

with protease inhibitor on myocardial infarction occurrence in HIV infected men. In: Abstracts of the Eighth Conference on Retroviruses and Opportunistic Infections, Chicago, February 4–8, 2001: 241. abstract.

3. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360:1747-8.

4. Friis-Møller N, Weber R, D'Arminio Monforte A. Exposure to HAART is associated with an increased risk of myocardial infarction: the D:A:D Study. In: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003: 103. abstract.

5. Klein D, Hurley L, Quesenberry C Jr, Sidney S. Hospitalizations for coronary heart disease and myocardial infarction among men with HIV-1 infection: additional follow-up. In: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003:326. abstract.

THE AUTHORS REPLY: Our investigation, which was an outcome study, clearly showed that antiretroviral therapy has a benefit that is enormous relative to the risk of cardiovascular or cerebrovascular disease (Fig. 1). Some clinical studies have suggested

that HAART has only a small effect or no effect on this risk, but these studies had a small number of events or short follow-up or failed to correct for selection or the amount of drug exposure.¹⁻⁵ Our conclusions were no different for the approximately 1000 patients treated with protease inhibitors for 48 months or more. Ascertainment may have affected the point estimates but probably did not change over time in a way that would attenuate a putative drug effect. Furthermore, we obtained similar results from national death-index data.

We reported the stage of disease at first presentation and the treatment for risk factors, accounting for the appearance of an atypically healthy population. We found that traditional risk factors increased risk. We join Klein and colleagues in encouraging risk reductions when appropriate. We also look forward to analyses of our outcome and clinical-study data bases and those of others as they mature.

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1. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360:1747-8.

2. Friis-Møller N, Weber R, D'Arminio Monforte A. Exposure to HAART is associated with an increased risk of myocardial infarction: the D:A:D Study. In: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003: 103. abstract.

3. Iloeje U, Yuan Y, Tuomari A, L'Italien G, Mauskopf J, Moore R. Protease inhibitors may increase risk of cardiovascular disease in HIV-infected patients. In: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003. abstract.

4. Klein D, Hurley L, Quesenberry C Jr, Sidney S. Hospitalizations for coronary heart disease and myocardial infarction among men with HIV-1 infection: additional follow-up. In: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003:326. abstract.

5. Carrier J, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003;33:506-12.

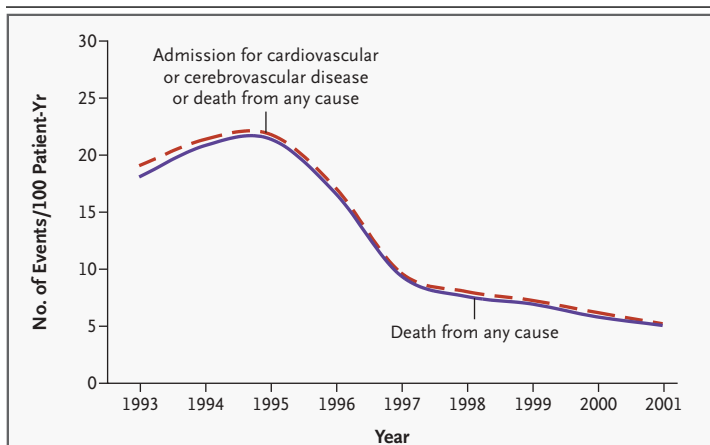


Figure 1. Rates of Death and of Death or Admission for Cardiovascular or Cerebrovascular Disease.

The rate of the combined end point is only slightly higher than the rate of death alone, and declines in the former mirror declines in the latter.

Ethics and Genetics

TO THE EDITOR: Clayton's description of the case of Sierra Creason misrepresents the facts (Aug. 7 issue).¹ The thyroid values were not "abnormally low." Thousands of unaffected newborns had the same negative results. The case was not one of congeni-

tal hypothyroidism, but rather one of hypopituitarism with multiple medical problems. Although the case was defensible on medical grounds, the Attorney General's office decided that newborn screening was such an important public health policy that

the state should be protected from suits for discretionary, non-negligent screening decisions. The decision was just, ethical, and in the public's interest.

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1. Clayton EW. Ethical, legal, and social implications of genomic medicine. *N Engl J Med* 2003;349:562-9.

TO THE EDITOR: Clayton states that advisory bodies say “no” to the disclosure of a patient’s genetic information to relatives, but many do allow such disclosure to benefit relatives under conditions short of “a last resort.”^{1,2} Furthermore, geneticists can favor such disclosure, even without the patient’s consent and despite the patient’s refusal.³ And there are earlier cases that address such a duty to disclose.^{4,5} Although court decisions recognize a duty to disclose genetic information to relatives, the requirement for disclosure is quite low.^{1,2} The court in *Safer v. Pack* required “reasonable steps,” and the court in *Pate v. Threlkel* required only that the patient be informed of the genetic nature of the disease.

Although obtaining a patient’s consent to disclose genetic information to relatives can obviate many of the legal and ethical problems of genetic privacy, patients can deny disclosure for both trivial and substantial reasons.^{1,2} Furthermore, relatives may not want to know of their genetic propensity for disease and could sue the physician who discloses the information for invasion of privacy, an additional risk of this “least risky option.”^{1,2}

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1. Deftos LJ. Genomic torts: the law of the future — the duty of physicians to disclose the presence of a genetic disease to the relatives of their patients with the disease. *Univ San Francisco Law Rev* 1997;32:105-37.
2. *Idem*. The evolving duty to disclose the presence of genetic disease to relatives. *Acad Med* 1998;73:962-8.
3. Wertz DC, Fletcher JC. An international survey of attitudes of medical geneticists toward mass screening and access to results. *Public Health Rep* 1989;104:35-44.
4. *Schroeder v. Perkel*, 87 N.J. 53 (N.J., 1881).
5. *Olson v. Children’s Home Society of California*, 204 Cal. App. 3d 1362 (CA. 1988).

TO THE EDITOR: As the rationale for “creating the necessary legislative and regulatory responses” to genetic discrimination, Clayton offers only the popular misperception that people “tend to see genetic

information as more definitive and predictive than other types of data.” But as she herself concedes, genetic information is in fact much less definitive and predictive than knowledge of an established disease process. This reality is reflected in the consistent finding that purely genetic discrimination in employment and insurance is so rare as to be undetectable.^{1,2} Moreover, Plantinga et al.³ found that once patients are specifically questioned on the subject, they have very similar attitudes about the confidentiality of genetic and nongenetic information.

It is becoming increasingly apparent that the current policy focus on genetic discrimination is artificial and arbitrary. Those who advocate legislative “solutions” have been unable to articulate convincingly the problem that they seek to correct. As genomics becomes integrated into mainstream medicine, perhaps the utility of genetic discrimination as a distinct entity ought to be reexamined.

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1. Hall MA, Rich SS. Laws restricting health insurers’ use of genetic information: impact of genetic discrimination. *Am J Hum Genet* 2000;66:293-307.
2. Armstrong K, Weber B, FitzGerald G, et al. Life insurance and breast cancer risk assessment: adverse selection, genetic testing decisions, and discrimination. *Am J Med Genet* 2003;120A:359-64.
3. Plantinga L, Natowicz MR, Kass NE, Hull SC, Gostin LO, Faden RR. Disclosure, confidentiality, and families: experiences and attitudes of those with genetic versus nongenetic medical conditions. *Am J Med Genet* 2003;119C:51-9.

DR. CLAYTON REPLIES: When Sierra Creason was born, California’s newborn screening program, which Dr. Cunningham directs, did not report actual test values, as commercial and hospital laboratories would have done, and reported as “unproblematic” the low levels of thyroxine and thyrotropin that should have led her physicians to pursue further evaluation for hypothyroidism. According to the California Supreme Court, “During his deposition, Dr. Cunningham admitted that the ‘Negative’ test report for plaintiff Sierra inaccurately purported to cover potential ‘congenital hypothyroidism,’ rather than ‘primary’ congenital hypothyroidism.”¹ Prompt diagnosis of Sierra’s secondary but nonetheless congenital hypothyroidism, a part of her hypopituitarism, might not have ameliorated all her medical problems, but those issues should have been subject to proof at trial.

In response to Dr. Deftos, most advisory groups

concur with the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in concluding that patients' confidentiality should almost always be respected. The commission states that it is permissible to warn relatives of genetic risks

only if . . . (1) reasonable efforts to elicit voluntary consent to disclosure have failed; (2) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (3) the harm that identifiable individuals would suffer is serious; and (4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.²

Clinicians understandably view the *Safer v. Pack* and *Pate v. Threlkel* cases, which I have argued were wrongly decided,³ as more onerous than Dr. Deftos suggests. Unlike Dr. Deftos, I believe that patients will usually share information, given enough time and support. Finally, if a physician gave the relative of a patient information about a serious but avert-

able risk and that information saved the relative's life, it is hard to believe that a jury would be sympathetic if the relative then sued for invasion of privacy.

The data regarding the incidence of genetic discrimination are not as unequivocal as Dr. Nowlan suggests.⁴ Patients' fear of discrimination dramatically affects their willingness to seek genetic services. Dr. Nowlan is appropriately concerned with genetic exceptionalism. His desire to reexamine "the utility of genetic discrimination as a distinct entity" is consistent with my argument that even when genetic variations do exist, deciding whether they should affect access to social goods inevitably requires competing social values to be weighed.

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1. *Creason v. State Department of Health Services*, 957 P.2d 1323 (Cal. 1998).
2. President's Commission for the Study of Ethical Problems in Medicine and Biochemical and Behavioral Research, *Screening and Counseling for Genetic Conditions*. The ethical, social, and legal implications of genetic screening, counseling, and education programs. Washington, D.C.: Government Printing Office, 1983:43-4.
3. Clayton EW. What should the law say about disclosure of genetic information to relatives? *J Health Care Law Policy* 1998;1:373-90.
4. Silvers S, Stein MA. An equality paradigm for preventing genetic discrimination. *Vanderbilt Law Rev* 2002;55:1341-95.

Molecular Mechanisms of Amyloidosis

TO THE EDITOR: In the review article by Merlini and Bellotti (Aug. 7 issue),¹ familial Mediterranean fever was listed as one of the common periodic-fever syndromes that may lead to reactive (amyloid protein A, or AA) amyloidosis. However, there is no correlation between the frequency and severity of periodic febrile attacks and AA amyloidosis.² The serum level of amyloid protein A is not constantly elevated. Some patients with frequent periodic febrile attacks are spared from the development of amyloidosis, whereas in other patients there is very early amyloid deposition. The major effect of colchicine seems to be the prevention of the formation and deposition of amyloid A.

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1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003;349:583-96.
2. Cakar N, Yalcinkaya F, Ozkaya N, et al. Familial Mediterranean fever (FMF)-associated amyloidosis in childhood: clinical features, course and outcome. *Clin Exp Rheumatol* 2001;19:Suppl 24:S63-S67.

TO THE EDITOR: Merlini and Bellotti highlight AA amyloidosis as a complication of the hereditary periodic fever syndromes (in Table 1 of their article), and they specifically list the hyper-IgD periodic-fever syndrome (HIDS). Although AA amyloidosis is indeed a frequent complication of familial Mediterranean fever (affecting 10 to 37 percent of patients),¹ the tumor necrosis factor receptor-associated periodic syndrome (affecting 14 percent of patients),² and the Muckle-Wells syndrome (affecting 35 percent of patients), it has never been reported in patients with HIDS, nor has it been seen in any of the patients listed in the international Nijmegen HIDS registry. This registry contains clinical data on 195 published and unpublished cases worldwide (information is available at <http://hids.net>).

HIDS is a periodic-fever syndrome caused by a genetic defect in mevalonate kinase.³ Despite a frequent, often persistent,⁴ and vigorous acute-phase response similar to that seen in patients with other periodic-fever syndromes, amyloidosis does not develop in patients with HIDS. This intriguing find-