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The editors asked several experts to share their perspectives on the crisis in U.S. primary care. Their articles, which address this crisis from six different angles, follow. We also brought the five U.S. contributors together for a roundtable discussion of the problems and potential solutions for training, practice, compensation, and systemic change. A video of the discussion and reader comments can be seen at www.nejm.org. Overstressed by large patient panels, many primary care practices are performing below par. In one study, patients explaining their problem to a physician were interrupted after an average of 23 seconds. Fifty percent of patients . . .


In the wake of the often bitter presidential election, with its emphasis on negative campaigning and intermittent controversies over the release of candidates’ health information, it is not too soon to begin planning for the next presidential campaign. By then, advances in genomics will make it more likely that DNA will be collected and analyzed to assess genetic risk information that could be used for or, more likely, against presidential candidates. Since 1972, when George McGovern was forced to replace his vice-presidential running mate, Thomas Eagleton, after it was revealed that he had been hospitalized for depression, the health status . . .


The editors asked several experts to share their perspectives on the crisis in U.S. primary care. Their articles, which address this crisis from six different angles, follow. We also brought the five U.S. contributors together for a roundtable discussion of the problems and potential solutions for training, practice, compensation, and systemic change. A video of the discussion and reader comments can be seen at www.nejm.org. The United Kingdom takes the importance of primary care for granted. The U.K. primary care is in crisis. Primary care physicians must care for more and more patients, with more and more chronic conditions, in less and less time, for which they are compensated far less than subspecialists. They must absorb increasing volumes of medical information and complete more paperwork than ever, as they try to function in a poorly coordinated health care system. As a result, their ranks are thinning, with practicing physicians burning out and trainees shunning primary care fields. In a roundtable discussion moderated by Dr. Thomas Lee, four experts in primary care and related policy — Drs. Thomas . . .


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government is effectively the country’s single payer, and successive administrations have been convinced by mounting evidence that primary care promotes high-quality, cost-effective, . . .


The editors asked several experts to share their perspectives on the crisis in U.S. primary care. Their articles, which address this crisis from six different angles, follow. We also brought the five U.S. contributors together for a roundtable discussion of the problems and potential solutions for training, practice, compensation, and systemic change. A video of the discussion and reader comments can be seen at www.nejm.org. Robust evidence shows that patient care delivered with a primary care orientation is associated with more effective, equitable, and efficient health services. Countries more oriented to primary care have residents in better health at lower . . .


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ARTICLES


Type 2 diabetes mellitus is thought to develop from an interaction between environmental and genetic factors. We examined whether clinical or genetic factors or both could predict progression to diabetes in two prospective cohorts. We genotyped 16 single-nucleotide polymorphisms (SNPs) and examined clinical factors in 16,061 Swedish and 2770 Finnish subjects. Type 2 diabetes developed in 2201 (11.7%) of these subjects during a median follow-up period of 23.5 years. We also studied the effect of genetic variants on changes in insulin secretion and action over time.

Strong predictors of diabetes were a family history of the disease, an increased body-mass index, elevated liver-enzyme levels, current smoking status, and reduced measures of insulin secretion and action. Variants in 11 genes (TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKL1, IGF2BP2, SLC30A8, JAZF1, and HHEX) were significantly associated with the risk of type 2 diabetes independently of clinical risk factors; variants in 8 of these genes were associated with impaired beta-cell function. The addition of specific genetic information to clinical factors slightly improved the prediction of future diabetes, with a slight increase in the area under the receiver-operating-characteristic curve from 0.74 to 0.75; however, the magnitude of the increase was significant (P=1.0x10–4). The discriminative power of genetic risk factors improved with an increasing duration of follow-up, whereas that of clinical risk factors decreased. As compared with clinical risk factors alone, common genetic variants associated with the risk of diabetes had a small effect on the ability to predict the future development of type 2 diabetes. The value of genetic factors increased with an increasing duration of follow-up.


Severe, refractory obsessive–compulsive disorder (OCD) is a disabling condition. Stimulation of the subthalamic nucleus, a procedure that is already validated for the treatment of movement disorders, has been proposed as a therapeutic option. In this 10-month, crossover, double-blind, multicenter study assessing the efficacy and safety of stimulation of the subthalamic nucleus, we randomly assigned eight patients with highly refractory OCD to undergo active stimulation of the subthalamic nucleus followed by sham stimulation and eight to undergo sham stimulation followed by active stimulation. The primary outcome measure was the severity of OCD, as assessed by the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), at the end of two 3-month periods. General psychopathologic findings, functioning, and tolerance were assessed with the use of standardized psychiatric
scales, the Global Assessment of Functioning (GAF) scale, and neuropsychological tests. After active stimulation of the subthalamic nucleus, the Y-BOCS score (on a scale from 0 to 40, with lower scores indicating less severe symptoms) was significantly lower than the score after sham stimulation (mean [±SD], 19±8 vs. 28±7; P=0.01), and the GAF score (on a scale from 1 to 90, with higher scores indicating higher levels of functioning) was significantly higher (56±14 vs. 43±8, P=0.005). The ratings of neuropsychological measures, depression, and anxiety were not modified by stimulation. There were 15 serious adverse events overall, including 1 intracerebral hemorrhage and 2 infections; there were also 23 nonserious adverse events. These preliminary findings suggest that stimulation of the subthalamic nucleus may reduce the symptoms of severe forms of OCD but is associated with a substantial risk of serious adverse events.


Previous studies have relied predominantly on the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) to assess the association of adiposity with the risk of death, but few have examined whether the distribution of body fat contributes to the prediction of death. We examined the association of BMI, waist circumference, and waist-to-hip ratio with the risk of death among 359,387 participants from nine countries in the European Prospective Investigation into Cancer and Nutrition (EPIC). We used a Cox regression analysis, with age as the time variable, and stratified the models according to study center and age at recruitment, with further adjustment for educational level, smoking status, alcohol consumption, physical activity, and height. During a mean follow-up of 9.7 years, 14,723 participants died. The lowest risks of death related to BMI were observed at a BMI of 25.3 for men and 24.3 for women. After adjustment for BMI, waist circumference and waist-to-hip ratio were strongly associated with the risk of death. Relative risks among men and women in the highest quintile of waist circumference were 2.05 (95% confidence interval [CI], 1.80 to 2.33) and 1.78 (95% CI, 1.56 to 2.04), respectively, and in the highest quintile of waist-to-hip ratio, the relative risks were 1.68 (95% CI, 1.53 to 1.84) and 1.51 (95% CI, 1.37 to 1.66), respectively. BMI remained significantly associated with the risk of death in models that included waist circumference or waist-to-hip ratio (P<0.001). These data suggest that both general adiposity and abdominal adiposity are associated with the risk of death and support the use of waist circumference or waist-to-hip ratio in addition to BMI in assessing the risk of death.
Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine, 359 (21), 2195-2207.

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment. We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes. In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

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Survival of patients with acute lung injury or the acute respiratory distress syndrome (ARDS) has been improved by ventilation with small tidal volumes and the use of positive end-expiratory pressure (PEEP); however, the optimal level of PEEP has been difficult to determine. In this pilot study, we estimated transpulmonary pressure with the use of esophageal balloon catheters. We reasoned that the use of pleural-pressure measurements, despite the technical limitations to the accuracy of such measurements, would enable us to find a PEEP value that could maintain oxygenation while preventing lung injury due to repeated alveolar collapse or overdistention. We randomly assigned patients with acute lung injury or ARDS to undergo mechanical ventilation with PEEP adjusted according to measurements of esophageal pressure (the esophageal-pressure–guided group) or according to the Acute Respiratory Distress Syndrome Network standard-of-care recommendations (the control group). The primary end point was improvement in oxygenation. The secondary end points included respiratory-system compliance and patient outcomes. Results The study reached its stopping criterion and was terminated after 61 patients had been enrolled. The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen at 72 hours was 88 mm Hg higher in the esophageal-pressure–guided group than in the control group (95% confidence interval, 78.1 to 98.3; P=0.002). This effect was persistent over the entire follow-up time (at 24, 48, and 72 hours; P=0.001 by repeated-measures analysis of variance). Respiratory-system compliance was also significantly better at 24, 48, and 72 hours in the esophageal-pressure–guided group (P=0.01 by repeated-measures analysis of variance). As compared with the current standard of care, a ventilator strategy using esophageal pressures to estimate the transpulmonary pressure significantly improves oxygenation and compliance. Multicenter clinical trials are needed to determine whether this approach should be widely adopted.


In countries with a high seroprevalence of human immunodeficiency virus type 1 (HIV-1), HIV infection contributes significantly to infant mortality. We investigated antiretroviral-treatment strategies in the...
Children with HIV Early Antiretroviral Therapy (CHER) trial. HIV-infected infants 6 to 12 weeks of age with a CD4 lymphocyte percentage (the CD4 percentage) of 25% or more were randomly assigned to receive antiretroviral therapy (lopinavir–ritonavir, zidovudine, and lamivudine) when the CD4 percentage decreased to less than 20% (or 25% if the child was younger than 1 year) or clinical criteria were met (the deferred antiretroviral-therapy group) or to immediate initiation of limited antiretroviral therapy until 1 year of age or 2 years of age (the early antiretroviral-therapy groups). We report the early outcomes for infants who received deferred antiretroviral therapy as compared with early antiretroviral therapy. At a median age of 7.4 weeks (interquartile range, 6.6 to 8.9) and a CD4 percentage of 35.2% (interquartile range, 29.1 to 41.2), 125 infants were randomly assigned to receive deferred therapy, and 252 infants were randomly assigned to receive early therapy. After a median follow-up of 40 weeks (interquartile range, 24 to 58), antiretroviral therapy was initiated in 66% of infants in the deferred-therapy group. Twenty infants in the deferred-therapy group (16%) died versus 10 infants in the early-therapy groups (4%) (hazard ratio for death, 0.24; 95% confidence interval [CI], 0.11 to 0.51; P<0.001). In 32 infants in the deferred-therapy group (26%) versus 16 infants in the early-therapy groups (6%), disease progressed to Centers for Disease Control and Prevention stage C or severe stage B (hazard ratio for disease progression, 0.25; 95% CI, 0.15 to 0.41; P<0.001). Stavudine was substituted for zidovudine in four infants in the early-therapy groups because of neutropenia in three infants and anemia in one infant; no drugs were permanently discontinued. After a review by the data and safety monitoring board, the deferred-therapy group was modified, and infants in this group were all reassessed for initiation of antiretroviral therapy.

CLINICAL PRACTICE


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations. A female high-school soccer athlete reacts to a defender, plants her leg, cuts to the left without contact, feels her leg give out, hears a pop, and has acute pain. She is unable to walk off the field or return to play. That evening her knee progressively swells. The next day she presents for evaluation. How should her case be managed?

REVIEW ARTICLES


Rare, large families with multiple cases of early-onset cancer affecting several generations provide clear evidence that inherited factors are important causes of cancer.1 The range of cancers, the age at onset, and the number of generations affected all suggest familial risk. In this review, I discuss the five cancers in the United States that are associated with the highest number of deaths: lung, breast, colorectal, prostate, and pancreatic cancer. In the late 1980s and early 1990s, numerous cancer susceptibility genes were identified, including those for breast and colorectal cancer (Glossary and Table 1). These genes confer high relative risks . . .


The inheritance of two copies of a mutant -globin gene, one from each parent, is the underlying cause of sickle cell disease. The mutation, GAG substitutes valine for glutamic acid at position 6 in the -globin chain of hemoglobin A, resulting in a hemoglobin called hemoglobin S.1,2,3 Sickle cell disease is one of the most common autosomal recessive disorders in the world. Approximately 8% of black Americans are heterozygous and have the sickle cell trait, whereas approximately 1 in 600 is homozygous and has sickle cell disease. In certain areas of sub-Saharan Africa, an estimated 40 to 60% of . . .


Persons who survive a myocardial infarction are at increased risk for sudden death from cardiac causes, owing largely to ventricular tachyarrhythmias.1,2 The risk of sudden death after a myocardial infarction is highest during the first 12 months and then declines.3,4,5,6 Although survival during the acute and early convalescent phases after a myocardial infarction has improved as a result of therapies introduced during the past 25 years,7 a delayed increase in the risk of sudden death from cardiac causes after the initial convalescent phase has become evident. Those in whom ventricular remodeling and heart failure develop are at greatest risk.
A 49-year-old man was struck by a truck traveling at high speed. Cervical computed tomography showed a dislocation between the C5 and C6 vertebrae (Panel A, sagittal reconstruction). Physical examination revealed less than antigravity strength in the bilateral deltoids with no other movement in the limbs. A C7 level with no sacral sensation was found. Gardner–Wells tongs were applied, and a closed reduction was performed within 4 hours after the initial injury. After reduction, the patient immediately regained antigravity strength in both arms and both legs. A posterior cervical fusion was performed in the operating room to stabilize normal alignment.


A 34-year-old woman with a 3-year history of systemic lupus erythematosus was admitted to the hospital with sore throat and headache that had lasted for 3 weeks. She had been receiving cyclophosphamide for lupus nephritis for the previous 2 years. On the eighth hospital day, she reported severe headache and bilateral pain and bruising of the eyes. A day later, proptosis developed, with severe chemosis and eyelid edema, and her pupils were bilaterally nonreactive to light on examination. A preliminary diagnosis of extensive intracranial venous thrombosis was confirmed on magnetic resonance imaging. Axial T2-weighted imaging at the level of . . .


Dr. Roy N. Alcalay (Neurology): A 65-year-old right-handed man was transferred to this hospital because of confusion and memory loss. He had been well until approximately 4 weeks before admission, when he began to have decreased energy and a change in mood. He told his family that he felt as if he was "living in a fog." Three weeks before admission, he lost his way while driving to his sister's house; 9 days before admission, he did not arrive for his weekly visit with his aunt. When reached by telephone at home, the patient stated that he did not know . . .


Dr. Adam B. Cohen (Neurology): A 59-year-old man was admitted to the neurology service of this hospital because of chronic daily headache, fever, and myalgia. Approximately 6 months earlier, the patient had begun having headache, accompanied by muscle spasms, generalized myalgia, weakness, fatigue, difficulty sleeping, and anxiety. The headache was constant, affected both temporal and frontal regions, and was not affected by posture. The temperature rose daily but remained below 37.8°C. Five months before admission to this hospital, he saw his internist at another hospital. The physical examination was normal. Amitriptyline at bedtime was prescribed, without improvement. The patient took . . .
Peripheral Intravenous Cannulation Introduction The ability to obtain peripheral intravenous access is an essential skill for all physicians. Although considered one of the simplest invasive procedures, mastering this potentially lifesaving intervention requires refined skills and experience. Cannulating a vein, particularly a small one, can be challenging. The purpose of this video is to demonstrate how to access peripheral veins using an intravenous catheter. Indications Peripheral intravenous catheterization is required in a broad range of clinical applications, including intravenous drug administration, for intravenous hydration, transfusions of blood or blood components, during surgery, during emergency care, and in other situations.