— ocular ischemia resulting from the intravenous injection of drugs of abuse. A 26-year-old woman presented to our emergency department with blurred tunnel vision after the intravenous injection of cocaine and methamphetamine into her neck vessels.[1,2] She indicated that her use of this site of injection was longstanding and that she had unintentionally punctured her carotid artery on several occasions. On presentation, her visual acuity was 20/30 in both eyes. On examination, visual-field testing revealed constriction of peripheral vision in both eyes and no pupillary defects. Optic neuropathy with pallor of both optic disks was identified. The retinal arteries were markedly narrowed and beaded in appearance, and the retinal veins were mildly dilated. Pinpoint erythematous marks were noted at the injection sites, and ultrasonography of the vessels and soft tissues on both sides of the neck revealed no abnormality. We suggest that clinicians obtain a detailed history of both recent and past injection-drug use when evaluating patients with acute or chronic optic neuropathy.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The limited length and specific focus of our review did not allow us to comment on many aspects of ION or to go into greater depth on a variety of important related topics, such as giant-cell arteritis and perioperative ION. As discussed by Silberberg, the recent reports of VZV in the temporal arteries of patients with giant-cell arteritis are interesting and open the door to innovative avenues for treatment. We hope that future clinical trials that examine the efficacy of antiviral agents for the treatment of giant-cell arteritis will guide us in treating these patients more efficiently and successfully.

Although it is true that elevated intraocular pressure may play a role in some cases of perioperative anterior ION, it seems unlikely that the medical reduction of intraocular pressure during the perioperative period would play a role in preventing visual loss. Although Rubin presents an attractive idea, it would probably be impossible to design a study that would test his hypothesis given the rarity of perioperative visual loss and the many mechanisms that may be simultaneously involved in this complication.

Diffuse ocular ischemia (most often retinal arterial ischemia) is indeed a classic complication of the use of systemic vasoconstricting drugs, particularly when directly injected into an artery. The case described by McKeever et al. is interesting and rather unusual. The narrowing of the retinal arteries in association with optic-nerve pallor suggests retinal ischemia that is probably the result of drug use or the presence of particulate emboli in the retinal arteries over a period of months rather than the result of acute isolated ION. As suggested by the authors, there are numerous causes of ION that were not detailed in our review, and it is of course important to inquire about drug use in relation to any vascular event.

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The 21st Century Cures Act

TO THE EDITOR: In their Perspective article (June 25 issue),[1] Avorn and Kesselheim argue that the 21st Century Cures Act, which is currently being debated in Congress, would lower the regulatory standards of the Food and Drug Administration (FDA) by giving it greater discretion to approve drugs on the basis of less rigorous data. In particular, the authors argue that the legislation would authorize the FDA to "rely" on observational analyses, which are less rigorous than random-

ized controlled trials (RCTs). But the Cures Act does not diminish the FDA's standards for requiring that new medical products are safe and effective. Rather, it recognizes that recent developments in genomics, systems biology, electronic data systems, and other fields can provide additional tools and resources to support better premarketing and postmarketing regulation and more efficient development of drugs and medical devices.

The authors note that the FDA now relies on evidence beyond RCTs. Patients with coexisting conditions or rare diseases are not studied much in traditional RCTs; further progress in precision medicine is likely to make RCTs even more difficult. The Cures Act facilitates the use of new types of evidence, enabling a more comprehensive understanding of risks and benefits for particular patients. The authors argue that such uses of adaptive trials, Bayesian statistics, biomarkers and surrogate end points, and data from postmarketing registries and surveillance systems will adversely affect the FDA's ability to approve safe and effective drugs. However, as the authors state, such tools have been valuable in many situations. For example, progress in therapies for the human immunodeficiency virus and the hepatitis C virus reflects the use of validated biomarkers. The point of the legislation on biomarkers is to develop better evidence on other markers that could be valuable for evaluating treatments for currently unmet needs. Similarly, the point of developing better evidence on patient-reported outcomes, and better systems for studying clinical experience, is to better assess the disease experience of particular groups of patients.

As such, the legislation's provisions can increase the feasibility, efficiency, and influence of RCTs by enabling them to be better targeted and more effectively designed — and perhaps to be carried out in more routine clinical practice. The law empowers the FDA to use its expertise to guide the development of better science for the regulation of medical products.

Better evidence and up-to-date regulatory science are the best foundation for regulatory decisions and meaningful progress in biomedical innovation. They are also the best way to avoid turning back the clock on new opportunities to develop safe and effective treatments for unmet medical needs.

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1. Avorn J, Kesselheim AS. The 21st Century Cures Act — will it take us back in time? N Engl J Med 2015;372:2473-5.

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TO THE EDITOR: Avorn and Kesselheim raise concerns about the 21st Century Cures Act, a bipartisan piece of legislation with provisions for billions in additional funding for the National Institutes of Health (NIH), as well as a section on the use of biomarkers as surrogate end points. It is important to note that the FDA's standards are not altered by the bill. Rather, the bill will create a solid scientific framework for the use of biomarkers for drug development.

Biomarkers can be precise and accurate measures of disease and efficacy. Phenylalanine, for example, is strongly associated with a decline in IQ in patients with phenylketonuria. But IQ as an end point can take years to observe and can be difficult to measure. Without the biomarker end point, phenylketonuria treatments based on IQ would not be developed.[1]

The use of qualified biomarkers as surrogate end points is crucial for quickly bringing therapies to patients with rare diseases.[2] The 21st Century Cures Act provides hope to millions of patients who for too long have surrendered their lives to devastating rare diseases.

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TO THE EDITOR: We agree with Avorn and Kesselheim that increased funding for the NIH in the 21st Century Cures initiative is a highly needed step. However, we disagree with their opposition to the Limited Population Antibacterial Drug (LPAD) approval pathway, also in the legislation, which facilitates the evaluation of new antibiotics for serious infections for which current therapies are inadequate. Every year, at least 2 million Americans contract antibiotic-resistant infections, and 23,000 die.[1] For many of these infections, the limited number of patients and lack of appropriate comparator therapies make standard clinical trials impractical. The LPAD pathway was recommended by the President's Council of Advisors on Science and Technology.[2] This pathway is also supported by the Infectious Diseases Society of America (IDSA), representing more than 10,000 physicians and scientists.[3] Antibiotics studied as proposed in the Cures bill would be approved only for that specific, limited population, similar to drugs for orphan diseases. Concerns expressed about approving potentially riskier drugs must be balanced against the greater risk of not being able to provide the antibiotics desperately needed by patients.

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THE AUTHORS REPLY: McClellan and Sigal contend that 21st Century Cures "does not diminish the FDA's standards," but that is not true. Several provisions codify lower approval standards: section 2062 instructs the FDA to develop a process to approve new uses for existing drugs on the basis of lower-quality evidence than that provided by clinical trials, including "experience," "observational studies," and "registries"; section 2222 permits approval of high-risk devices on the basis of case studies of patients or poorly conducted studies, as long as they are published in a journal; and section 2121 appears to encourage the approval of antimicrobials and antifungals on the basis of effects observed in laboratory tests or preliminary studies involving small numbers of patients.[1] Section 2121 also permits the secretary of health and human services to apply this bypass track to other drug categories if "public health would benefit," language open to abuse by future administrations inclined to further reduce FDA authority. Of course regulatory flexibility is warranted to address urgent unmet needs, but the FDA already has this authority[2] and uses it frequently.[3] Once Congress starts providing detailed instructions for altering the FDA processes used to scientifically evaluate products (an odd proposition at best), such guidance could become standard practice beyond the uncommon instances in which these approaches' benefits may outweigh their risks.

We agree with Kakkis and Bronstein that high-quality biomarkers can be essential for approving new drugs, particularly for rare diseases. However, the FDA can already approve new drugs on this basis, as it approved sapropterin (Kuvan) for phenylketonuria on the basis of its effect on blood phenylalanine levels. What's needed is research to discover and validate more such biomarkers, a prospect the bill advances only marginally, with its modest proposed increase in NIH funding. By contrast, pushing the FDA to approve drugs

on the basis of biomarkers that are not rigorously linked to patient outcomes, as other provisions do, can hurt patients by exposing them to ineffective or unsafe treatments,[4] wasting resources, and giving false hope.

Calderwood et al. do not adequately consider the likelihood of substantial off-label use of antibiotics approved through the proposed "limited population" pathway, already common practice with certain drugs approved only for limited populations.[5] Few clinical situations warrant authorizing physicians to prescribe antibiotics not known to improve clinical outcomes. Such a policy for antibiotics would be particularly self-defeating, since it would induce resistance to those drugs and to other, related drugs. A better solution would be to encourage the enrollment of patients with serious infections in trials of investigational antibiotics to offer the chance of treatment even as we advance the understanding of the medications.

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Since publication of their article, the authors report no further potential conflict of interest.

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Intravenous Immune Globulin for Statin-Triggered Autoimmune Myopathy

TO THE EDITOR: Although treatment with statins may cause muscle-related symptoms in 10 to 20% of patients, these symptoms usually resolve within weeks after the medication is stopped. In rare instances, however, the medication causes statin-triggered autoimmune myopathy, a condition characterized by proximal muscle weakness, prominent necrosis of muscle fibers (detected on biopsy), elevated serum levels of creatine kinase, and the presence of autoantibodies that recognize 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the pharmacologic target of statins.[1-3] Moreover, statin-triggered autoimmune myopathy progresses despite the discontinuation of statins and requires control with immunosuppressive therapy.

No clinical trials have been conducted to establish effective treatments for statin-triggered autoimmune myopathy. However, most clinicians use glucocorticoids as first-line therapy. Statin-triggered autoimmune myopathy can be especially difficult to treat; achieving remission frequently requires the addition of not only a second oral agent (e.g., methotrexate) but also intravenous immune globulin (IVIG).[1,3,4]

Among 82 patients with statin-triggered autoimmune myopathy evaluated at the Johns Hopkins Myositis Center, 3 patients with diabetes declined glucocorticoids because of concerns about potential side effects but agreed to try monotherapy with IVIG, administered at a rate of 2 g per kilogram of body weight per month. Detailed clinical characteristics of these patients are shown in Table 1. Immediately before IVIG, the mean (±SD) creatine kinase level for these patients was 4919±3523 IU per liter, and all 3 patients had documented weakness in the proximal arms and legs. No infusion reactions occurred in any of the patients during treatment. After two or three rounds of IVIG, the mean creatine kinase level declined to 1125±1101 IU per liter, quantitative dynamometry showed an increase in the mean strength of arm abduction from 3.5 to 6.2 kg, and hip-flexion strength improved or normalized. These gains persisted without the addition of another agent. Between 9 and 19 months after starting IVIG, 2 patients had no subjective muscle-related symptoms and had normal strength on examination. Patient 1 continued to have mild hip-flexor weakness but declined our advice to add another agent.

The mechanisms underlying the effects of IVIG in statin-triggered autoimmune myopathy