TO THE EDITOR: As usual, the U.S. Preventive Services Task Force (USPSTF) carried out an outstanding and comprehensive assessment of health services (1). However, we would like to express 3 concerns. First, should the test really be offered only to women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2? We believe that we should consider any criteria—individual or familial—that gives us a clue that a woman is at risk for carrying the mutation, and we believe that every woman with the same level of risk should be treated in the same way (that is, offered a test or not offered a test) as a matter of equity. The familial history may not accurately reflect pathologic confirmation. Small pedigrees may also downgrade the predictive value of familial history because of the low birth rate in western countries; more than 10% of women may have mothers who were the only first- or second-degree female relative who was old enough to have breast cancer. For all these reasons, it may be useful to consider individual characteristics that may predict that a woman has a high probability of being a carrier of the mutation, such as age at onset of disease, pathologic findings (2), combination of age and pathologic findings, or gene profiling of the tumor. Some of these criteria might not yet reach the level of confidence required by the USPSTF, but some do (such as a single family member who received a diagnosis of cancer before the age of 30 years).

Second, we are concerned about the role of discrimination. The Task Force states that genetic testing “may lead to potential adverse ethical, legal, and social consequences, such as insurance and employment discrimination; these issues should be discussed...” Annals is among the most prestigious international journals and is widely read and quoted. Scientists in the United States are obviously providers of “good” science that deserves wide diffusion. The editors should, however, be cautious about a Trojan horse phenomenon in which discriminatory cultural and social practices evolve under the guise of science. Genetic-based health insurance discrimination is a threat in countries in which premiums are calculated on the basis of risk (as they are in the United States) but not in other countries in which premiums are determined by income.

Third, we question the relevance of monthly breast self-examination in adult women (we do not dispute that clinical breast examination is useful). There is evidence that monthly breast self-examination may not be effective in the general population and may be harmful (3) in high-risk populations, which has led to recommendations for the delivery of preventive services in the United States. In other countries in which premiums are calculated on the basis of risk (as they are in the United States) but not in other countries in which premiums are determined by income. We reiterate the USPSTF conclusion that the potential harms for women who are not at increased risk outweigh the benefits.

To the degree that USPSTF recommendations inform international decisions regarding preventive services, Drs. Eisinger and Horsman raise a clearly relevant point regarding the differences in insurance policy. The Task Force identified additional areas of social harms beyond those of insurability, including important issues in family dynamics and individual responses to information on personal susceptibility. Because the mission of the USPSTF is to provide recommendations for the delivery of preventive services in the United States, we believe these elements are critical to include. These were not, however, the predominant issues in weighing potential harms and benefits; instead, we focused on the harms of unnecessary treatment.

Finally, the USPSTF has no recommendation for or against the use of breast self-examination or clinical breast examination for breast cancer screening (a grade I recommendation on the basis of insufficient evidence). These services may or may not provide more benefit than harm, but the USPSTF concludes that the current body of evidence does not allow an evidence-based recommendation.
There certainly may be cultural differences in the ways in which scientists in other settings judge the quality and certainty of research evidence. In applying the well-documented methods used by the USPSTF (1), however, the Task Force could not make recommendations for these services.

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Reference

TO THE EDITOR: We must disagree with some of the concepts described by Hoffman and Langford (1) in their editorial written in response to our evaluation of relapse and treatment resistance in antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis (2). The editorial primarily addressed 1) the clinical value of our results given that our cohort was not homogeneous and included patients with small-vessel vasculitis manifesting as Wegener granulomatosis, microscopic polyangiitis, and renal-limited pauci-immune necrotizing glomerulonephritis; 2) the usefulness of our requirement for ANCA seropositivity as the primary classification criterion; and 3) the risks and benefits of prolonged therapy. The authors disagreed with our suggestion that physicians should carefully weigh the risk for therapeutic complications associated with prolonged prophylactic therapy against the risk for relapse with or without therapy. This final point is one that we anticipated might generate discussion as our study challenges the current rote therapy used in this disease.

With respect to inclusion of “4 diseases as a single disease,” we contend that these are phenotypic variants of a single entity, small-vessel vasculitis. There are discrepancies in categorization of these diseases between the most commonly used definitions from the American College of Rheumatology (3) and the Chapel Hill Consensus Conference (4). In fact, any single study that claims inclusion of only Wegener granulomatosis or microscopic polyangiitis by either of these definitions would lead to overlapping categories with use of the other definition (5), making the notion of a “pure” sample with either categorization impossible. Of importance, the standard induction therapy across this disease spectrum remains the same despite the presence of clinical differences at onset: cyclophosphamide and corticosteroid therapy is usually given, and treatment response has been consistent across many studies. Analysis of our cohort did not suggest that Wegener granulomatosis, microscopic polyangiitis, or renal-limited disease differed in predictors of relapse or response to treatment. This finding suggests that there are more similarities than differences in these phenotypic variants and challenges the contention by Hoffman and Langford that there are well-delineated disease subgroups within the spectrum of ANCA-associated small-vessel vasculitis. Instead of confusing the non-expert by academic haggling over criteria for diagnosis, our study proposes a simple, straightforward assessment of risk for relapse on the basis of objective, reproducible, and simple criteria: ANCA antigenic specificity and disease involvement of the lungs or upper respiratory tract.

We required confirmation of ANCA seropositivity for inclusion in our patient cohort because of the emerging and compelling evidence that ANCA is indeed capable of causing disease (6, 7). Sable-Fourtassou and colleagues (8) describe the various symptoms and organ involvement seen in ANCA-seropositive patients with the Churg–Strauss syndrome, which suggests that there may be different pathogenesis and disease progression between patients who are ANCA-seropositive and those who are not. There is no evidence of such differences in Wegener granulomatosis or microscopic polyangiitis, 2 conditions in which ANCA seropositivity is far more common than in the Churg–Strauss syndrome. Only approximately 10% of patients with pauci-immune small-vessel vasculitis are ANCA-seronegative (9). A recent study of ANCA-seronegative pauci-immune vasculitis showed that these patients have clinical features that are quite similar to those seen in patients with ANCA-seropositive vasculitis (10). Therefore, the exclusion of this uncommon category from our study probably had a negligible impact on the conclusions.

Most concerning to us is that Hoffman and Langford recommend the use of maintenance therapy over the course of at least 1 year beyond unequivocal remission when no clinical trials have compared a specific duration of maintenance therapy against a control (1). Our cohort evaluation includes the necessary caveats to prevent overinterpretation of our results regarding treatment duration. The editorial compares the treatment results of our studies with 2 treatment trials (11, 12), but, as the authors point out, comparing the results of different trials is “risky” and may introduce bias. Therefore, both our study and the editorial highlight the fact that clinicians have no evidence-based guidance for how long to treat these patients to prevent disease relapse. Even among the various trials by the European Vasculitis Study Group (11–13), the relapse rates have been vastly different with various treatment approaches and regimens. These mixed findings demonstrate that we do not know which drug is effective and that subtle differences in patient populations may greatly affect the risk for relapse. The stakes for disease relapse and for adverse events from treatment are too high to leave these decisions to unsubstantiated contentions. Large, collaborative clinical trials designed specifically to address these questions objectively must be conducted.

Ironically, the 2 trials cited in the editorial (11, 12) included patients with Wegener granulomatosis and microscopic polyangiitis and required patients to be ANCA-seropositive, the very characteristics criticized with regard to our study. Sustained remission rates in patients with Wegener granulomatosis were similar to those seen in patients with microscopic polyangiitis (11), further supporting similar treatment responses across the disease spectrum of ANCA-associated small-vessel vasculitis.

In summary, ANCA-associated small-vessel vasculitis represents a spectrum of diseases that are diagnosed, treated, and managed similarly and may have a related pathogenesis. Induction therapy is reasonably well established. The critical questions are: Does long-
term immunomodulating therapy prevent relapse? If so, which patients would benefit and which could be spared long-term treatment? Decisions by patients and physicians to stop or continue maintenance therapy must be based on evidence, not on the ominous unknown. Although our cohort study does not answer all of the questions, it challenges the concept that long-term maintenance therapy should be considered the standard of care, especially among patients at low risk for relapse.

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IN RESPONSE: Hogan and colleagues have restated their belief that so-called “phenotypic variants of a single entity, small-vessel vasculitis.” This assertion ignores abundant evidence of important differences among these diseases that influence presentation, complications, selection of treatment strategies, and outcomes.

These disease entities have unique clinical differences. Consider, for example, the patient with Wegener granulomatosis who presents with chronic ear, nose, throat, or tracheal damage, none of which are complications of microscopic polyangiitis or renal-limited pauci-immune glomerulonephritis and rarely emerge in the context of the Churg–Strauss syndrome. The strategies to treat such complications extend beyond deciding which cytotoxic agent to add to corticosteroid therapy. In Wegener granulomatosis, one must consider whether chronic otitis media and conductive hearing loss may require placement of tympanotomy tubes, whether nasal complications require debridement of crusts or measures to improve moisturization, and whether subglottic or large bronchus stenosis requires surgical interventions. Unlike microscopic polyangiitis or renal-limited disease, active Wegener granulomatosis can also present with inflammatory mass lesions that may appear in any organ and must be differentiated from a comorbid malignancy or abscess. Although asthma and peripheral eosinophilia are infrequently found in Wegener granulomatosis, microscopic polyangiitis, and renal-limited disease, they are characteristic manifestations of the Churg–Strauss syndrome that can influence clinical decision making.

Microscopic characteristics of lesions also demonstrate striking histopathologic differences that provide further testimony to the distinct nature of these diseases. Whereas the renal histopathologic characteristics of all 4 diseases are similar, lesions in other organs are quite distinct. Nonspecific inflammation and granulomatous lesions are common in Wegener granulomatosis and are often present in the absence of vasculitis. However, granulomatous changes are not pathologic characteristics in microscopic polyangiitis or renal-limited disease. Biopsies from patients with the Churg–Strauss syndrome usually show an abundance of eosinophils, which is not characteristic for the other disease entities.

Hogan and colleagues argue that these diseases may be characterized within a common spectrum on the basis of patient responses to broad-based immunosuppressive therapy. We find this analytic approach to be no more sound than to argue that rheumatoid arthritis and inflammatory bowel disease are more similar than different because both diseases respond to similar treatment regimens.

Hogan and associates also note that the ideal treatment duration remains uncertain for patients with Wegener granulomatosis, microscopic polyangiitis, and the Churg–Strauss syndrome. We agree that large clinical trials will be required to best determine duration of treatment after induction of remission for each disease (and perhaps even for subsets within each disease). However, until such studies have been performed, our previously cited data support the notion that relapses may be diminished with more prolonged therapy and that such therapy need not include cyclophosphamide. The findings of De Groot (1) and Jayne and colleagues (2) and the European Vasculitis Study Group resulted from trials that were conducted in a prospective, standardized manner. Furthermore, other researchers who support the withdrawal of maintenance therapies have acknowledged increased rates of relapse with this management strategy (3, 4).

We believe that it is not wise to assume that these diseases are phenotypic variants of ANCA-associated small-vessel vasculitis. Despite important and insightful investigations of these antibodies that have come from in vitro studies and murine models, we lack defin...
itive evidence to prove that ANCA seropositivity is crucial to disease pathogenesis in humans. The absence of ANCA in many patients with Wegener granulomatosis and the Churg–Strauss syndrome supports the notion of a nonessential role. However, it does not rule out the possibility that ANCA, when present, may influence disease expression in certain organs. Vasculitis is not a constant feature of lesions in Wegener granulomatosis or the Churg–Strauss syndrome.

To think of these disease entities as merely expressions of small-vessel vasculitis is an oversimplification that does not serve to inform discussions of pathogenesis. We conclude that differences in disease presentation, organ involvement, and complications that require unique treatment strategies make this debate clinically relevant and not one that should be dismissed as being merely a matter of “academic haggling.”

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Potential Financial Conflicts of Interest: None disclosed.

References

The Metabolic Syndrome as a Predictor of Nonalcoholic Fatty Liver Disease

TO THE EDITOR: We found the article by Hamaguchi and colleagues (1) to be valuable and insightful. The authors provided new evidence that characterized the natural history of nonalcoholic fatty liver disease (NAFLD), defined the distribution of risk factors in other populations, and confirmed a strong association between the metabolic syndrome and NAFLD. This report represents an important contribution to the field, but we would like to comment on some of the authors’ methods.

First, the authors made their diagnoses by using ultrasonographic images that were interpreted by a single gastroenterologist. However, the lack of a second evaluation by a different reviewer (with an interreliability analysis) restricts the authors’ claims because of the questionable accuracy of this specific diagnostic method (2).

Second, they used body mass index (BMI) instead of waist circumference as a measure of obesity in all patients. As Feskens and colleagues (3) showed, this strategy alters the diagnosis of obesity because it is not a useful marker of adiposity in older people and because the patient’s ethnicity could modify the metabolic profiles that were associated with a categorical value. The value of 25 kg/m² that Hamaguchi and colleagues used as an index of obesity may not be adequate for the Japanese population. Furthermore, differences between the sexes should be considered (4) because the prevalence of the metabolic syndrome could differ depending on the sex of the population (5).

Third, the most effective strategy to treat both the metabolic syndrome and NAFLD is weight reduction (6). In this paper, patients with a baseline diagnosis of NAFLD who had normal ultrasonography findings on follow-up evaluation were also found to have lost weight, but no information about physical activity or other pharmacologic and nonpharmacologic treatments was provided.

Fourth, the adjusted odds ratios indicate an increased risk for NAFLD among patients with the metabolic syndrome. The dose-dependent effect analysis (that is, evidence of increased risk for NAFLD with an increased number of diagnostic criteria for the metabolic syndrome) should be useful to demonstrate a stronger association between both factors.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: Hamaguchi and colleagues (1) reported that the metabolic syndrome is a strong predictor of NAFLD; however, only a small portion of patients with NAFLD have features of nonalcoholic steatohepatitis (NASH). The authors referred to the roles of adipocytokines, such as leptin and adiponectin; however, serum leptin levels in patients with NASH were not statistically different from those in their matched controls (2). In addition, the investigators observed no correlation between serum leptin levels and hepatic histologic findings (2). In contrast, multivariate analysis revealed that patients with NASH had serum adiponectin levels that were lower than those in controls (3). Furthermore, when compared with simple steatosis, NASH was associated with lower serum adiponectin
levels and higher insulin resistance (3). Most patients (77%) with NASH had serum adiponectin levels of less than 10 μg/mL, but only 33% of those with pure steatosis had these findings (3).

When treating patients with the metabolic syndrome, physicians should consider that the serum adiponectin level could be one of the key factors that distinguish the patients who may develop NASH from those likely to develop NAFLD alone.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Drs. Chavez-Tapia, Mendez-Sanchez, and Uribe argue that our study’s lack of a second ultrasonographic evaluation by a different reviewer restricts the accuracy of the diagnosis of NAFLD. We understand that ultrasonography is not a perfect test and may lead to an incorrect diagnosis of NAFLD in many patients. However, as reported in the reference they quoted (1), interobserver variability is much greater than intraobserver variability for evaluation of the pattern and severity of NAFLD. The inclusion of a second reviewer would have decreased the power to detect longitudinal changes of ultrasonographic images. We believe that ultrasonographic interpretation by a single experienced gastroenterologist was a better approach for our longitudinal study.

Dr. Chavez-Tapia and colleagues raised a concern regarding our substitution of BMI for waist circumference for the diagnosis of the metabolic syndrome. We used BMI because we could not obtain waist circumference measurements for the entire study sample. A recent large study (2) found a close correlation between BMI and waist circumference, and similar correlations between BMI and waist circumference and metabolic abnormalities have been identified in Japanese people (3); we believe these reports support our methods. As stated by Dr. Chavez-Tapia and colleagues, the cutoff value of 25 kg/m² may not be optimal for diagnosis of the metabolic syndrome in the Japanese population; however, we adopted this value because it is used as a criterion of obesity for people in East Asia.

We also found that many criteria for the metabolic syndrome were positively associated with the development of NAFLD and negatively associated with regression of the disease, although we did not report these particular observations.

We had no data regarding NASH; however, we appreciated Dr. Kida’s and Dr. Sato’s extension of our discussion regarding the role of adipocytokines in the pathophysiology of NAFLD.

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References

CORRECTIONS

Correction: Screening for Hereditary Hemochromatosis: A Clinical Practice Guideline from the American College of Physicians
An article regarding screening for hereditary hemochromatosis (1) incorrectly reported the locations of two of the authors’ affiliated institutions. Beth Israel Deaconess Medical Center is located in Boston, Massachusetts, and North Shore Medical Group is located in Huntington, New York.

Reference

Correction: Hepatotoxicity Associated with Supplements Containing Chinese Green Tea (Camellia sinensis)
A research letter regarding hepatotoxicity associated with supplements containing Chinese green tea (1) contained errors. The study listed in the first and second rows of the Table was published in 2006 (not 2005), and the first 2 rows list only conventional units for the peak serum total and direct bilirubin levels. For row 1, the peak serum total bilirubin level was 200 μmol/L (11.7 mg/dL) and the peak serum direct bilirubin level was 169 μmol/L (9.9 mg/dL). For row 2, the peak serum total bilirubin level was 153 μmol/L (9.0 mg/dL) and the peak serum direct bilirubin level was 125 μmol/L (7.3 mg/dL).

Reference