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**Will Cell Reprogramming Resolve the
Embryonic Stem Cell Controversy?
A Narrative Review**

C. Power and J. E. Rasko

In the past few years, relatively straightforward laboratory techniques have been developed to reprogram normal body cells to enter an embryonic stem cell-like state. Not only do these induced pluripotent stem cells hold great medical promise—perhaps greater than that of embryonic stem cells—but they also have escaped the ethical controversy in which the latter is mired. This article examines how cell reprogramming is likely to transform regenerative and reproductive medicine and highlights some of the medical, moral, and political hurdles that it faces. It also argues that induced pluripotent stem cells are more ethically problematic than most people believe and that cell reprogramming will not solve the stem cell controversy but complicate it further.

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**Ethics and the Law:
Is There Common Ground on
Informed Consent for Disparities
in Hospital Outcomes?**

N. Housri et al.

The association between procedure volume at institutions and outcomes of cancer surgeries has been widely published in the medical literature; discussed in the lay press;

and, during the past 15 years, incorporated into quality improvement endeavors. In certain cases, institutional volume has become a proxy for quality. Despite the vast amount of retrospective data on this topic, physicians generally have been unsure how to approach the information and interpret it for their patients. Even more challenging to some physicians has been deciding whether the data oblige them to either direct patients with cancer to high-volume centers for care or discuss the data with these patients as part of informed consent. An additional challenge is that physicians must understand laws related to these issues and that these laws are unclear. This article reviews the ethical arguments for including disparities in hospital outcomes as part of informed consent and examines whether legal precedent can shed light on this debate.

Critical Care Medicine

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**Patient and Healthcare Professional
Factors Influencing End-of-Life
Decision-Making during Critical Illness:
A Systematic Review**

D. W. Frost et al.

Objectives: The need for better understanding of end-of-life care has never been greater. Debate about recent U.S. healthcare system reforms has highlighted that end-of-life decision-making is contentious. Providing compassionate end-of-life care that is appropriate and in accordance with patient wishes is an essential component of critical care. Because discord can undermine optimal end-of-life care, knowledge of factors that influence decision-making is important. We performed a systematic review to determine which factors are known to influence end-of-life decision-making among patients and healthcare providers. *Data Sources, Selection and Abstraction:* We conducted a structured search of Ovid Medline for interventional and observational research articles

incorporating critical care and end-of-life decision-making terms. *Data Synthesis:* Of 6259 publications, 102 were relevant to our review question. Patient factors predicting less intensive end-of-life care include increasing age, comorbidity, and limited functional status; these factors appear to be influential for both clinicians and patients. Patient and clinician race, ethnicity, and nationality also appear to influence the technological intensity of end-of-life care. In general, white patients and those in North America and Northern Europe may be less likely to desire intensive end-of-life care than others. Physicians of similar geo-ethnic origin to patients appear less likely to prescribe such therapy. Physicians with more clinical experience and those routinely working in the intensive care unit are less likely than other physicians to recommend technologically intense care for critically ill patients at the end-of-life. *Conclusions:* Patients and clinicians may approach end-of-life discussions with different expectations and preferences, influenced by religion, race, culture, and geography. Appreciation of those factors associated with more and less technologically intense care may raise awareness, aid communication, and guide clinicians in end-of-life discussions.

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**Reversible Brain Death after
Cardiopulmonary Arrest and
Induced Hypothermia**

A. C. Webb and O. B. Samuels

Objective: To describe a patient with transient reversal of findings of brain death after cardiopulmonary arrest and attempted therapeutic hypothermia. *Design:* Case report. *Setting:* Intensive care unit of an academic tertiary care hospital. *Patient:* A 55-yr-old man presented with cardiac arrest preceded by respiratory arrest. Cardiopulmonary resuscitation was performed, spontaneous perfusion restored, and therapeutic hypothermia was attempted for neural protection. After rewarming to 36.5°C, neurologic examination showed no eye opening or

response to pain, spontaneous myoclonic movements, sluggishly reactive pupils, absent corneal reflexes, and intact gag and spontaneous respirations. Over 24 hrs, remaining cranial nerve function was lost. The neurologic examination was consistent with brain death. Apnea test and repeat clinical examination after a duration of 6 hrs confirmed brain death. Death was pronounced and the family consented to organ donation. Twenty-four hrs after brain death pronouncement, on arrival to the operating room for organ procurement, the patient was found to have regained corneal reflexes, cough reflex, and spontaneous respirations. The care team faced the challenge of offering an adequate explanation to the patient's family and other healthcare professionals involved. *Interventions:* Induced hypothermia and brain death determination. *Measurements and Main Results:* This represents the first published report in an adult patient of reversal of a diagnosis of brain death made in full adherence to American Academy of Neurology guidelines. Although the reversal was transient and did not impact the patient's prognosis, it impacted his eligibility for organ donation and cast doubt about the ability to determine irreversibility of brain death findings in patients treated with hypothermia after cardiac arrest. *Conclusions:* We strongly recommend caution in the determination of brain death after cardiac arrest when induced hypothermia is used. Confirmatory testing should be considered and a minimum observation period after rewarming before brain death testing ensues should be established.

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**Brainstem Responses Can
Predict Death and Delirium in
Sedated Patients in Intensive Care Unit**

T. Sharshar et al.

Objectives: In critically ill patients, the assessment of neurologic function can be difficult because of the use of sedative agents. It is not known whether neurologic signs observed under sedation can predict

short-term outcomes. The objective of this study was to assess whether abnormal brainstem responses within the first 24 hrs of sedation are associated with mortality and altered mental status postsedation. *Design:* Observational prospective study including an initial single-center and a subsequent multicenter study to develop and then validate the prognostic models. *Setting:* Three mixed and two medical intensive care units. *Patients:* Mechanically ventilated intensive care unit patients sedated with midazolam (\pm sufentanyl). *Interventions:* Neurologic examination including the Glasgow Coma Scale, the Assessment to Intensive Care Environment score, cranial nerve examination, response to noxious stimuli, and the cough reflex was performed. *Measurements and Main Results:* Seventy-two patients were included in the initial group and 72 in a subsequent validation study. Neurologic responses were independent of sedative dose. Twenty-two patients in the development cohort and 21 (29%) in the validation group died within 28 days of inclusion. Adjusted for Simplified Acute Physiology Score II score, absent cough reflex was independently associated with 28-day mortality in the development (adjusted odds ratio [OR], 7.80; 95% confidence interval [CI], 2.00–30.4; $p = .003$) and validation groups (adjusted OR, 5.44; 95% CI, 1.35–22.0; $p = .017$). Absent oculocephalic response, adjusted for Simplified Acute Physiology Score II score, was independently associated with altered mental status after the withdrawal of sedation in the development (adjusted OR, 4.54; 95% CI, 1.34–15.4; $p = .015$) and validation groups (adjusted OR, 6.10; 95% CI, 1.18–25.5; $p = .012$). *Conclusions:* Assessment of brainstem responses is feasible in sedated critically ill patients and loss of selected responses is predictive of mortality and altered mental status.

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Advance Directives for Euthanasia in Dementia: How Do They Affect Resident Care in Dutch Nursing Homes? Experiences of Physicians and Relatives

M. E. de Boer et al.

Objectives: To gain insight into how advance directives for euthanasia affect resident care in Dutch nursing homes. *Design:* Survey of elderly care physicians and additional qualitative interviews with a selection of elderly care physicians and relatives of people with dementia who had an advance directive for euthanasia. *Setting:* Dutch nursing home practice. *Participants:* Four hundred thirty-four elderly care physicians completed the general part of the questionnaire; 110 physicians provided case histories. Interviews were conducted with 11 physicians and eight relatives. *Measurements:* The questionnaire contained general questions about the incidence of advance directives for euthanasia in people with dementia. A second part involved questions about the most recent case of a person with dementia and an advance directive for euthanasia who had died. The interviews with elderly care physicians and relatives focused on further exploration of the decision-making process regarding adherence to the advance directive for euthanasia. *Results:* Despite law-based possibilities, advance directives for euthanasia of people with dementia were rarely adhered to, although they seem to have a supportive role in setting limitations on life-sustaining treatments. Elderly care physicians and relatives were found to be reluctant to adhere to advance directives for euthanasia. Not being able to engage in meaningful communication played a crucial role in this reluctance. *Conclusion:* Advance directives for euthanasia are never adhered to in the Netherlands in the case of people

with advanced dementia, and their role in advance care planning and end-of-life care of people with advanced dementia is limited. Communication with the patient is essential for elderly care physicians to consider adherence to an advance directive for euthanasia of a person with dementia.

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Timing of Do-Not-Resuscitate Orders for Hospitalized Older Adults Who Require a Surrogate Decision-Maker

A. M. Torke et al.

Objectives: To examine the frequency of surrogate decisions for in-hospital do-not-resuscitate (DNR) orders and the timing of DNR order entry for surrogate decisions. *Design:* Retrospective cohort study. *Setting:* Large, urban, public hospital. *Participants:* Hospitalized adults aged 65 and older over a 3-year period (1/1/2004–12/31/2006) with a DNR order during their hospital stay. *Measurements:* Electronic chart review provided data on frequency of surrogate decisions, patient demographic and clinical characteristics, and timing of DNR orders. *Results:* Of 668 patients, the ordering physician indicated that the DNR decision was made with the patient in 191 cases (28.9%), the surrogate in 389 (58.2%), and both in 88 (13.2%). Patients who required a surrogate were more likely to be in the intensive care unit (62.2% vs 39.8%, $P < 0.001$) but did not differ according to demographic characteristics. By hospital Day 3, 77.6% of patient decisions, 61.9% of surrogate decisions, and 58.0% of shared decisions had been made. In multivariable models, the number of days from admission to DNR order was higher for surrogate (odds ratio (OR)=1.97, $P < 0.001$) and shared decisions (OR=1.48, $P = 0.009$) than for patient decisions. The adjusted hazard ratio for hospital death was higher for patients with surrogate than patient decisions (2.61, 95% confidence interval (CI)=1.56–4.36). Patients whose DNR orders were written on Day 6 or later were twice as likely to die in the hospital (OR=2.20, 95% CI=1.45–3.36) than patients

with earlier DNR orders. *Conclusion:* For patients who have a DNR order entered during their hospital stay, order entry occurs later when a surrogate is involved. Surrogate decision-making may take longer because of the greater ethical, emotional, or communication complexity of making decisions with surrogates than with patients.

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External Validation of an Index to Predict Up to 9-Year Mortality of Community-Dwelling Adults Aged 65 and Older

M. A. Schonberg et al.

Objectives: To further validate an index predicting mortality in community-dwelling older adults. *Design:* A comparison of the performance of the index in predicting mortality among new respondents to the National Health Interview Survey (NHIS, 2001–2004) with that of respondents from the original development and validation cohorts (1997–2000) and a test of its performance over extended follow-up (up to 9 years) using the original cohorts. Follow-up mortality data were available through 2006. *Setting:* NHIS. *Participants:* Twenty-two thousand fifty-seven new respondents to the NHIS (2001–2004) and 24,139 respondents from the original development and validation cohorts (1997–2000). *Measurements:* A risk score was calculated for each respondent based on the presence or absence of 11 factors (function, illnesses, behaviors, demographics) that make up the index. Using the Kaplan-Meier method, 5-year mortality estimates were computed for the new and original cohort respondents and 9-year mortality estimates for the original cohorts. *Results:* New respondents were similar to original cohort respondents but were slightly more likely to be aged 85 and older, report diabetes mellitus, and have a body mass index of 25.0 kg/m² or greater. The model performed as well in the new cohort as it had in the original cohort. New respondents with risk scores of 0 to 1 had a 2% risk of 5-year mortality, whereas respondents who

scored 18 or higher had a 69% risk of 5-year mortality (range 3–71% risk of 5-year mortality in the development cohort). The index also demonstrated excellent calibration and discrimination in predicting 9-year mortality (range 7% risk for scores of 0–1 to 92% risk for scores of ≥ 18 , original validation cohort extended). *Conclusions:* These results further justify use of this index to estimate life expectancy in clinical decision-making.

Does Hospice Improve Quality of Care for Persons Dying from Dementia?

J. M. Teno et al.

Objectives: To examine the effectiveness of hospice services for persons dying from dementia from the perspective of bereaved family members. *Design:* Mortality follow-back survey. *Setting:* Death certificates were drawn from five states (AL, FL, TX, MA, and MN). *Participants:* Bereaved family members listed as the next of kin on death certificates when dementia was listed as the cause of death. *Measurements:* Ratings of the quality of end-of-life care, perceptions of unmet needs, and opportunities to improve end-of-life care. Two questions were also asked about the peacefulness of dying and quality of dying. *Results:* Of 538 respondents, 260 (48.3%) received hospice services. Family members of decedents who received hospice services reported fewer unmet needs and concerns with quality of care (adjusted odds ratio (AOR)=0.49, 95% confidence interval (CI)=0.33–0.74) and a higher rating of the quality of care (AOR = 2.0, 95% CI=1.53–2.72). They also noted better quality of dying than those without hospice services. *Conclusions:* Bereaved family members of people with dementia who received hospice reported higher perceptions of the quality of care and quality of dying.

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Hospital Do-Not-Resuscitate Orders: Why They Have Failed and How to Fix Them

*J. K. Yuen, M. C. Reid,
and M. D. Fetters*

Do-not-resuscitate (DNR) orders have been in use in hospitals nationwide for over 20 years. Nonetheless, as currently implemented, they fail to adequately fulfill their two intended purposes—to support patient autonomy and to prevent non-beneficial interventions. These failures lead to serious consequences. Patients are deprived of the opportunity to make informed decisions regarding resuscitation, and CPR is performed on patients who would have wanted it withheld or are harmed by the procedure. This article highlights the persistent problems with today's use of inpatient DNR orders, i.e., DNR discussions do not occur frequently enough and occur too late in the course of patients' illnesses to allow their participation in resuscitation decisions. Furthermore, many physicians fail to provide adequate information to allow patients or surrogates to make informed decisions and inappropriately extrapolate DNR orders to limit other treatments. Because these failings are primarily due to systemic factors that result in deficient physician behaviors, we propose strategies to target these factors including changing the hospital culture, reforming hospital policies on DNR discussions, mandating provider communication skills training, and using financial incentives. These strategies could help overcome existing barriers to proper DNR discussions and align the use of DNR orders closer to their intended purposes of supporting patient self-determination and avoiding non-beneficial interventions at the end of life.

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**Artificial Nutrition and Hydration:
The Evolution of Ethics,
Evidence, and Policy**

H. Brody et al.

Introduction: The debate over use of artificial nutrition and hydration (ANH) in terminal illness, including advanced dementia, remains contentious despite extensive ethical and empirical investigation. *Methods:* For this narrative review we undertook a focused, selective review of literature reflecting ethical analysis, empirical assessment of outcomes, legal responses, and thinking within the Roman Catholic religious tradition. *Results:* The history of the debate over the past 60 years results from a complex interplay of ethical concerns, a growing empirical database, legal changes, public opinion, and financial as well as institutional concerns. Discussions of ANH today are often conducted without any understanding of this historical context. *Discussion:* Patients' interests could be better protected through remedial action at both the individual and the policy levels.

Pediatrics

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**Decision-Making around
Gastrostomy-Feeding in Children
with Neurologic Disabilities**

*S. Mahant, V. Jovcevska,
and E. Cohen*

Objectives: The objective of this study was to understand the decision-making

experiences, perspectives, and beliefs of parents of children with a neurologic disability around gastrostomy tube-feeding. *Design and Methods:* We conducted a systematic review of qualitative studies to explore the experiences of parents of children with a neurologic disability around gastrostomy-feeding. We searched 5 electronic databases from inception to July 2010. Two authors independently selected articles and extracted data. Concepts and themes relevant to decision-making were constructed by using thematic analysis. *Results:* Eleven studies were selected in which experiences relevant to decision-making were reported. The decision-making process was characterized by decisional conflict. Concepts important to understanding conflict were categorized under 3 themes: values; context; and process. The value and meaning of feeding by mouth and, in contrast, with a gastrostomy tube was the dominant theme that led to internal distress for parents in decision. Feeding by mouth was seen as an enjoyable activity, an important social process, but also a struggle. Gastrostomy-feeding represented a loss of normality, a sign of disability, and a disruption of maternal nurturing and bonding. Context (child and family characteristics) and process (information sharing and support) modified the decision-making experience. *Conclusions:* Values associated with gastrostomy-feeding and feeding by mouth, the context of child and family, and the process of decision-making facilitated by the health care system shape parental experiences and decisional conflict. This framework will help guide interventions, such as patient decision aids, that are aimed at improving parental decision-making.