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THE AUTHORS REPLY: Our international clinical study compared machine perfusion with cold storage of kidneys obtained from donors after brain death or from donors after cardiocirculatory death (in Maastricht category III). The organs studied in our trial are the most common deceased-donor kidneys. We very much agree with Ray and colleagues that machine perfusion is also likely to be useful for renal allografts obtained from donors after cardiocirculatory death who are in Maastricht categories I, II, or IV, because their organs have sustained more severe ischemic injury. The study by Ray et al. presents promising results. Our group has found that perfusion settings are critical for maintaining the viability of the vascular endothelium.¹

Currently, in our prospective data set, we are investigating whether vascular resistance and various perfusate biomarkers during machine perfusion have independent predictive value for determining which kidneys have a high risk of complications or failure after transplantation. We speculate that with the use of such data, machine perfusion might become an additional diagnostic tool for selecting kidneys that are sufficiently viable for transplantation but that might otherwise have been discarded.² In addition, normothermic machine perfusion and normothermic recirculation are interesting new techniques that may improve the viability of marginal donor kidneys.³⁻⁵

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THE EDITORIALISTS REPLY: We thank Cartwright for highlighting the importance of corneal transplants, both in the history of transplantation and in regard to the clinical significance of this procedure.

Since our editorial focuses on perfusion techniques in vascularized organ transplants, we do not address corneal transplantation. Nevertheless, it is important to mention that, as compared with other organs, corneas are less sensitive to prolonged ischemia. Indeed, an average preservation time of 11 days for corneas, as compared with preservation times of hours for other organs, has been reported.¹ Corneas are usually preserved in medium under tissue-culture conditions at 37°C before transplantation. In contrast, cold preservation at 4°C is in general the preferred method for preserving organ transplants.

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Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome

TO THE EDITOR: In their report on the Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) study, Burn et al. (Dec. 11 issue)¹ conclude that the use of aspirin, resistant starch, or both had no effect in reducing the risk of adenoma and carcinoma among carriers of the Lynch syndrome, on the basis of Cox proportional-hazards

models adjusted for age and sex. However, the effect of the genotype-by-environment interaction on the risk of colorectal neoplasia was neglected.

According to two studies,^{2,3} germline mutations or polymorphisms in DNA mismatch-repair genes may be associated with a significant difference in the risk of colorectal cancer. The effective-

ness of adjustment for age and sex in the study by Burn et al. may not be sufficient; the type of mutation should have been taken into account in the multivariable analysis of potential risk factors.

In addition, the authors provide no information about cigarette smoking in the study population. This may lead to bias if there is a difference in exposure between the groups, since cigarette smoking contributes to microsatellite instability in colon tumors and seems to increase the risk of Lynch syndrome–associated colorectal tumors.^{2,4,5} It would be more informative if cigarette smoking could be adjusted for in the statistical analysis.

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TO THE EDITOR: Burn et al. report that resistant starch did not suppress colorectal neoplasms in patients with the Lynch syndrome. We suggest that this conclusion needs considerable qualification. Resistant starch is the fraction of ingested starch that reaches the large bowel, where it affects bacterial fermentation products in the colon, especially short-chain fatty acids.¹ Laboratory studies indicate that resistant starch provides protection against experimental colorectal cancer² and diet-induced colonocyte genetic damage³ through these acids. Burn et al. report that their subjects consumed 30 g of starch per day, implying that this was the resistant-starch intake. However, their article shows that the supplement provided only 9 g of resistant starch per day, and no data are given to assess its effect on the colon. Studies in humans (e.g., the study reported by Noakes et al.⁴) show that more than 20 g of resistant starch per

day is needed to increase fecal levels of short-chain fatty acids. We suggest that resistant-starch consumption in the study by Burn et al. was insufficient to affect the production of short-chain fatty acids.

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THE AUTHORS REPLY: In response to Yang et al.: the basic concept of a randomized trial is to guard against imbalances of potential confounders such as smoking or differences in risks according to the type of mutation. To provide further protection against an imbalance, we performed block randomization according to geographic group, as we discuss in our report. Although we cannot absolutely guarantee that there is no imbalance of any measured or unmeasured confounder, the large sample size and absence of any evidence of a treatment effect argue against an important imbalance. In terms of different effects of germline mismatch-repair mutations on the risk of a neoplasm, analysis of screening histories before enrollment in CAPP2 showed no evidence of major mutation-specific differences, at least for the common (founder) mutations¹ (and unpublished data).

In response to Topping et al.: the 30 g of resistant starch (Novelose, National Starch and Chemical) that we used is thought to deliver more than 13.2 g of resistant starch. This is in addition to the estimate of 4.1 g per day in the typical diet, or an estimated total of 17.3 g per day on average.

We were constrained by the pragmatic challenge of being able to deliver a powder supplement

daily for up to 4 years. Novelose was used because it was relatively easy to mix with a variety of foods. The dose used was as much as we thought we could ask participants to add to their diet. There were 97 withdrawals on the basis of “minor disorders,” as compared with 76 among participants receiving placebo starch. The difference was attributable to symptoms of bloating, suggesting that we had delivered a clinically significant dose. Analysis of crypt-cell proliferation and dissected crypt dimensions in mucosal-biopsy specimens (unpublished data) revealed no difference between the placebo group and either of the treatment groups.

We agree that the literature supports the case for an antineoplastic effect of resistant starch. The

lack of support for this hypothesis in our trial may simply reflect the major challenge of testing nutritional chemoprevention with the use of the traditional approach of a randomly assigned supplement.

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Anterior Cruciate Ligament Tear

TO THE EDITOR: Spindler and Wright (Nov. 13 issue)¹ clearly point out that the appropriate management of anterior cruciate ligament (ACL) injury remains under debate. An important question in the field of ACL reconstruction concerns the correct indications for reconstruction.²⁻⁴

In their article, the authors state that to their knowledge there are no published professional guidelines for the management of ACL tears. In fact, such a guideline was published in the United Kingdom in 2001. This document, “Best Practice for Primary Isolated Anterior Cruciate Ligament Reconstruction,”⁵ represents a consensus statement from the British Orthopaedic Association, the British Association for Surgery of the Knee, and the British Orthopaedic Sports Trauma Association; updated guidelines have been developed and their publication is awaited.

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THE AUTHORS REPLY: We thank Maffulli and colleagues for noting the expert-opinion guidelines on indications for ACL reconstruction in the United Kingdom. We should have specified that there are no North American guidelines on ACL reconstruction. The ongoing Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment (KANON) trial in Lund, Sweden (Current Controlled Trials number, ISRCTN84752559), should provide important data on the outcomes of ACL reconstruction as compared with rehabilitation.

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