

COMMENTS AND RESPONSES

What Is the Best End Point for Hepatitis B Treatment?

TO THE EDITOR: We write in response to the editorial by Degertekin and Lok (1), which addressed our article on standard treatment criteria and end points for hepatitis B (2). Degertekin and Lok state that “[a]lthough HBV [hepatitis B virus] replication after HBeAg [hepatitis B e antigen] seroconversion can be reactivated . . . an occurrence of 30% over 10 years does not justify continuing treatment for all patients” (1). A 30% occurrence rate is very high. The risk for myocardial infarction with hypercholesterolemia in a placebo-controlled trial is 7.9% at 5 years (3); no physician would consider stopping the treatment of hypercholesterolemia once the lipid levels are normalized. More important, Degertekin and Lok consider only the risk for reactivation of viral replication, but the most serious risks in HBeAg-negative patients are those for cirrhosis complications and hepatocellular carcinoma, which occur more often in HBeAg-negative patients with HBV DNA levels greater than 10 000 copies/mL and are independent of HBeAg status (4).

Degertekin and Lok further state that “transition [from the inactive carrier state to HBeAg-negative hepatitis] is not unique to patients with perinatal HBV infection; in fact, it is most commonly associated with HBV genotype D, which is usually acquired during childhood or during adulthood” (1). This is not true. A recent study (5) of 173 children from northern Greece, all with genotype D, showed that 61.8% of Thracian Muslims acquired HBV infection from infected mothers and another 26.2% acquired it horizontally through family contact (that is, 87% are infected during early childhood), similar to Asians (5). This explains the high risk for cirrhosis complications and hepatocellular carcinoma in these populations.

Finally, Degertekin and Lok state that “HBeAg seroconversion seems an appropriate treatment end point in most patients This is particularly true when a strict definition of HBeAg seroconversion—namely, HBeAg loss, HBe antibody detection, a nondetectable (or very low) serum HBV DNA level, and normalization of ALT [alanine aminotransferase] values—is used as the treatment end point” (1). This “strict” definition of HBeAg seroconversion is not implied in the 2007 guidelines of the American Association for the Study of Liver Diseases (6), which do not mention HBV DNA level as an end point. Adopting this strict definition is indeed what we advocate: HBeAg seroconversion is not an ideal sole criterion for a treatment end point, but it should be accompanied by low HBV DNA levels (preferably to below the threshold of detectability by polymerase chain reaction assay) and ALT normalization (2).

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We appreciate Drs. Lai and Yuen's comments. We agree that lifelong maintenance therapy would be preferred when safe, affordable, and effective treatment is available to prevent disease recurrence. However, the safety of lifetime use of nucleoside or nucleotide analogues for hepatitis B has not been established. Adefovir is associated with a small risk for nephrotoxicity. Entecavir at high doses in rodents was associated with a variety of tumors, prompting the manufacturer to pledge a 10-year follow-up study to establish its long-term safety in humans. Furthermore, currently available hepatitis B treatments are very expensive, and their efficacy in maintaining viral suppression is diminished by the selection of drug-resistant mutations during long-term therapy. Even in cancer that has the propensity for late recurrence, treatment is discontinued after disease remission or a finite duration of consolidation therapy (1).

We completely agree that cirrhosis and hepatocellular carcinoma are the key outcomes of chronic HBV infection. However, as Drs. Lai and Yuen indicated, a persistently high HBV DNA level is the most important predictor of these outcomes. Thus, the risk for adverse outcomes after treatment discontinuation is related to the risk for reactivation of viral replication.

Drs. Lai and Yuen cited a recent study (2) in Greek children showing that 21 of 34 Thracian Muslims (62%) had an HBV-infected mother. However, this study did not determine whether the mothers were the source of infection and whether the infection was acquired perinatally. In the same study, only 47 of 121 Thracian Christians (39%) had an HBV-infected mother. Other studies from Italy and Greece, where HBV genotype D is preponderant, reported increased prevalence of chronic HBV infection with age, with the highest prevalence in those older than 40 years of age. This supports the idea that HBV infection in these countries is mostly acquired during childhood and adult life (3, 4).

Although the strict definition of HBeAg seroconversion was not clearly described in the 2007 American Association for the Study of Liver Diseases Practice Guidelines (5), a recent analysis of 74 patients who lost HBeAg after 48 weeks of entecavir therapy found that 70 had HBeAg seroconversion, 71 had undetectable HBV DNA by polymerase chain reaction, and 63 had normalization of aminotransferases. These findings support the idea that most patients who achieve HBeAg seroconversion during nucleoside or nucleotide analogue therapy meet the strict definition of HBeAg seroconversion (6).

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Potential Financial Conflicts of Interest: None disclosed.

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Fondaparinux in Patients with Impaired Renal Function: The Right Choice?

TO THE EDITOR: Investigators from OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) (1) report more bleeding events with enoxaparin than with fondaparinux among patients with non-ST-segment elevation myocardial infarction. However, because fondaparinux has a longer half-life than enoxaparin (17 hours vs. <10 hours) (2, 3), we are concerned that the trial failed to demonstrate that enoxaparin is safer than fondaparinux in patients with impaired renal function, which is a reasonable expectation. We agree with the investigators that, in addition to the glomerular filtration rate, many other features, such as the direct antithrombin activity or the binding to endothelial cells and plasma proteins, should be accounted for to estimate as precisely as possible the probability of bleeding when fondaparinux rather than enoxaparin is being used. However, the severity of renal function impairment remains the most accurate single determinant of hemorrhagic risk in patients treated with either fondaparinux or enoxaparin.

One important point is that patients in OASIS-5 were randomly assigned to receive fondaparinux, 2.5 mg/d, or enoxaparin, 1 mg per kg of body weight twice daily, even though the enoxaparin dose in the latter group was reduced to 1 mg/kg daily if creatinine clearance decreased to less than 30 mL/min. Fondaparinux at 2.5 mg/d is the current recommended dose for preventing venous thromboembolism rather than treating acute venous or arterial thrombosis (4), whereas enoxaparin was given at the full dose used for the treatment of acute thrombosis. It is also worth noting that the OASIS-6 trial (5), which compared fondaparinux, 2.5 mg/d, with placebo or unfractionated heparin in patients with acute ST-segment

elevation myocardial infarction, showed only a marginal reduction, if any, in bleeding events among patients treated with fondaparinux. Use of this relatively low dose of fondaparinux could explain the lower hemorrhagic burden with fondaparinux than with enoxaparin in OASIS-5 patients with impaired renal function. We believe that the advantages of fondaparinux relative to enoxaparin in terms of a greater antithrombotic efficacy and a lower bleeding risk are firmly established.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We thank Drs. Famularo and Minisola for their comments, but it is important to note that the dose of enoxaparin used in our study was the dose approved by regulatory agencies and recommended by acute coronary syndrome guidelines. To optimize both safety and efficacy, we chose the dose of fondaparinux on the basis of the PENTUA (Pentasaccharide in Unstable Angina) trial, a phase II study in patients with acute coronary syndromes, and other data. Using the "full dose" of an experimental drug may not be appropriate when the goal is to minimize bleeding risk yet provide appropriate efficacy. Our findings suggest that similar considerations need to be applied to the dose selection of enoxaparin, and that, especially in patients with moderate or more severe renal dysfunction, a lower dose may provide a better balance between efficacy and safety. This is speculative, however, and has yet to be proven in randomized trials.

In addition to renal function and patient risk features, age and many other factors, such as direct antithrombin activity or the binding to endothelial cells and plasma proteins, should be considered in relation to bleeding risk. In the OASIS-6 trial (1), the lack of an increase in cases of bleeding with fondaparinux versus placebo (in stratum 1) or unfractionated heparin (in stratum 2) is noteworthy, because a significant reduction in mortality and re-infarction and a trend toward fewer strokes occurred. The results of both OASIS-5 and OASIS-6 reinforce the concept that efficacy benefits can be achieved without compromising patient safety.

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Potential Financial Conflicts of Interest: Dr. Fox received grants, consultancies, and honoraria from Sanofi-Aventis, Merck-Sharpe-Dohme, and GlaxoSmithKline.

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The Importance of Efficient Depression Management in Primary Care

TO THE EDITOR: In their recent article, Hepner and colleagues (1) mention that depression rarely leads to death. This is astonishing, because patients with major depression have an increased overall relative risk for death (1.81 [95% CI, 1.58 to 2.07]) compared with people without depression (2). Even for subclinical depression, this risk is no smaller than the relative risk associated with clinical depression (2). A large part of the increased mortality in depression is due to the risk for suicide (4 to 16 times higher than that in persons without depression) (3).

In this context, we consider the results of Hepner and colleagues' study to be alarming. Complex interventions that combine clinician education, an enhanced management role for the nurse, a better integration between primary and secondary care, and telephone medication counseling by trained clinicians might help considerably in improving depression management in the primary care setting (1, 4). On the other hand, simple educational strategies and the mere implementation of treatment guidelines might not be so effective (4, 5).

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Depression decision support in primary care: a cluster randomized trial. *Ann Intern Med*. 2006;145:477-87. [PMID: 17015865]

IN RESPONSE: We thank Drs. Theleritis and colleagues for pointing out the importance of depression in causing increased mortality due to suicide. As they say, the adverse effects of depression on cardiovascular health and other chronic disease outcomes are well documented. We agree that these effects, in combination with the low quality of care we observed, are cause for alarm. Our comments on mortality related to depression come from a different perspective, however, and we are grateful for the opportunity to clarify.

For many conditions, avoidance of death and hospitalization are critical drivers for quality improvement. For patients hospitalized with congestive heart failure, for example, the observed high short-term rates of death and repeated hospitalization have enabled studies to validate quality improvement programs against both economic and mortality outcomes. In the case of depression, however, hospitalization is relatively rare and effects on death occur over a prolonged period. Also, in our studies, we protect people from death due to suicide by intervening if they disclose significant suicidal risk. So, despite having screened more than 50 000 patients to identify our samples and having enrolled more than 1000 patients with major depression, we have no documented episodes of suicide and few deaths during our period of observation.

Hospitalizations during a 6-month period ranged from 19% at the Veterans Affairs Greater Los Angeles Healthcare System to around 5% to 7% for the remaining organizations, with very few admissions due to poor mental health. In the absence of mortality or mental health hospitalization as outcomes, we must validate our quality measures or improvements against such outcomes as depression symptoms, as we did in our study, or against intermediate consequences of those symptoms, such as functional status deficits or employment loss.

Effective care models for improving depression outcomes have been developed and validated in many randomized trials. The quality deficits we identify show why education and reminders alone do not improve care. Had the quality deficits been found in the primary care clinicians' ability to recognize depression, trials testing reminders might have had significant effects. In our study, however, clinicians accurately suspected depression. The deficits were in areas less easily addressed through reminders. We found, for example, a deficit in clinicians' assessments of the factors necessary to decide on an appropriate treatment for depression. Assessment includes ascertaining the presence of diagnostic criteria and other critical treatment factors, such as history of depression, suicidality, alcohol use, anxiety, and bereavement. Improving primary care clinician assessment of depression requires time for and experience with psychological interviewing or testing, and this is hard to find in a 10-minute, multipurpose primary care visit. Similarly, improving patient completion of depression treatment requires methods for actively monitoring and encouraging adherence, objectively monitoring symptoms, and changing medications when necessary—processes that are not consistent with the usual primary care pattern of 3- to 6-month return visits. In the studies reviewed by Gilbody and colleagues (1), the most effective interventions provided primary care clinicians with access to depression care management and collaboration with mental health specialists.

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Skeletal Toxicity of Thiazolidinediones

TO THE EDITOR: Patients with type 2 diabetes mellitus are at increased risk for fracture compared with their euglycemic peers (1). In their review of the comparative safety of oral therapies for type 2 diabetes mellitus, Bolen and colleagues (2) refer to evidence from the ADOPT (A Diabetes Outcome Progression Trial) study that fracture incidence increased by about 2-fold in women with type 2 diabetes mellitus taking rosiglitazone compared with those taking either glyburide or metformin. An increased fracture risk in women has also been reported from a preliminary analysis of an ongoing rosiglitazone trial (3) and from a pooled analysis (4) of randomized trials comparing pioglitazone with either placebo or active comparators. The likely mechanism of thiazolidinedione-induced skeletal fragility is inhibition of bone formation by peroxisome proliferator-activated receptor- γ -mediated diversion of mesenchymal progenitor cells into the adipocyte lineage at the expense of osteoblastogenesis (1, 5). Clinicians should be mindful of this additional adverse effect of thiazolidinedione therapy when prescribing oral hypoglycemic therapy, particularly to older women. Skeletal end points should also be evaluated in prospective, comparative studies of oral therapies in type 2 diabetes mellitus.

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Potential Financial Conflicts of Interest: Dr. Grey received consulting fees from GlaxoSmithKline.

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Guideline Adaptation: An Appealing Alternative to De Novo Guideline Development

TO THE EDITOR: The ADAPTE Collaboration (www.adapte.org) is an international group aiming to enhance the use of evidence through more efficient development and implementation of guidelines by guideline adaptation. We read with great interest about the process used by the American College of Physicians (ACP) to develop their statement for glycemic control (1). The development and maintenance of high-quality guidelines require substantial time, expertise, and resources, and the ACP has used an attractive alternative to de novo guideline development. Yet guideline adaptation also presents challenges. Although guideline developers often consider existing guidelines as a source of evidence, few are using a formal process for reviewing and selecting high-quality guidelines among the heterogeneous, ever-expanding volume of sometimes different or even contradictory recommendations.

The ACP performed a comprehensive search to identify existing guidelines and assessed their quality by using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. This instrument has become a widely accepted standard for assessing guideline methodological quality, but it does not assess guideline content. We think it is important to explicitly assess how current the source guidelines are and whether recommendations are consistent with the underlying evidence, clinically useful, and applicable within the targeted context of use (2, 3). Evidence supporting recommendations may be outdated within 3 years (4). Not all guidelines assessed by the ACP provide an explicit link between the recommendations and the underlying evidence, and 7 of the 9 guidelines are older than 3 years. Furthermore, organizational and cultural differences between countries can lead to legitimate variations in recommendations, even if those recommendations are based on the same evidence (5). Thus, guidelines produced in one setting may not be appropriate for another without modification.

The ADAPTE Collaboration has developed a systematic approach for the adaptation of guidelines and has produced a manual and a resource toolkit. The process is designed to help customize existing guidelines to a different setting while preserving evidence-based principles and to encourage confidence in, acceptance of, and use of adapted guidelines by targeted users.

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TO THE EDITOR: We read with interest the ACP guidelines (1) on glycemic control in type 2 diabetes mellitus. The use of the AGREE instrument to compare the methodological rigor of various guidelines is a meaningful step forward. To our knowledge, it is used regularly only by a few groups, such as the Guidelines Advisory Committee in Ontario (www.gacguidelines.ca), and more widely in Europe by the Belgian Centre for Evidence-Based Medicine (www.cebam.be) and others (www.agreetrust.org/links.htm). Using well-developed guidelines as a basis for forming recommendations is an important strategy to improve quality of care and may also lead to efficiencies in the development process.

Nevertheless, we have 2 concerns with the methods used to assess the guidelines. First, using a total AGREE score, as the authors do in Table 2 (1), and averaging the scores of all 6 domains assumes that each domain is of similar importance. However, the developers of the AGREE instrument (2) specifically state that the domain scores should not be aggregated into a composite score, because they are independent. Each domain score is calculated by standardizing the summed scores of individual items. Moreover, the relative importance of the domains is not static and depends on the values of the raters. In other words, total scores provide no data on perfor-

mance within each domain, and we do not know in which domains bias is more likely to influence recommendations or practice (3).

Our second concern regarding the methods of the ACP guideline is the use of only 2 raters. It is considered standard for systematic reviews to have 2 abstractors for data, but interrater agreement is optimized when at least 4 trained raters are used to apply the AGREE score. Although current efforts with the AGREE Next Steps Project (phases 1 and 2) (4) are aimed to address this human resource demand, the current standard to achieve acceptable reliability is 4 raters (3).

The methods of guideline development are evolving rapidly, with such groups as the Guidelines International Network (www.g-i-n.net) and the ADAPTE Collaboration (www.adapte.org) (5) providing collaborative guidance to interested developers. We hope that the ACP will consider participating in these activities and sharing wisdom acquired over many years of developing evidence-based guidelines.

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IN RESPONSE: We thank Dr. Fervers and colleagues and Dr. Palda and associates for their comments on ACP's guidance statement. We concur that the AGREE instrument is not comprehensive enough to capture such issues as those raised by Dr. Fervers and colleagues. In our article, we acknowledged the limitations of the AGREE instrument, such as the inability to capture guideline development processes that lie outside the guideline document. Because of these limitations, ACP developed additional criteria, listed in Table 1 of the

guidance statement, that address such concerns as translation of evidence into recommendations. However, we agree with Dr. Fervers and colleagues that our criteria did not account for organizational and cultural differences between different countries, and we hope for a new and improved evaluation instrument that can account for the shortcomings the writers pointed out in their letters.

The concern related to the use of aggregate scores versus individual domain scores is valid. We included a table in the article showing scores for each individual question to give the reader an idea of how guidelines fared against each other. In addition, we evaluated each guideline and summarized their strengths and weaknesses in ways that were not necessarily based on the AGREE instrument.

We also considered the issue of using 2 raters. In addition to the 2 raters, other members of the committee also reviewed selected parts of the guidelines. However, we agree that more reviewers are helpful, and we are investigating ways to increase the number of reviewers for assessments with the AGREE instrument.

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Relevance of Recertification for Primary Care Physicians

TO THE EDITOR: In his recent letter, Volpintesta (1) made a statement about the burden of recertification for generalists. He observed that the scope of knowledge and skill is narrowed after being in practice for many years, and therefore taking examinations is a waste of time and money. Nonetheless, it is important for generalists, even in nonacademic settings (office-based or not), to stay up to date. Generalists focus on the broad field of internal medicine and family practice. At any time, they could see a case of an uncommon disease that has common signs and symptoms. All of us have seen missed and near-missed cases; uncommon diseases do not have a flashing neon sign to declare themselves to practicing physicians. The whole objective of recertification is therefore to keep us informed about new and ever-evolving fields of medicine.

The American Board of Internal Medicine, along with the computer-based, open-book, and chart-oriented Medical Knowledge Self-Assessment Program and Practice Improvement Modules, gives us the opportunity to stay current, improve ourselves, and practice better medicine. Not staying informed will turn generalists into dinosaurs. This is not good medicine, and it's not good for our patients.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Volpintesta EJ. Tailoring to the needs of one's practice: it's about time [Letter]. *Ann Intern Med.* 2007;147:592. [PMID: 17938403]

IN RESPONSE: In response to Dr. Aleali's letter, I agree that it is important to stay current to avoid, as he warns, becoming a dinosaur. But I wasn't implying that physicians don't need to stay current and informed. What I suggested was that the current methods of recertification for generalists, particularly family doctors, are burdensome and out of sync with the real world of medicine. This is particularly true for family physicians, but it applies to all physicians who consider themselves providers of primary care.

Most primary care physicians customize their practices over time and according to the types of patients they see, procedures they do, and diseases they feel comfortable treating. This customization even includes the number of patients they see per day, whether they use or do not use physician extenders, and the number of specialists in the area.

The point is that after 10 or 15 years, if not sooner, some skills and knowledge that a physician had at the end of residency are no longer relevant. Physicians are much too busy dealing with regulations, the ever-increasing demands of patients, and administrative red tape to take time off for board review courses, and many of them cannot afford the time off and the costs involved.

As Dr. Aleali says, many unusual diseases may present, and it is important to be aware of them. But these are matters of judgment more than rote memory. If a physician's judgment is good, he or she will recognize when a patient with an unusual set of symptoms or signs presents and will seek consultation. Most errors in medicine are not because of lack of knowledge but because of poor judgment or poor timing in getting consultations.

It seems ironic that trying to conform to the boards' vision of what a generalist is has caused many generalists to come close to the "dinosaur" status that Dr. Aleali mentioned. How? Because by trying to do it all and know it all—in the hospital, intensive care unit, office, and nursing home—many generalists have spread themselves too thin. This creates a vacuum that has been filled by physician assistants and advanced practical nurses. In this context, maybe generalists are already on the way to becoming dinosaurs. As the saying goes, the road to hell is paved with good intentions. In fact, the "generalist" of the future just may be one of these midlevel providers, and current generalists may end up being medical managers.

For generalists in particular, the boards need to change their focus. They should uncover areas of weakness in a physician's practice and offer remedial study, and they need to move away from the current pass/fail approach. If a physician has passed initial certification or is board-eligible, that should be sufficient to take the tests and qualify for remedial education.

The very name "board certification" implies a degree of excellence that is not necessary to deliver good medical care. Its significance is more academic than practical and is more appropriate for teachers in medical schools or residency programs and anyone who simply strives to acquire certification as a personal accolade.

Finally, although the boards are said to be voluntary, many doctors are afraid of being dropped from HMO panels if they are not board-certified. In this sense, the boards are anything but voluntary. In fact, they are coercive. Many primary care physicians believe that the boards need to change.

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Potential Financial Conflicts of Interest: None disclosed.

CLINICAL OBSERVATIONS

Support for National Health Insurance among U.S. Physicians: 5 Years Later

Background: The increasing costs of health care and health insurance have concerned Americans for some time (1). The number of uninsured Americans increased by 2.2 million to 47 million in the most recent census. This is the largest increase reported by the U.S. Census Bureau since 1992 (2). In a 2002 survey of physicians, we reported that 49% supported government legislation to establish national health insurance (3).

Objective: To determine whether physician opinion has changed in the 5 years since the 2002 survey and assess physicians' support for government legislation to establish national health insurance and their support for achieving universal coverage through more incremental reform.

Methods: We randomly sampled 5000 physicians from the American Medical Association Masterfile. We sent each physician a survey asking 2 questions: 1) In principle, do you support or oppose government legislation to establish national health insurance? and 2) do you support achieving universal coverage through more incremental reform? Question 1 was identical to the one we used in our 2002 study (3). Respondents answered using a 5-point Likert scale. We also gathered data on physician membership organizations and demographic, personal, and practice characteristics.

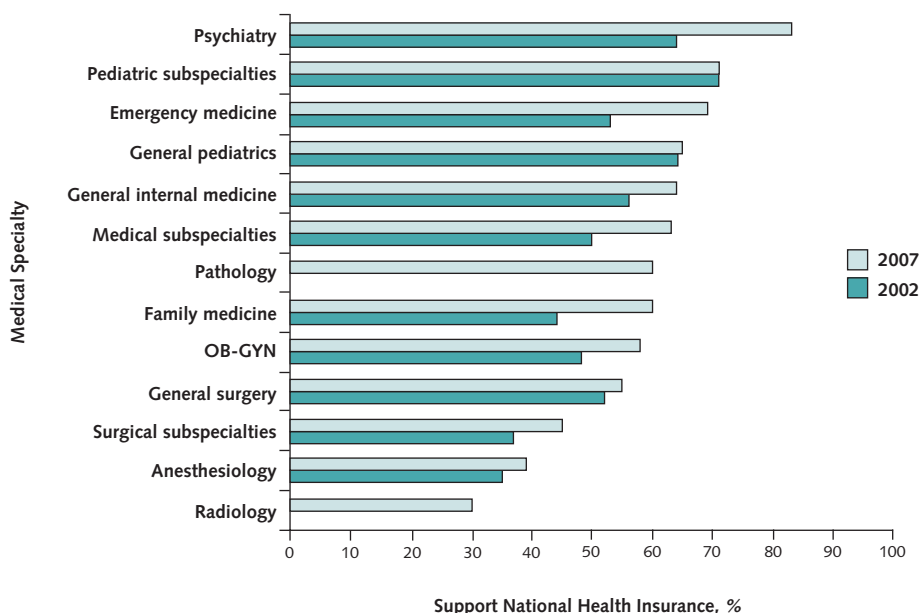
Results: Of 5000 mailed surveys, 509 were returned as undeliverable and 197 were returned by physicians who were no longer practicing. We received 2193 surveys from the 4294 eligible participants, for a response rate of 51%. Respondents did not differ significantly from nonrespondents in sex, age, doctoral degree type, or specialty. A total of 59% supported legislation to establish national health insurance (28% "strongly" and 31% "generally" supported), 9% were neutral on the topic, and 32% opposed it (17% "strongly" and 15% "generally" opposed). A total of 55% supported achieving universal coverage through more incremental reform (14% "strongly" and 41% "generally" supported), 21% were neutral on the topic, and 25% opposed incremental reform (14% "strongly" and 10% "generally" opposed). A total of 14% of physicians were opposed to national health insurance but supported more incremental reforms. More than one half of the respondents from every medical specialty supported national health insurance legislation, with the exception of respondents in surgical subspecialties, anesthesiologists, and radiologists. Current overall support (59%) increased by 10 percentage points since 2002 (49%). Support increased in every subspecialty since 2002, with the exception of pediatric subspecialists, who were highly supportive in both surveys (**Figure**).

Conclusion: Most physicians in the United States support government legislation to establish national health insurance. Support is high among physicians in all but some of the procedural specialties.

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Potential Financial Conflicts of Interest: None disclosed.

Figure. Support for government legislation to establish National Health Insurance in 2007 and 2002, by specialty.



2002 data are not available for pathology and radiology because of lack of response in those categories. OB-GYN = obstetrics and gynecology.

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Response to Sunitinib in Medullary Thyroid Cancer

Background: Medullary thyroid cancer (MTC) is the most aggressive form of well-differentiated thyroid cancer. Of all known cases, 80% are sporadic. Sporadic cases tend to present with advanced disease. In advanced disease, systemic chemotherapy is associated with low response rates of short duration. The rearranged in transformation (*RET*) proto-oncogene has a high frequency of aberrant expression in MTC, and trials of agents directed against this target are ongoing. In preclinical work, Kim and colleagues (1) have shown that sunitinib is a potent inhibitor of the *RET*/papillary thyroid cancer (*PTC*) kinase, and iatrogenic hypothyroidism is increasingly recognized in patients treated with this agent (2, 3).

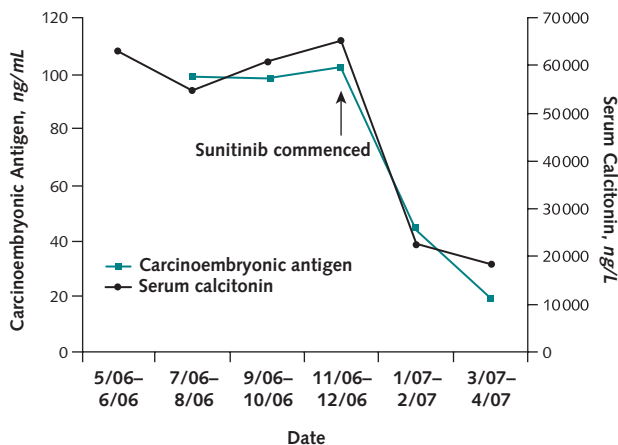
Objective: To describe a case of metastatic MTC responsive to sunitinib.

Case Report: A 70-year-old woman presented with metastatic MTC in December 2005. The cancer was considered sporadic because of her age and because no relevant history suggested familial MTC or multiple endocrine neoplasia. She had total thyroidectomy with modified radical right-neck dissection in December 2005 for compressive neck symptoms. Pathology showed a 6.7-cm medullary carcinoma with extensive lymphovascular invasion involving the right thyroid lobe. The absence of C-cell hyperplasia was evidence against a familial origin. On computed tomography, cervical, mediastinal, and hilar lymphadenopathy with multiple pulmonary metastases were evident. She received an initial trial of octreotide therapy for persistent diarrhea, which led to brief stabilization of serum markers without clinical or radiographic benefit.

In the absence of other available effective treatments for metastatic MTC (4) and in view of the striking biological rationale, the patient was given sunitinib, 50 mg/d for 28 days, followed by 14 days of no treatment. After 2 cycles of therapy, the patient's long-standing diarrhea had resolved and a clinically enlarged right cervical lymph node had become impalpable. A serum calcitonin level of 65 361 ng/L (normal range, 0 to 10 ng/L) before treatment decreased to 18 404 ng/L, and a carcinoembryonic antigen level of 102 μ g/L (normal range, 0 to 5 μ g/L) decreased to 19 μ g/L (Figure). Comparative computed tomography before sunitinib treatment and 12 weeks after demonstrated a reduction in the size and number of pulmonary metastases.

Discussion: Conceptually, treatment with an inhibitor of the *RET* proto-oncogene, such as sunitinib, should play an important therapeutic role in familial MTC and MTC in the context of multiple endocrine neoplasia—conditions that are characterized by activating mutations in this gene. Sunitinib should also be effective in clinically sporadic MTC, because sporadic MTC is associated with germline mutations, point mutations, and heterogeneously distrib-

Figure. Response to sunitinib.



uted mutations involving the *RET* proto-oncogene. Finally, mutations in *RET* have been implicated in the development of papillary thyroid cancer (5). The kinetics of the marker response in this case and the incidence of iatrogenic hypothyroidism in patients treated with sunitinib are highly suggestive of a role for sunitinib in treating thyroid cancer. A phase II clinical trial (ClinicalTrials.gov identification number NCT00381641) sponsored by the National Cancer Institute may provide more definitive evidence of the role of sunitinib in MTC and differentiated thyroid cancer.

Conclusion: A woman with sporadic metastatic MTC had a dramatic clinical response to sunitinib, a potent inhibitor of *RET*/*PTC* oncogenic kinase. Sunitinib may have a therapeutic role in this disease.

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Acknowledgment: The authors thank P. Dwyer for assistance in the preparation of this manuscript.

Potential Financial Conflicts of Interest: None disclosed.

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