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As researchers have explored the environmental and inherited causes of common diseases, they have often amassed clinical and laboratory data collected from people with common complex disorders. Many have also collected biologic material, including DNA. These resources represent an essential component for ferreting out genes relevant to disease with the use of the genome-wide association study. This method entails the matching of a given human genome sequence with an annotated, high-resolution map of common genetic variation; it benefits from a large collection of DNA samples obtained from a population whose clinical characteristics are well defined, as well as cost-effective genotyping.


What garners attention when it comes to Medicare’s payment rates for physicians is the annual drama over possible 11th-hour congressional intervention to prevent cuts under the sustainable growth rate formula. But behind the scenes, Medicare policymakers have been focusing on another aspect of the periodic adjustments: the updating of the relative values in the physician fee schedule and the accuracy of the data on which it relies. Since 1992, Medicare has paid physicians through a fee schedule according to a resource-based relative-value scale (RBRVS). This approach was intended to address distortions produced by basing payments on prevailing charges, which had...


More than 90 human enterovirus serotypes have now been identified in three distinct waves of discovery. The three poliovirus serotypes were first isolated from nonhuman primates in the course of painstaking experiments performed during the first half of the 20th century. The use of small laboratory animals and the advent of cell culture in midcentury led to the description of 61 more enteroviruses that we know as coxsackieviruses, echoviruses, and the “newer” enteroviruses. The application of polymerase chain reaction and genomic sequencing has recently permitted characterization of approximately 30 previously unidentified enterovirus serotypes and undoubtedly...


Robert M.D. Since the human immunodeficiency virus (HIV) was found in Chennai in 1986, India has had an AIDS epidemic. In many respects, however, its extent and complexities have only recently begun to be appreciated (see map). India has a population of 1.1 billion people — one sixth of the world’s population — and is home to perhaps one of every eight people with HIV infection. According to Denis Broun, the country coordinator for the Joint United Nations Program on HIV/AIDS (UNAIDS) in India, “It is not possible to control the overall HIV epidemic if it is out of control in India. Whatever success is recorded in India will immediately have an impact on the overall world situation just because of the sheer numbers.”


On April 1, 2007, India will launch a new phase of its National AIDS Control Program (NACP). Its goals include reducing the number of new human immunodeficiency virus (HIV) infections — currently, an estimated 98.5 to 99.5% of India’s 1.1 billion people remain uninfected — improving treatment, and providing therapy to more people. The 5-year program, known as NACP-III, has a budget of about $2.6 billion, two thirds of which is earmarked for prevention and one sixth for treatment (with the remainder primarily for management), and represents a substantial increase in the attention to and spending on HIV—AIDS. More than 80% of the funds will come from outside India — from the World Bank and other international organizations, governments, and philanthropies. Most of the funding has already been committed.


Tuberculosis is the most common HIV-related opportunistic infection in India, and caring for patients with both diseases is a major public health challenge. India has about 1.8 million new cases of tuberculosis annually, accounting for a fifth of new cases in the world — a greater number than in any other country (see pie chart).1 Patients with latent Mycobacterium tuberculosis infection are at higher risk for progression if they are infected with HIV. Patients with HIV infection have a similar bacteriologic response to tuberculosis treatment as those who are not infected but have higher risks of recurrence and death. The influence of tuberculosis coinfection on the progress of HIV disease is controversial.

ORIGINAL ARTICLES


In this trial of the treatment of newly diagnosed multiple myeloma, we compared a protocol that entailed a hematopoietic stem-cell autograft followed by an HLA-identical sibling allograft to a protocol that entailed a hematopoietic stem-cell autograft followed by an HLA-matched unrelated donor allograft. Each of the 332 patients was randomly assigned to one of two treatment groups. The cumulative incidence rates of grades II, III, and IV graft-versus-host disease...
Enterovirus 71 is a common cause of hand, foot, and mouth disease and encephalitis in Asia and elsewhere. The long-term neurologic and psychiatric effects of this viral infection on the central nervous system (CNS) are not well understood. We conducted long-term follow-up of 142 children after enterovirus 71 infection with CNS involvement — 61 who had aseptic meningitis, 53 who had severe CNS involvement, and 28 who had cardiopulmonary failure after CNS involvement. At a median follow-up of 2.9 years (range, 1.0 to 7.4) after infection, the children received physical and neurologic examinations. We administered the Denver Developmental Screening Test (DDST II) to children 6 years of age or younger and the Wechsler intelligence test to children 4 years of age or older. Nine of the 16 patients with a poliomyelitis-like syndrome (56%) and 1 of the 5 patients with encephalomyelitis (20%) had sequelae involving limb weakness and atrophy. Eighteen of the 28 patients with cardiopulmonary failure after CNS involvement (64%) had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Among patients who underwent DDST II assessment, delayed neurodevelopment was found in only 1 of 20 patients (5%) with severe CNS involvement and in 21 of 28 patients (75%) with cardiopulmonary failure (P < 0.001 for the overall comparison). Children with cardiopulmonary failure after CNS involvement scored lower on intelligence tests than did children with CNS involvement alone (P = 0.003). Enterovirus 71 infection with CNS involvement and cardiopulmonary failure may be associated with neurologic sequelae, delayed neurodevelopment, and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well on neurodevelopmental tests.

Chaves, S.S., Paul Gargiullo, John X. Zhang, Rachel Given, Dalya Guris, Laurene Malcolm, and Jane F. Seward. (2007). Loss of vaccine-induced immunity to varicella over time. New England Journal of Medicine, 356 (11), 1121-1129. The introduction of universal varicella vaccination in 1995 has substantially reduced varicella-related morbidity and mortality in the United States. However, it remains unclear whether vaccine-induced immunity wanes over time, a condition that may result in increased susceptibility later in life, when the risk of serious complications may be greater than in childhood. We examined 10 years (1995 to 2004) of active surveillance data from a sentinel population of 350,000 subjects to determine whether the severity and incidence of breakthrough varicella (with an onset of rash > 42 days after vaccination) increased with the time since vaccination. We used multivariate logistic regression to adjust for the year of disease onset (calendar year) and the subject's age at both disease onset and vaccination. A total of 11,356 subjects were reported to have varicella during the surveillance period, of whom 1080 (9.5%) had breakthrough disease. Children between the ages of 8 and 12 years who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than those who had been vaccinated less than 5 years previously (risk ratio, 2.6; 95% confidence interval [CI], 1.2 to 5.8). The annual rate of breakthrough varicella significantly increased with the time since vaccination, from 1.6 cases per 1000 person-years (95% CI, 1.2 to 2.0) within 1 year after vaccination to 9.0 per 1000 person-years (95% CI, 6.9 to 11.7) at 5 years and 58.2 per 1000 person-years (95% CI, 36.0 to 94.0) at 9 years.

Jin, Y., Christina M. Mailloux, Katherine Gowan, Sheri L. Riccardi, Gregory LaBerge, Dorothy C. Bennett, Pamela R. Fain, and Richard A. Spritz. (2007). NALP1 in vitiligo-associated multiple autoimmune disease. New England Journal of Medicine, 356 (12), 1216-1225. Autoimmune and autoinflammatory diseases involve interactions between genetic risk factors and environmental triggers. We searched for a gene on chromosome 17p13 that contributes to a group of epidemiologically associated autoimmune and autoinflammatory diseases. The group includes various combinations of generalized vitiligo, autoimmune thyroid disease, latent autoimmunity diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison’s disease. We tested 177 single-nucleotide polymorphisms (SNPs) spanning the 17p13 linkage peak for association with disease and identified a strong candidate gene. We then sequenced DNA in and around the gene to identify additional SNPs. We carried out a second round of tests of association using some of these additional SNPs, thus elucidating the association with disease in the gene and its extended promoter region in fine detail. Association analyses resulted in our identifying as a candidate gene NALP1, which encodes NACHT leucine-rich-repeat protein 1, a regulator of the innate immune system. Fine-scale association mapping with the use of DNA from affected families and additional SNPs in and around NALP1 showed an association of specific variants with vitiligo alone, with an extended autoimmune and autoinflammatory disease phenotype, or with both. Conditional logistic-regression analysis of NALP1 SNPs indicated that at least two variants contribute independently to the risk of disease. DNA sequence variants in the NALP1 region are associated with the risk of several epidemiologically associated autoimmune and autoinflammatory diseases, implicating the innate immune system in the pathogenesis of these disorders.

Kales, S.N., Elpidoforos S. Soteriades, Costas A. Christofi, and David C. Christiansi.(2007). Emergency Duties and Deaths from Heart Disease among Firefighters in the United States. New England Journal of Medicine, 356 (12), 1207-1215. Heart disease causes 45% of the deaths that occur among U.S. firefighters while they are on duty. We examined duty-specific risks of death from coronary heart disease among on-duty U.S. firefighters from 1994 to 2004. We reviewed summaries provided by the Federal Emergency Management Agency of the deaths of all on-duty firefighters between 1994 and 2004, except for deaths associated with the September 11, 2001, terrorist attacks. Estimates of the proportions of time spent by firefighters each year performing various duties were obtained from a municipal fire department, from 17 large metropolitan fire departments, and from a national database. Odds ratios and 95% confidence intervals for death from coronary heart disease during specific duties were calculated from the ratios of the observed odds to the expected odds, with nonemergency duties as the reference category. Deaths from coronary heart disease were associated with suppressing a fire (32.1% of all such deaths), responding to an alarm (13.4%), returning from an alarm (17.4%), engaging in physical training (12.5%), responding to nonfire emergencies (9.4%), and performing nonemergency duties (15.4%). As compared with the odds of death from coronary heart disease during nonemergency duties, the odds were 12.1 to 136 times as high during fire suppression, 2.8 to 14.1 times as high during alarm response, 2.2 to 10.5 times as high during alarm return, and 2.9 to 6.6 times as high during physical training. These odds were based on three estimates of the time that firefighters spend on their duties. Certain emergency firefighting duties were associated with a risk of death from coronary heart disease that was markedly higher than the risk associated with nonemergency duties. Fire suppression was associated with the
highest risk, which was approximately 10 to 100 times as high as that for nonemergency duties.


Management of acute myocardial infarction requires urgent diagnostic and therapeutic procedures, which may not be uniformly available throughout the week. We examined differences in mortality between patients admitted on weekends and those admitted on weekdays for a first acute myocardial infarction, using the Myocardial Infarction Data Acquisition System. All such admissions in New Jersey from 1987 to 2002 (231,164) were included and grouped in 4-year intervals. There were no significant differences in demographic characteristics, coexisting conditions, or infarction site between patients admitted on weekends and those admitted on weekdays. However, patients admitted on weekends were less likely to undergo invasive cardiac procedures, especially on the first and second days of hospitalization (P<0.001). In the interval from 1999 to 2002 (59,786 admissions), mortality at 30 days was significantly higher for patients admitted on weekends (12.9% vs. 12.0%, P=0.006). The difference became significant the day after admission (3.3% vs. 2.7%, P<0.001) and persisted at 1 year (1% absolute difference in mortality). The difference in mortality at 30 days remained significant after adjustment for demographic characteristics, coexisting conditions, and site of infarction (hazard ratio, 1.048; 95% confidence interval [CI], 1.022 to 1.076; P<0.001), but it became nonsignificant after additional adjustment for invasive cardiac procedures (hazard ratio, 1.023; 95% CI, 0.997 to 1.049; P=0.09). For patients with myocardial infarction, admission on weekends is associated with higher mortality and lower use of invasive cardiac procedures. Our findings suggest that the higher mortality on weekends is mediated in part by the lower rate of invasive procedures, and we speculate that better access to care on weekends could improve the outcome for patients with acute myocardial infarction.


Two assumptions underpin the implementation of pay for performance in Medicare: that with the use of claims data, patients can be assigned to a physician or to a practice that will have primary responsibility for their care, and that a meaningful fraction of the care physicians deliver is for patients for whom they have primary responsibility. We analyzed Medicare claims from 2000 through 2002 for 1.79 million fee-for-service beneficiaries treated by 8604 respondents to the Community Tracking Study Physician Survey in 2000 and 2001. In separate analyses, we assigned each patient to the physician or primary care physician with whom the patient had had the most visits. We determined the number of physicians and practices seen annually, the percentage of care received from the assigned physician or practice, the stability of assignments over time, and the percentage of physicians’ Medicare patients who were their assigned patients. Beneficiaries saw a median of two primary care physicians and five specialists working in four different practices. A median of 35% of beneficiaries’ visits each year were with their assigned physicians; for 33% of beneficiaries, the assigned physician changed from one year to another. On the basis of all visits to any physician, a primary care physician’s assigned patients accounted for a median of 39% of the physician’s Medicare patients and 62% of Medicare visits. For medical specialists, the respective percentages were 6% and 10%. On the basis of visits to primary care physicians only, 79% of beneficiaries could be assigned to a physician, and a median of 31% of beneficiaries’ visits were with that assigned primary care physician. In fee-for-service Medicare, the dispersion of patients’ care among multiple physicians will limit the effectiveness of pay-for-performance initiatives that rely on a single retrospective method of assigning responsibility for patient care.


Although pulsed-dye–laser therapy is currently the gold standard for the treatment of port-wine stains, few objective data are available on its long-term efficacy. Using objective color measurements, we performed a 10-year follow-up of a previously conducted prospective clinical study of the treatment of port-wine stains with a pulsed-dye laser. We invited the patients to undergo repeated color measurements performed by the same procedures as in the previous study. The results at long-term follow-up were compared with color measurements obtained before treatment and after completion of an average of five laser treatments of the complete port-wine stain. A questionnaire was used to investigate patients’ satisfaction with the treatment and their perception of long-term changes in the stain. Of the 89 patients from whom color measurements were obtained in the previous study, 51 were included in this study. The patients had received a median of seven additional treatment sessions since the last color measurement, which had been made after an average of five treatments. The median length of follow-up was 9.5 years. On average, the stain when measured at follow-up was significantly darker than it was when measured after the last of the initial five laser treatments (P=0.001), but it was still significantly lighter than it was when measured before treatment (P<0.001). Fifty-nine percent of patients were satisfied with the overall treatment result. Six percent of patients reported that the stain had become lighter since their last treatment, 59% that it was unchanged, and 35% that it had become darker. Using objective color measurements, we observed significant redarkening of port-wine stains at long-term follow-up after pulsed-dye–laser therapy. Patients should be informed about the possibility of redarkening before beginning treatment.

REVIEW ARTICLE
(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


Heart failure is an enormous medical and societal burden.1,2 It is a common disease: more than 2% of the U.S. population, or almost 5 million people, are affected, and 30 to 40% of patients die from heart failure within 1 year after receiving the diagnosis.3 Heart failure can be disabling, and it can severely reduce a patient’s quality of life. It consumes approximately 2% of the National Health Service budget in the United Kingdom, and in the United States, the total annual cost of treatment for heart failure is approximately $28 billion. Moreover, the financial burden . . .

IMAGES IN CLINICAL MEDICINE


A 49-year-old woman was admitted to the hospital for evaluation of abdominal pain. Her hospital course was complicated by contrast-medium–induced renal failure requiring dialysis. She subsequently
underwent resection of an adnexal mass, 16 cm in diameter. Four hours after surgery, the patient was found to have bright green serum that persisted for 4 days. Intraoperative angiography with a fluorescent dye (total dose, approximately 800 mg) and a Wood’s lamp had been used to evaluate mesenteric-vessel viability. Although this dye normally clears rapidly from the blood, it persisted in this patient owing to the acute renal failure. The mass was diagnosed as colon cancer, which was found to be metastatic. The patient died from complications of the cancer 7 months later.


A 57-year-old man with a history of diabetes mellitus and alcohol consumption was referred to the hand surgery unit owing to contractures of fingers of both hands. He reported that his brother and father had similar contractures. Physical examination revealed flexion contractures involving the bilateral third digits and the right fifth digit. The patient had a severe contracture of 100 degrees at the proximal interphalangeal joint of the right small finger and thickened palmar fascia with multiple cords ending in firm nodules. The condition was diagnosed as Dupuytren’s contracture, a fibroproliferative disorder of the palmar fascia, and the patient subsequently underwent bilateral partial fasciectomy. Common risk factors for Dupuytren’s contracture include a family history of the disorder, diabetes, alcohol consumption, and the use of vibratory machinery. In this case, healing was uneventful, and no recurrence of contracture was observed on follow-up.


An 84-year-old man with a history of gastric cancer and hypertension was admitted to the emergency department in shock after loss of consciousness. Ten years earlier he had been given a diagnosis of a thoracic aortic aneurysm, 56 mm in diameter, and had declined surgical treatment. Although the aneurysm had increased in size over the decade — as documented at various years of age on computed tomographic (CT) studies — and had reached 98 mm in diameter, he had been asymptomatic until the current episode. CT scans revealed a rupturing aneurysm involving the ascending aorta, aortic arch, and descending aorta.


A 48-year-old healthy woman presented with anorexia of 2 days’ duration and abdominal pain in the right lower quadrant. Since appendicitis was suspected, she underwent a laparoscopic examination. An inflamed mass was seen near the cecum, and diverticulitis was diagnosed. She was treated with bowel rest, fluids, and antimicrobial agents. Two days later, her symptoms worsened, with increased pain in the right lower quadrant, abdominal distention, and decreased bowel sounds. Abdominal radiography showed dilatation of the small intestine, suggestive of obstruction, in the supine position (Panel A) and the upright position (Panel B). An axial computed tomographic scan of the...