*. 2000;284:1954-1961.
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To the Editor: In the cost-effectiveness analysis of colorectal cancer screening by Dr Frazier and colleagues,¹ it was reported that "Double-contrast barium enema [DCBE] remained a dominated strategy over a wide range of values for both sensitivity and specificity." However, there are 2 major problems with this statement. First, the values assigned for both the base case and the "plausible ranges of uncertain parameters" do not reflect a thorough review of the literature regard-

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Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

ing the accuracy of DCBE. Second, it appears that Frazier et al performed a 1-way sensitivity analysis, which only permits manipulation of 1 variable at a time. If multiple parameters are incorrect, then adjustment for a single variable can still be misleading. Other studies have found DCBE sensitivity to be 40% to 70% for low-risk polyps, 50% to 80% for high-risk polyps, and 80% to 90% for cancer.^{2,3} Based on my review of the dominant figures within these ranges, I think that the most accurate estimate of DCBE sensitivity for low-risk polyps is 60%; for high-risk polyps, 75%; and for cancer, 85%. In contrast, the base-case figures used in the study were 30%, 50%, and 70%, respectively. Furthermore, the authors used an overall specificity of 86% (range, 80%-98%), which is lower than the more realistic values of 90% for low-risk polyps and 98% for high-risk polyps and cancer.^{2,3}

Frazier et al assigned a cost of \$296 for DCBE (range, \$50-\$300), which is at the upper end of their threshold. Medicare currently reimburses \$150 for this procedure. It is not surprising that DCBE was dominated in this study. It would be of interest to see how DCBE would fare if Frazier et al inserted all the above values for performance and cost into their base-case example.

Several cost-effectiveness analyses on colorectal cancer screening have yielded differing outcomes.^{2,4} To avoid confusion, it would be beneficial when such discrepancies exist for authors to explain the basis of such variance and what factors in their design represent an improvement over existing analyses that justify accepting conflicting results.

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1. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA*. 2000;284:1954-1961.
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In Reply: Drs Budenholzer and Welch assert that discussions about the cost-effectiveness of colorectal cancer screening may be premature in light of the insufficient evidence about the effectiveness of colonoscopy. We agree that the ideal evidence would be from randomized clinical trials. However, a screening trial of the general population would require a fairly large sample size and long time horizon. Even with a large anticipated risk reduction, the baseline incidence of colorectal cancer is relatively small.

In the interim, we believe that the use of economic models can provide a valuable framework for understanding the trade-offs between the costs and benefits of screening, particularly in the face of imperfect data. A number of strategies for colo-

rectal cancer screening have been endorsed and are currently being practiced despite imperfect evidence, and we hope that the availability of cost-effectiveness studies will facilitate a more informed discussion of resource allocation. More importantly, current discussions about the cost-effectiveness of screening in no way preclude the continuing search for better effectiveness data. Comprehensive cost-effectiveness analyses that include all proposed strategies for screening can help narrow the choices about which strategies warrant definitive evaluation in a clinical trial.

We agree with Dr Donohoe that the cost of colonoscopy could be reduced if nonphysician technicians performed the test. This would result in more favorable cost-effectiveness ratios for colonoscopy. However, reducing costs would not affect the health gains associated with colonoscopy. In our model, the combined strategy of the FOBT plus sigmoidoscopy every 5 years would remain the most effective strategy. We concur with Donohoe that it behooves health care organizations and the media to more strongly promote and make available preventive health care services that have such potential to save lives.

As in any modeling effort there are uncertainty and variability in the parameter estimates. Dr Glick questions our assumptions regarding the sensitivity, specificity, and cost of DCBE. Our estimates of sensitivity and specificity were based on a double-blinded assessment of the diagnostic performance of colonoscopy vs DCBE conducted as part of the National Polyp Study.¹ We chose that study because we felt that its design best avoided the problems of work-up bias, which tend to overestimate the sensitivity of a test. While our estimate of the cost of DCBE may not reflect the current Medicare reimbursement, our cost estimates for all screening tests were obtained from a single source and thereby should reflect the relative costs of these tests. However, we recognize that variability in the performance and cost of DCBE may exist from center to center. Using the estimates proposed by Glick, we found that offering patients DCBE every 10 years remained dominated in our model and offering DCBE every 5 years had an incremental cost-effectiveness ratio of \$19 000 per life-year gained compared with sigmoidoscopy every 10 years. Offering DCBE every 5 years remained less effective than the combination of FOBT plus sigmoidoscopy every 10 years, which had an incremental cost-effectiveness ratio of \$27 000 per life-year gained compared with DCBE every 5 years.

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1. Winawer SJ, Stewart ET, Zauber AG, et al, for the National Polyp Study Work Group. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. *N Engl J Med*. 2000;342:1766-1772.

Drug Dependence as a Chronic Medical Illness

To the Editor: Dr McLellan and colleagues¹ state that drug addiction should be treated as a chronic medical disease. This contradicts our experiences as a sheriff (L.A.) and an emergency department physician (D.L.S.) who regularly encounter patients who provide false histories concerning trauma or pain syndromes, insist on narcotic analgesics, and vigorously refuse nonnarcotic analgesics or follow-up with an office-based physician. Our experience has been that the overwhelming majority of such patients will not agree to enter a drug rehabilitation program or to go to Alcoholics Anonymous or Narcotics Anonymous.

Anecdotally, most patients who have been in rehabilitation experience a relapse or a loss of control of their drug dependency. Only a tiny minority of these patients will follow up with a single physician or medical office for ongoing medical management of their chronic illness. The vast majority of drug-dependent individuals do not view their condition as an illness, but rather spend tremendous resources and take great risks, including that of jail or even death, to continue their lifestyle. In our area we have discovered organized groups that travel from physician to physician for the express purpose of obtaining drugs.

Most people who use illegal drugs make a conscious decision to do so. Although we believe that treatment should be available, it must also be accompanied by consequences, such as jail or involuntary commitment, for noncompliance with detoxification. From our observations, many individuals use drugs to insulate themselves from life and its problems. It is impossible to view all drug users and addicts together, but practical experience provides insight into a world that they choose to inhabit.

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1. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284:1689-1695.

In Reply: Mr Amerson and Dr Smith have failed to understand 3 key points in our article: (1) that substance-dependent individuals are responsible for the onset of their illness; (2) that they are also responsible for active participation in their recovery; and (3) that they should be treated because of the demonstrated public health and safety benefits of treatment, not merely because of compassion for those affected.

Responsibility for Onset of Illness. Addiction is initiated by a voluntary act—but it is also true that this initial voluntary behavior is shaped by preexisting genetic factors. These are also brain changes that begin with the very first drug or alcohol uses, which may evolve into compulsive drug taking that is less subject to voluntary control. We are not yet able to explain the

brain and cellular changes that transform the initial, voluntary drug-taking behavior into a compulsion.

Responsibility for Recovery. Drug dependence erodes but does not erase a dependent individual's responsibility for control of their behavior. All patients, regardless of their illness, are responsible for actively participating in their recovery. Many patients with chronic illnesses fail to see the importance of their symptoms and thus may ignore physician advice, fail to comply with medication, and engage in behaviors that exacerbate their illnesses. While such patients may not be as disruptive, demanding, or manipulative as alcohol- or drug-dependent patients, the patterns of denial of symptoms, failure to comply with medical care, and subsequent relapse are not peculiar to addiction. One thing that does separate addiction from other illnesses is the waiting lists for treatment throughout the United States, which contradict assertions that addicted persons do not want treatment.

Efficacy as Basis for Treatment. Compassion or sympathy is not the basis for our argument that physicians should treat addicted individuals. Medically oriented treatments are much more effective than socially oriented responses such as incarceration. Also, addiction treatments have been combined effectively with legal sanctions (eg, drug courts and court-mandated treatments) and with civil sanctions (eg, welfare-to-work programs and involvement of child protection services).

Research has provided physicians with even more effective medications and brief interventions to address addiction problems. These new interventions should be taught in medical schools and primary care residencies. Our review suggests that if physicians develop and apply the skills available to diagnose, treat, monitor, and refer patients in the early stages of substance dependence, there will be fewer late-stage emergency department cases such as those that have frustrated and disillusioned Amerson and Smith.

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Dextromethorphan and Ecstasy Pills

To the Editor: In their Research Letter, Mr Baggott and colleagues¹ report that they performed a chemical analysis of 3,4-methylenedioxymethamphetamine (MDMA) tablets, also known as "ecstasy," and found that such tablets frequently contain dextromethorphan. The authors imply that findings of "lethargy or

hyperexcitability, tachycardia, ataxia, and nystagmus, as well as a phencyclidine-like psychosis" can occur only in dextromethorphan toxicity. Furthermore, they suggest that these findings in patients admitting ecstasy use, but in whom the results of toxicology screens are negative for MDMA and amphetamines, should lead clinicians to consider dextromethorphan toxicity. Both of these statements are misleading.

Each of the above symptoms may arise from MDMA use. Effects of MDMA include tachycardia, hypertension, hyperthermia, hepatitis, myocardial ischemia, elevated antidiuretic hormone levels, serotonin syndrome, cerebral hemorrhage, and psychosis.² In those who use pure MDMA, lethargy may represent a postictal state caused by hyponatremia, hyperthermia, or cerebral hemorrhage. Tachycardia, hyperexcitability, tremor, ataxia, nystagmus, and seizures arise from the hyperadrenergic state produced by the drug. Cerebral hemorrhage may also produce seizures as well as focal neurologic findings, and psychosis may arise from chronic amphetamine use. Contrary to the authors' views, these symptoms may arise not from an adulterant, but from the intended drug.

Urine toxicology screens vary in their ability to detect MDMA.^{3,4} A recent survey assessed the proficiency with which clinical laboratories detected MDMA in standardized samples.⁵ Approximately one third of the 2734 laboratories evaluated did not detect MDMA, irrespective of method used. The results of urine immunoassay toxic screens, therefore, may be negative in individuals taking MDMA. Consequently, such results may lead to an incorrect diagnosis of dextromethorphan toxicity in patients who actually have MDMA poisoning. The management of toxicity for MDMA is different than that for dextromethorphan. Clinicians should continue to suspect MDMA toxicity even in the presence of a negative urine screen result.

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In Reply: We described another potential complication of MDMA abuse. It is not logical to suggest that by describing

possible dextromethorphan toxicity we somehow minimize the dangers of illicit MDMA. The adverse effects of MDMA are well-documented and well-known to medical personnel. We reluctantly omitted an explicit comparison of MDMA and dextromethorphan toxicity due to space constraints but strongly agree that both drugs may produce toxic syndromes with similar signs and symptoms. We also agree that currently available qualitative urine toxicology screening systems may not detect MDMA in as many as one third of samples.

Our point is that dextromethorphan, which may be ingested with or instead of illicit MDMA, is not detected using any available urine screening techniques or by clinical examination. Because people who take ecstasy are unlikely to know exactly what they ingested, physicians may make an incorrect diagnosis and provide less than optimal treatment. We feel that it is better for physicians to be aware of possible dextromethorphan toxicity, even if this makes treatment decisions more difficult. Shannon¹ made the same point in a recent review on MDMA toxicity: "Because other street drugs are referred to as Ecstasy, including ephedrine, Ma-Huang (herbal ecstasy), caffeine, and gammahydroxybutrate (GHB), clinical and laboratory assessment should be thorough to correctly diagnosis MDMA ingestion." We would now add dextromethorphan to that list.

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1. Shannon M. Methylenedioxyamphetamine. *Pediatr Emerg Care*. 2000; 16:377-380.

Health Insurance Status of Recent US Immigrants

To the Editor: Dr Ayanian and colleagues¹ state that a significant number of uninsured adults in the United States forgo needed medical attention. However, many of these uninsured persons are not US citizens. A recent Kaiser Family Foundation report states that immigrants make up about 10% of the population, yet account for 20% to 25% of the uninsured population.² A significant fraction of these immigrants are in the United States illegally. Legal immigrants are ineligible for Medicare for 5 years. Each legal immigrant must have a sponsor who pledges to provide support for 5 years so that the immigrant does not become a public charge. Even then, Medicaid still provides support for emergency situations.

The insurance problems will only increase as more people immigrate legally and illegally to the United States. A significant part of the problem of adults not being insured in this country can be traced directly to US immigration policy. Illegal immigration must be controlled. Sponsors should be held to their pledges and provide for the health needs of the legal immigrants they sponsor. Immigration should not be a

drain on US taxpayers or have a negative impact on health care.

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1. Ayanian JZ, Weissman JS, Schneider EC, Ginsberg JA, Zaslavsky AM. Unmet health needs of uninsured adults in the United States. *JAMA*. 2000;284:2061-2069.
2. Landers SJ. Immigrants swell ranks of uninsured: welfare policy changes and a lack of job-based health insurance leave increased numbers of immigrants without health coverage. *American Medical News*. August 21, 2000. Available at: http://www.ama-assn.org/sci-pubs/amnews/pick_00/gvsa0821.htm. Accessibility verified January 5, 2001.

In Reply: Dr LaPorta implies that recent US immigrants account for a substantial proportion of the uninsured population, but this assumption is incorrect. In an analysis of the Census Bureau's Current Population Survey (CPS) by the Kaiser Commission on Medicaid and the Uninsured, only 6% of the 42.1 million uninsured US residents (approximately 2.4 million people) in 1999 were noncitizens who had lived in the US for less than 5 years (Catherine Hoffman, personal communication, December 5, 2000). In contrast, 34.7 million uninsured people (82%) were US citizens, and 5.0 million uninsured people (12%) were noncitizens who had lived in the United States for more than 5 years.

Furthermore, a forthcoming Kaiser Commission report that used earlier CPS data found the number of uninsured recent immigrants actually declined by approximately 100 000 from 1994 to 1998, while the total uninsured population increased by 4.2 million people during this period.¹ Thus, although LaPorta is correct in noting that immigrants face a greater risk of being uninsured than the US-born population, the remedies he suggests would have little impact on the number of uninsured people in the United States.

The United States is a nation of immigrants. Not only do immigrants represent 10% of the US population, but another 10% of US citizens have 1 or 2 immigrant parents, and many more citizens have 1 or more immigrant grandparents. Most immigrants arrive in the United States legally (including 85% of current immigrants²) and become contributing members of society. For example, in the first of the 2 Kaiser Commission analyses described above, 68% of uninsured recent immigrants were members of households with 1 or 2 full-time workers, but many had wages too low to afford health insurance. These facts should be recognized when potential solutions to the problems of the uninsured are considered.

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1. Holohan J, Ku L, Pohl M. *Is Immigration Responsible for the Growth in the Number of Uninsured People?* Washington, DC: Kaiser Commission on Medicaid and the Uninsured. In press.
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Overpopulation as a Public Health Challenge

To the Editor: Drs Koplan and Fleming¹ proffer a list of 10 public health challenges for the decades ahead. But they do not go far enough in focusing on the greatest threat to human health: environmental degradation on a global scale. A growing human population consuming resources at an unsustainable rate has put humanity's future in jeopardy. Global warming, emerging infections, massive human migrations, and species extinctions all stem from our inability to confront or control our fertility and our appetite.

While no one would argue with the 10 challenges Koplan and Fleming have identified, physicians need to address the uncomfortable reality that global environmental change is a greater threat to human health than any other factor, short of world war. The challenge is to leave future generations a world in which physicians can meaningfully address the important issues identified by Koplan and Fleming.

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1. Koplan JP, Fleming DW. Current and future public health challenges. *JAMA*. 2000;284:1696-1698.

To the Editor: Drs Koplan and Fleming¹ present a list of 10 public health challenges for the next century. I imagine many readers will be tempted to add pet projects of their own. One unmentioned challenge seems to me to be so fundamental and to have such a profound impact on several of the original 10 challenges that I offer it for consideration.

Overpopulation has a great negative effect on eliminating health disparities, cleaning up and protecting the environment, focusing on child development, and reducing the toll of violence. The problem of too many people is not acute in most industrialized countries and its solution is controversial from many political and religious perspectives; however, it behooves the medical, scientific, and public health communities to devise cheaper and more effective methods of birth control than now exist and campaign strongly for their widespread use throughout the world in the coming century.

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1. Koplan JP, Fleming DW. Current and future public health challenges. *JAMA*. 2000;284:1696-1698.

In Reply: While we limited our list of public health challenges to 10, there are comparably worthy additions of which global environmental degradation and overpopulation are excellent examples.

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(Reprinted) *JAMA*, January 24/31, 2001—Vol 285, No. 4 411

RESEARCH LETTER

The Pills Identification Test: A Tool to Assess Adherence to Antiretroviral Therapy

To the Editor: Adherence to antiretroviral (ARV) treatment among patients with HIV (human immunodeficiency virus) infection is a key issue in controlling viral replication¹ and preventing progression to AIDS (acquired immunodeficiency syndrome) or death.² Assessment of adherence by prescribers often results in overestimating the patient's level of adherence.³ Therefore, simple and reliable tools to independently assess adherence are needed.

Methods. During an ongoing multisite cross-sectional study of adherence to ARV therapy, we tested a pills identification test (PIT). Two hundred twenty-four HIV-infected patients attending outpatient clinics in Caen and Paris-Bichat University hospitals in France were asked to identify the ARV pills they had been prescribed on a board containing 23 ARV pills with 2 similar appearing pills (referred to as twin pills) for each ARV pill (FIGURE). All patients had received the same ARV therapy for at least 3 months. An independent investigator measured the patient's adherence prior to the prescriber's routine consultation using a 4-item adherence scale⁴ validated for other chronic diseases.

The PIT score was calculated as the sum of misidentifications weighted according to the degree of resemblance of the pills (0.5 for the twin, 1 for other or omission). The patient's knowledge of ARV treatment was considered satisfactory if the PIT score was lower than 1. The association between the 4-item adherence scale and PIT results was measured with the χ^2 test and logit odd ratio (OR); the adjusted OR was calculated in a multivariate logistic regression model of the 4-item adherence test score including PIT results and adjusting for number of ARV drugs, age, CD4 cell count, income, and education (SAS, version 6.12; SAS Institute Inc, Cary, NC).

Results. All but 1 patient completed the PIT, in an average time of 2 minutes. Based on the 4-item adherence scale, adherence to ARV therapy was good (4-item adherence scale score <2) for 150 patients (67%). The PIT score was satisfactory for 175 patients (78%). Among the patients who had good adherence according to self-report on the 4-item adherence scale, 21 patients (14%) had poor treatment knowledge based on PIT score and the remaining 129 (86%), satisfactory treatment knowledge. Forty-six patients (62%) with a 4-item adherence scale score showing nonadherence to treatment had a PIT score of less than 1, indicating satisfactory knowledge of ARV treatment, while 28 of these patients (38%) had a PIT score of 1 or greater. The bifurcated adherence scale scores and PIT scores were closely related ($\chi^2=16.5, P<.001$; OR, 3.7, 95% confidence interval [CI], 1.9-7.2). This association remained significant (OR, 6.5; 95% CI, 1.4-8.4) after adjusting for all covariates.

Figure. Pills in the Pills Identification Test



Example of an antiretroviral pill (center) and its 2 twin pills (right and left).

Comment. Our study shows that the PIT is easy to perform and well accepted by patients. The association between results of the 4-item adherence test and PIT shows that PIT could be used in addition to the 4-item adherence test to assess adherence to ARV treatment. The PIT is unaffected by the identity of person administering it. In clinical practice, the PIT may be useful to assess adherence a few weeks after starting or switching an ARV treatment regimen. It is also a simple way to ensure and improve patients' knowledge of their treatment regimen, and might be useful to assess adherence to treatment in conditions other than HIV infection.

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Funding/Support: This study was supported by the Fondation pour la Recherche Médicale and Roche Pharma.

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