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Ethics of Hematopoietic Stem Cell Transplantation in Type 1 Diabetes Mellitus

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With regard to erythropoietin, we used Medicare billing records to assess the frequency of erythropoietin replacement therapy among statin users and control patients. We found that the rates of such therapy, either before initiation of dialysis (25.9% vs 23.3%, $P = .50$) or during dialysis (administration in first 6 months of treatment) (98.6% vs 98.7%, $P = .94$), did not differ between statin users and control patients, respectively.

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1. Chien JY, Jerng JS, Yu CJ, Yang PC. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Crit Care Med*. 2005; 33(8):1688-1693.
2. Chenaud C, Merlani PG, Bandshapp O, Ricou B. Serum lipids or apolipoprotein A-I and disease severity of meningococcal sepsis. *Crit Care Med*. 2006; 34(1):270-271.
3. McDonald MC, Dhady P, Cockerill GW, et al. Reconstituted high-density lipoprotein attenuates organ injury and adhesion molecule expression in a rodent model of endotoxic shock. *Shock*. 2003;20(6):551-557.
4. Pajkrt D, Doran JE, Koster F, et al. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. *J Exp Med*. 1996;184(5):1601-1608.
5. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE study. *J Am Soc Nephrol*. 2002;13(7):1918-1927.

Ethics of Hematopoietic Stem Cell Transplantation in Type 1 Diabetes Mellitus

To the Editor: We believe that the study of autologous hematopoietic stem cell transplantation for treatment of newly diagnosed type 1 diabetes mellitus (DM) by Dr Voltarelli and colleagues¹ raises serious ethical concerns regarding participant selection and study design.

Although the researchers were able to get research ethics approval in Brazil, the participant selection fails international standards of research ethics. Virtually every country in the world, including Brazil, is a signatory to the Declaration of Helsinki, international research ethics standards written by the World Medical Association. According to the Declaration of Helsinki, "For a research subject who is . . . a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot in-

stead be performed on legally competent persons."² Research involving pediatric participants is ethical if it will promote the health of children and the research cannot be performed on adults. Although the majority of individuals with type 1 DM present in childhood, a significant number present in young adulthood. Thus, it is possible to have performed this research first on adults instead of enrolling 8 minors (<18 years) among the first 15 participants.

One justification for including children might be that type 1 DM is more aggressive in children. This may justify not waiting for long-term results; however, it does not justify the inclusion of children in the first phase of this research. The first participant presented with diabetic ketoacidosis and his response was quite poor, leading to a change in study design and inclusion criteria. It was not known a priori whether this would happen in other patients, which is why such research should be performed first on competent adults.

Even if the only participants had been adults, it is not clear that the study as designed would have been ethical. Age-matched controls are needed to determine the extent of benefits and short-term and long-term harms. To what extent this protocol will lead to long-term insulin independence is unknown and requires long-term follow-up. The follow-up period in the protocol overlaps with the known and variable honeymoon period observed in individuals with type 1 DM,³ particularly those who have received immunosuppressive therapy.^{4,5}

These ethical concerns are particularly relevant given that the evolving standard of care for treatment of type 1 DM is reasonably effective, if highly demanding and imperfect.

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1. Voltarelli JC, Couri CE, Stracieri AB, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA*. 2007;297(14):1568-1576.
2. World Medical Association Declaration of Helsinki. World Medical Association Web site. <http://www.wma.net/e/policy/b3.htm>. Published October 9, 2004. Accessed April 11, 2007.
3. Knip M, Sakkinen A, Huttunen NP, et al. Postinitial remission in diabetic children: an analysis of 178 cases. *Acta Paediatr Scand*. 1982;71(6):901-908.
4. Yilmaz MT, Devrim AS, Biyal F, et al. Immunoprotection in spontaneous remission of type 1 diabetes: long-term follow-up results. *Diabetes Res Clin Pract*. 1993;19(2):151-162.
5. Bougneres PF, Carel JC, Castano L, et al. Factors associated with early remission of type 1 diabetes in children treated with cyclosporine. *N Engl J Med*. 1988; 318(11):663-670.

In Reply: Drs Ross and Philipson argue that our study of stem cell transplantation was unethical because (1) research involving pediatric participants is unethical unless it will promote the health of children and the research cannot be performed in adults, according to the Declaration of

Helsinki, and (2) age-matched controls were needed to determine the extent of the benefits and adverse effects of the treatment.

The study was approved by local and national institutional review boards, which imposed no lower limits for patient age (0-35 years). Nevertheless, we included only patients older than 13 years. All patients and 1 of their parents signed the informed consent. The first minor patient was included only after 3 adult patients had undergone transplantation, 2 of them successfully.

We note that other trials of chronic¹⁻³ or acute^{4,5} immunosuppression in type 1 DM have included minor patients. Hematopoietic stem cell transplantation has been performed for several decades for children with hematological disorders, with very low rates of adverse effects.⁶ Our non-myeloablative approach was designed to further minimize these adverse effects. Response to hematopoietic stem cell transplantation in adults with type 1 DM would not predict response in children; this group of patients would also have greater benefit from insulin-free periods than adults.

We agree that a control group is eventually needed to establish treatment efficacy, but it is standard for trials to progress in a sequential order of phase 1, 2, and 3 studies, in which a control group is usually not implemented until the phase 3 design.

Finally, it is unlikely that 14 of 15 patients with proven type 1 DM would spontaneously enter a honeymoon period and that 8 of them would maintain this status for 1 year or more, as occurred in our study.

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1. Elliott RB, Crossley JR, Berryman CC, James AG. Partial preservation of pancreatic beta-cell function in children with diabetes. *Lancet*. 1981;2(8247):631-632.
2. Cook JJ, Hudson I, Harrison LC, et al. Double-blind controlled trial of azathioprine in children with newly diagnosed type 1 diabetes. *Diabetes*. 1989;38(6):779-783.

3. Silverstein J, Maclaren N, Riley W, et al. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. *N Engl J Med*. 1988;319(10):599-604.
4. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med*. 2002;346(22):1692-1698.
5. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med*. 2005;352(25):2598-2608.
6. Sanders JE. Growth and development after hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FK, eds. *Thomas' Hematopoietic Cell Transplantation*. Maiden, MA: Blackwell Publishing; 2004:929-943.

Changing the Organization of Health Care

To the Editor: In their Special Communication, Drs Porter and Teisberg¹ make a number of reasonable suggestions for how to improve the quality of health care. However, I consider their fundamental assumption (better quality of care reduces health care costs) questionable. Many health care interventions increase health care costs.² This means that improving the quality of care by reducing an underuse of health care interventions will in general increase rather than decrease costs. Given that US adults receive only 55% of recommended care³ and that each unit reduction of a quality deficit results in an overproportional increase of costs,⁴ vast resources may be needed to achieve high quality of care.

Even if the target of quality improvement activities is the reduction of overuse and misuse, it is not clear that cost savings will result. Quality improvement activities themselves incur costs, and reducing errors or complications might increase costs in the long term because people live longer. For example, referral of hip fracture surgeries to high-volume hospitals in Germany does not lead to savings in the long run despite fewer deaths and complications in the short term.⁵

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1. Porter ME, Teisberg EO. How physicians can change the future of health care. *JAMA*. 2007;297(10):1103-1111.
2. Chapman RH, Stone PW, Sandberg EA, Bell C, Neumann PJ. A comprehensive league table of cost-utility ratios and a sub-table of "panel-worthy" studies. *Med Decis Making*. 2000;20(4):451-467.
3. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635-2645.
4. Gandjour A, Lauterbach KW. When is it worth introducing a quality improvement program? a mathematical model. *Med Decis Making*. 2003;23(6):518-525.
5. Gandjour A, Weyler EJ. Cost-effectiveness of referrals to high-volume hospitals: an analysis based on a probabilistic Markov model for hip fracture surgeries. *Health Care Manag Sci*. 2006;9(4):359-369.

To the Editor: We think that the Special Communication by Drs Porter and Teisberg¹ skirts around several central issues. First, how should medical practice be organized for patients with more than one medical condition? Coordinated care around a single condition can be powerful when there is only one dominant and well-defined problem, such as cancer or chronic kidney disease. But what about the common situation of a Medicare recipient with more than 10 conditions requiring care? Multiple related and unrelated