Medicine

> "For behold, darkness shall cover the earth, and thick darkness the peoples; but the Lord with arise upon you, and his glory will be seen upon you."
>
> —Isaiah 60:2

Easter is a season that can be a time of transformation, freedom, and new hope through the glory of Christ Jesus our risen Lord. The therapeutic significance of hope in all its manifestations must always be acknowledged as an important part of healing. As I prepare this column on the recent progress in medicine and clinical research, I reflect on how often scientific advances provide an opportunity to overcome the despair that would otherwise accompany illness. The proposed cuts to the US Department of Health and Human Services, especially to the research budget of the National Institutes of Health, threaten to put at risk the most vulnerable in our society. I pray that growing professional and civic engagement will succeed in shaping policy and funding priorities to do the most good.[1]

Physician-Assisted Suicide

The International Association for Hospice and Palliative Care issued a position statement on euthanasia and physician-assisted suicide in January 2017.[2] Espousing no political or religious affiliations, the IAHPC is dedicated to the global advancement of palliative care; it has a formal relationship with the World Health Organization, where its members serve on and advise expert committees. The IAHPC is committed to advancing the WHO definition of palliative care: "An approach that improves the quality of life of patients and their families facing the problems associated with

1. The new interactive site usafacts.org provides insight into US government spending.

2. Liliana De Lima et al., "International Association for Hospice and Palliative Care Position Statement: Euthanasia and Physician-Assisted Suicide," *Journal of Palliative Medicine* 20.1 (January 2017): 8–14, doi: 10.1089/jpm.2016.0290.

life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[3]

The position paper from the IAHPC begins by drawing on the positions of other national and pan-national health care organizations that have previously addressed these questions. Rather than developing a position from first principles, the IAHPC statement is largely constructed from elements derived from other organizations, many of which are themselves well thought out. This deflects potential criticism that might be directed at a unique platform, especially one on a controversial topic about which there is a diversity of opinion. However, this approach leaves the adopted elements vulnerable to revision if the source organizations later change their positions. For example, the IAHPC supports the International Children's Palliative Care Network, which states that "enabling good quality of life cannot include hastening death, and we do not believe that euthanasia or physician-assisted suicide is part of children's palliative care."[4] Though admirable, we must ask what will happen if the International Children's Palliative Care Network aligns itself differently in the future? To the credit of the IAHPC, the Hippocratic Oath is cited as an important professional code of conduct that exhorts physicians to preserve life. The statement concludes that in places where euthanasia or physician-assisted suicide are legal, palliative care units should not be responsible for overseeing or administering these practices, and the law should include provisions permitting any health professional who objects to take no part. Upholding a conscience clause is important, especially when regulations and laws governing euthanasia and physician-assisted suicide are rapidly evolving.

The passage of the Washington Death with Dignity (DWD) Act in November 2008 created the first program in the United States allowing terminally ill adults with a life expectancy of less than six months to access lethal doses of medication to end their lives. A recent paper in *JAMA Oncology*, "Drug Price Inflation and the Cost of Assisted Death for Terminally Ill Patients: Death with Indignity," examines an unanticipated problem associated with the medications approved for use in physician-assisted suicide. "Since 2009, the number of DWD prescriptions dispensed in Washington State has steadily increased, and the majority of patients (approximately 75 percent with a diagnosis of cancer) to whom the medications are dispensed ultimately ingest them. . . . Patients and their families are raising new concerns about the high cost of DWD medication and the unaffordability of ending their lives in this way."[5] The pharmaceutical industry has come under increasing scrutiny for the high

3. World Health Organization, *National Cancer Control Programmes: Policies and Managerial Guidelines,* 2nd ed. (Geneva: WHO, 2002), xv–xvi.

4. International Children's Palliative Care Network, "Position Statement on the Practice of Euthanasia and Assisted Suicide," May 2014, 2, http://www.icpcn.org/.

5. Veena Shankaran, Richard J. LaFrance, and Scott D. Ramsey, "Drug Price Inflation and the Cost of Assisted Death for Terminally Ill Patients: Death with Indignity," *JAMA Oncology* 3.1 (January 2017): 15–16, doi: 10.1001/jamaoncol.2016.3842. See also Washington State Department of Health, "2015 Death with Dignity Act Report: Executive Summary," 2016, http://www.doh.wa.gov/.

cost of drugs in the United States, especially when treating rare diseases or when a monopoly exists. The authors note that secobarbital, a commonly prescribed DWD agent, was "introduced to market in 1929, [and] represents one of the most poignant examples of pharmaceutical company profiteering from sales of older niche drugs and its effect on vulnerable patients. Secobarbital has few clinical uses outside of aid-in-dying and is currently the only DWD drug available in most participating pharmacies." Regardless of one's view on the morality of the medication's intended use, exorbitant drug price inflation at the expense of vulnerable patients is a growing problem that needs to be curbed through more transparency and better oversight.

An even more troubling development in the realm of euthanasia and physician-assisted suicide is the growing number of editorials and papers that call for the inclusion of patients suffering from serious depression that is unresponsive to treatment. Depression is common among individuals seeking euthanasia. In one study in the Netherlands that looked at patients with incurable cancer and an estimated life expectancy of less than six months, those who explicitly requested euthanasia were almost twice as likely to be depressed as those who did not request to end their lives.[6] A paper authored by Thomas Blikshavn et al. in the *Journal of Bioethical Inquiry* carefully explains why assisted dying should not be offered for depression.[7] The authors review the diagnostic categories of depression, psychiatric treatment, and prognosis, and they lay bare the concept of treatment-resistant depression. They also address the therapeutic significance of hope, as well as the consequences for mental health services if a shift toward allowing euthanasia and physician-assisted suicide for depression were to take place: "The very awareness that therapists may in principle come to give up hope in [a patient's] eventual improvement may be harmful." Institutionalization of assisted dying within mental health is not compatible with the therapeutic relationship and would erode the trust placed in providers.

End-of-Life Decisions and Palliative Care

Most studies of end-of-life decisions usually focus on situations where patients are either terminally ill or suffering from severe pain. Although these acute cases are among the most feared, a more common challenge faced by aging patients and their families is the dependency associated with increasing infirmity in old age. A recent study in the *Journal of Medical Ethics* examines attitudes toward end-of-life decisions in cases of long-term care dependency.[8] The human population is getting older as a result of shifting birth rates, increasing access to health care, and

6. Cees D. M. Ruijs et al., "Depression and Explicit Requests for Euthanasia in End-of-Life Cancer Patients in Primary Care in the Netherlands: A Longitudinal, Prospective Study," *Family Practice* 28.4 (August 2011): 393, doi:10.1093/fampra/cmr006.

7. Thomas Blikshavn, Tonje Lossius Husum, and Morten Magelssen, "Four Reasons Why Assisted Dying Should Not Be Offered for Depression," *Journal of Bioethical Inquiry* 14.1 (March 2017): 151–157, doi: 10.1007/s11673-016-9759-4.

8. Erwin Stolz et al., "Attitudes towards End-of-Life Decisions in Case of Long-Term Care Dependency: A Survey among the Older Population in Austria," *Journal of Medical Ethics* 43.6 (June 2017): 413–416, doi: 10.1136/medethics-2016-103731.

advancing medical technology.[9] Consequently, many more individuals will reach a stage in life where they need assistance with the activities of daily living. The study surveyed nearly one thousand Austrians aged fifty years and older who were asked a series of questions about their approval of assisted suicide and euthanasia when requested by an older, severely care-dependent person; strikingly, 42 percent and 34 percent of the respondents approved of allowing severely care-dependent persons to end their lives through assisted suicide and euthanasia, respectively. "Non-religious individuals, less trusting respondents and those concerned about constrictions associated with old age were more likely to approve [of] both."[10] A small qualitative survey of older adults who oppose physician-assisted dying in New Zealand found that past experience with death and dying influences how many older individuals think about physician-assisted dying; in particular, individuals who have witnessed well-managed dying tend to view physician assistance as unnecessary, while those who have witnessed poor dying and death experiences fear that physician assistance could be abused by others.[11] Further research into attitudes about end-of-life care should address situations of long-term care and dependency. As a society we need to provide greater assurance that individuals and families will have access to the support that they need to be sustained in old age.

Finally, I draw the reader's attention to the results of a survey published by the American Society for Radiation Oncology that examines the attitude of radiation oncologists to palliative and supportive care in the United States.[12] Radiation oncologists frequently deliver palliative radiation to patients with advanced cancers. An electronic survey of more than four thousand members of the society (16 percent return rate) revealed that "radiation oncologists are more confident in their ability to assess and manage pain than in their ability to manage depression, anxiety, anorexia, and fatigue." Most physicians who lack formal palliative-care training are likely to share many of these sentiments. The society suggests increasing training in palliative and supportive care for resident physicians early in their careers and increasing continuing-education initiatives for practicing physicians. Interestingly, "upsetting referring medical oncologists and lack of clinical time" were the concerns most commonly expressed by radiation oncologists who may have wanted to initiate discussions about the goals of care and advance care planning but failed to do so. Coordination on the part of the health care team requires good communication between patients, their families, and their physicians.

9. UN Department of Economic and Social Affairs, *World Population Ageing 2015*, ST/ESA/SER.A/390 (2015), 3–4.

10. Stolz et al., "Attitudes towards End-of-Life Decisions," 413.

11. Phillipa J. Malpas et al., "Why Do Older People Oppose Physician-Assisted Dying? A Qualitative Study," *Palliative Medicine* 28.4 (April 2014): 353–359, doi: 10.1177/0269216313511284.

12. Randy L. Wei et al., "Attitudes of Radiation Oncologists toward Palliative and Supportive Care in the United States: Report on National Membership Survey by the American Society for Radiation Oncology (ASTRO)," *Practical Radiation Oncology* 7.2 (March–April 2017): 113–119, doi: 10.1016/j.prro.2016.08.017.

Vaccines

Nearly 80 million Americans are infected with human papillomavirus (HPV), and around 14 million new infections occur each year.[13] In the United States, a two-dose series of HPV vaccine on a schedule of six to twelve months is recommended for all adolescents aged eleven or twelve years. The schedule can start as early as age nine and extend through age eighteen for those who were not previously adequately vaccinated.[14] In Europe, vaccination is routinely offered to girls aged twelve through seventeen years with a two- (Cervarix) or four-valent (Gardasil) vaccine. The nine-valent vaccine—Gardasil 9, human papillomavirus nine-valent vaccine, recombinant—received a European market authorization in 2015. A recent study in *Expert Review of Pharmacoeconomic Outcomes Research* compares the findings from the current vaccination program involving European girls to the potential effect of immunizing all adolescents with the nine-valent vaccine. The model suggests that the incidence of cervical cancer could be reduced further by as much as 24 percent over the next century.[15] In both males and females, substantial reductions in anal and oropharyngeal cancers could also be expected after implementing such a program. Preventing infection by high-risk serotypes covered by HPV vaccines is a key step in interrupting the pathogenesis of sexually transmitted cancers. Physicians and other health care providers should advocate timely and routine vaccination as well as efforts to increase abstinence and reduce high-risk sexual behavior; by doing so, we may be able to free the next generation from the burden of HPV infection and the associated risks of cancer.

In its March issue, the *New England Journal of Medicine* reported on the efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger.[16] Rotavirus gastroenteritis is characterized by vomiting, watery diarrhea, and low-grade fever. Although it is usually self-limiting, serious complications, such as severe diarrhea, dehydration, and even death, may develop, especially among individuals with underlying malnutrition, comorbid conditions, and limited access to restorative health care services like oral rehydration therapy. The disease is caused by rotavirus, a genus of double-stranded RNA virus in the family Reoviridae, usually spread by the fecal–oral route. Like most viral infections, there is no specific treatment. Hygiene and preventive vaccination are the most effective measures for limiting infection.

13. "HPV Vaccines: Vaccinating Your Preteen or Teen," Centers for Disease Control and Prevention, updated December 13, 2016, https://www.cdc.gov/. See also "HPV (Human Papillomavirus) VIS," CDC, reviewed January 10, 2017, https://www.cdc.gov/.

14. "Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, United States, 2017," CDC, accessed June 19, 2017, https://www.cdc.gov/.

15. Nathalie Largeron et al., "An Estimate of the Public Health Impact and Cost-Effectiveness of Universal Vaccination with a 9-Valent HPV Vaccine in Germany," *Expert Review of Pharmacoeconomics and Outcomes Research* 17.1 (February 2017): 85–98, doi: 10.1080/14737167.2016.1208087.

16. Sheila Isanaka et al., "Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger," *New England Journal of Medicine* 376.12 (March 23, 2017): 1121–1130, doi: 10.1056/NEJMoa1609462.

Before the oral rotavirus vaccination program was initiated in the United States, approximately sixty thousand children and adults were hospitalized and thirty-seven died annually from infectious complications.[17] Rotavirus morbidity and mortality have sharply declined in the United States and worldwide following the introduction of universal vaccination, but deaths from diarrhea among children younger than five years have continued to occur disproportionately in many high-poverty regions, such as sub-Saharan Africa.[18]

The Niger study, funded by Médecins sans Frontières (Doctors without Borders) and the United States–based Kavli Foundation, used a live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India). More than 3,500 infants in Niger were randomized to three doses of the oral vaccine or a placebo at six, ten, and fourteen weeks of age. The results of the study show an "efficacy of 66.7% against severe rotavirus gastroenteritis" comparable to other vaccines, without an excess risk of adverse events between the two groups, including no confirmed cases of intussusception, a rare complication that led to the withdrawal of the first rotavirus vaccine (RotaTeq, Merck). The development of this heat-stable, oral rotavirus vaccine could enhance access and uptake in regions where traditional vaccination is logistically difficult and costly.

Organ Donation and Transplantation

Organ donation can be an emotional and difficult decision for many families, especially when the loss of a loved one occurs unexpectedly. A recent study in *Annals of Transplantation* explores the factors associated with a family's delay in making a decision for organ donation after brain death.[19] The records of more than one hundred potential donors were reviewed and categorized according to the time interval between the initial counseling on the availability of organ donation and the final decision to donate. The authors defined the early-decision group as those who took less than forty-eight hours, while the delayed-decision group took longer than forty-eight hours. The final consent rate for donation was 58 percent, and successful donations were performed in 40 percent of cases. Low blood pressure (mean arterial pressure <60 mm) and coma therapy were found to be correlated with a delay in organ donation. The authors hypothesize that in cases where there is

17. Thea Kolsen Fischer et al., "Hospitalizations and Deaths from Diarrhea and Rotavirus among Children <5 Years of Age in the United States, 1993–2003," *Journal of Infectious Diseases* 195.8 (April 15, 2007): 1117–1125, doi: 10.1086/512863.

18. Minesh P. Shah et al., "Decline in Emergency Department Visits for Acute Gastroenteritis among Children in 10 US States after Implementation of Rotavirus Vaccination, 2003 to 2013," *Pediatric Infectious Disease Journal* 35.7 (July 2016): 782–786, doi: 10.1097/INF.0000000000001175; and Eleanor Burnett et al., "Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality from Diarrhea," *Journal of Infectious Diseases* 215.11 (April 18, 2017): 1666–1672, doi: 10.1093/infdis/jix186.

19. Sang Youb Han et al., "Factors Associated with a Family's Delay of Decision for Organ Donation after Brain Death," *Annals of Transplantation* 22 (January 17, 2017): 17–23, doi: 10.12659/AOT.901616.

evidence of impending circulatory death, "the primary decision maker among the family members might want to avoid additional physical injury to the loved one."

In the case of patients being maintained with coma therapy, the authors suggest that the hesitation to donate may stem from the delayed recovery generally expected in patients maintained in an induced coma. It is interesting to note that while more members of the delayed-decision group ultimately decided to donate, this group had a relatively greater proportion of cases where successful organ transplantation could not be performed, which may have been a consequence of the delay. Unfortunately, the small sample size of the study makes it difficult to draw any statistical inferences. The question of organ donation often arises in complex circumstances filled with emotional stress that makes "it difficult for families to understand the nature of brain death and to accept the real death of their loved one." Offering counseling to encourage organ donation even if the family cannot decide immediately is the best way to help individuals make decisions regarding organ donation.

Fertility and Reproduction

Inaccurate timing of sexual intercourse may be a reason for either a delay in conception or apparent subfertility. Because the cycle lengths and "fertile windows" of reproductive-age women may vary by a week or more as judged by observational studies, cues beyond the timing of menses alone are important.[20] The ability to achieve the desired outcome of natural family planning (NFP) requires accurate timing of sexual intercourse and may be enhanced by fertility-awareness education. The April 2017 issue of *Archives of Gynecology and Obstetrics* published a prospective observational cohort study that followed 187 subfertile women, defined as those who have unsuccessfully attempted to become pregnant over the course of one to eight years (average of 3.5 years) before study entry.[21] The participating couples were taught the Sensiplan fertility-awareness method that enables a woman to identify more accurately her fertile window by "recording the pattern of cervical secretion and changes in basal body temperature."[22] After fertility-awareness training, the cumulative pregnancy rate of subfertile couples was 38 percent after eight observation months (56 percent for couples who had been seeking to become pregnant for only one to two years). This is significantly higher than the estimated 21.6 percent baseline pregnancy rate for untrained couples in this group. Fertility-awareness methods are a reasonable first-line therapy for managing subfertility, with the benefits of NFP training continuing over a lifetime.

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20. Allen J. Wilcox, David Dunson, and Donna Day Baird, "The Timing of the 'Fertile Window' in the Menstrual Cycle: Day Specific Estimates from a Prospective Study," *British Medical Journal* 321.7271 (November 18, 2000): 1259–1262, doi: 10.1136/bmj.321.7271.1259.

21. Petra Frank-Herrmann et al., "Natural Conception Rates in Subfertile Couples following Fertility Awareness Training," *Archives of Gynecology and Obstetrics* 295.4 (April 2017): 1015–1024, doi: 10.1007/s00404-017-4294-z.

22. Petra Frank-Herrmann et al., "Determination of the Fertile Window: Reproductive Competence of Women—European Cycle Databases," *Gynecological Endocrinology* 20.6 (June 2005): 305–312, doi: 10.1080/09513590500097507.

Addiction Medicine

Opioid dependence is a chronic condition with tremendous health, economic, and social costs. An article in the March issue of *JAMA* reviewed the effectiveness of different opioid agonists, such as methadone and buprenorphine, for treating patients with prescription-opioid dependence, and it compared their efficacy to that of opioid-taper or psychological treatments alone.[23] Once detoxification has been achieved, the next stage in recovery is enabling a patient to overcome drug addiction through abstinence-based treatment, often complemented with long-term treatment with an opioid-agonist or opioid-substitution therapy. The preponderance of evidence indicates that long-term maintenance of opioid agonists results in better outcomes for patients, including less prescription-opioid abuse and greater adherence to interventional therapies, as compared with opioid-taper or psychological treatments alone. The largest clinical trial to date, the multi-site Prescription Opioid Addiction Treatment Study conducted by the National Drug Abuse Treatment Clinical Trials Network, found that while only 7 percent of patients achieved a successful outcome—abstinence or near-abstinence from opioids—during a four-week taper and eight-week follow-up, 49 percent of patients achieved success while subsequently stabilized on buprenorphine/naloxone.[24] Similar results have been shown for methadone-maintenance treatment. Opioid-substitution therapy better manages the long-term physical toll of opioid dependence and may help to improve an individual's functioning and quality of life.

David J. Ramsey, MD

23. Suzanne Nielsen, Briony Larance, and Nicholas Lintzeris, "Opioid Agonist Treatment for Patients with Dependence on Prescription Opioids," *JAMA* 317.9 (March 17, 2017): 967–968, doi: 10.1001/jama.2017.0001.

24. Roger D. Weiss and Vinod Rao, "The Prescription Opioid Addiction Treatment Study: What Have We Learned," *Drug and Alcohol Dependence* 173 suppl 1 (April 1, 2017): S48–S54, doi: 10.1016/j.drugalcdep.2016.12.001.

Medicine Abstracts

Acta Obstetricia et Gynecologica Scandinavica

Anni Ellenberg et al., **New guidelines for screening, diagnosing, and treating gestational diabetes: evaluation of maternal and neonatal outcomes in Finland from 2006 to 2012**, *Acta Obstet Gynecol Scand* 96.3 (March 2017): 372–381, doi: 10.1111/aogs.13074 • *Introduction:* In this study, we have assessed the changes in pregnancy outcomes following the implementation of national guidelines for gestational diabetes mellitus (GDM). These national guidelines changed the screening policy from risk-based to comprehensive screening. *Material and methods:* We designed a retrospective register-based cohort study based on the data from the Finnish Medical Birth Register and Hospital Discharge Register including 34794 singleton births in 2006-2008 and 36 488 in 2010-2012. Maternal characteristics and pregnancy outcomes were analyzed. *Results:* Overall, 29.6% of mothers underwent an oral glucose tolerance test in 2006-2008 compared with 59.7% in 2010-2012. The prevalence of GDM increased from 7.2 to 11.3% and was highest among obese women (body mass index ≥30 kg/m2) (from 30.0 to 34.7%; $p < 0.001$). The proportion of insulin-treated women remained unchanged (12.5/12.3%; $p = 0.70$). The main pregnancy outcomes for the women with GDM were the increased usage of oxytocin (19.5/40.0%, $p < 0.001$), increased number of inductions (27.2/33.0%; $p < 0.001$) and reduced birthweight (mean ± SD: 3647 ± 575 g/3567 ± 575 g). Healthy and unscreened women displayed similar results. Children of both women with GDM and healthy screened women had fewer admissions to the neonatal intensive care unit (16.3%/12.1%; $p < 0.001$) and less asphyxia (11.3%/6.3%; $p < 0.001$). However, the rates of cesarean delivery (26.5%/25.4%, $p = 0.31$), resuscitation (2.6%/2.0%; $p = 0.12$), and perinatal mortality (1.2‰/3.1‰, $p = 0.11$) among women with GDM did not change, whereas the number of hypoglycemia cases increased (2.3%/5.2%; $p < 0.001$). *Conclusions*: In conclusion, glucose tolerance tests were performed twice as often as a result of the implementation of the national GDM guidelines, but this comprehensive screening practice did not improve pregnancy and neonatal outcomes.

Annals of Transplantation

Sang Youb Han et al., **Factors associated with a family's delay of decision for organ donation after brain death**, *Ann Transplant* 22 (January 17, 2017): 17–23, doi: 10.12659/AOT.901616 • *Background:* This study aimed to explore the factors associated with a family's delay of decision for organ donation after brain death, and to investigate the effect of such a delay on organ donation. *Material and methods:* Medical records and data on counseling about organ donation with the families of 107 brain-dead potential donors between September 2012 and March 2016 at a single tertiary medical center were retrospectively reviewed. *Results:* The final consent rate was 58% (62/107), and successful donation was performed in 40% (43/107). Ninety-two families (86%) made a decision within 48 hours, whereas 15 (14%) required more than 48 hours for a final decision. In univariate and multivariate analyses, the independent factors associated with a decision delay were mean arterial pressure ≤60 mm Hg and coma therapy. In the early decision group (<48 hours), the consent and successful donation rates were 55% (51/92) and 39% (36/92), respectively, whereas in the delayed decision group (≥48 hours), these rates were 73% (11/15) and 47% (7/15), respectively. The consent and successful donation rates were

not inferior in the delayed decision group. *Conclusions:* These findings justify continuous efforts to maintain organ viability and to extend counseling to encourage donation even if the family cannot decide immediately.

Archives of Gynecology and Obstetrics

Petra Frank-Herrmann et al., **Natural conception rates in subfertile couples following fertility awareness training**, *Arch Gynecol Obstet* 295.4 (April 2017): 1015–1024, doi: 10.1007/s00404-017-4294-z • *Purpose:* To analyze cumulative pregnancy rates of subfertile couples after fertility awareness training. *Methods:* A prospective observational cohort study followed 187 subfertile women, who had received training in self-observation of the fertile phase of the menstrual cycle with the Sensiplan method, for 8 months. The women, aged 21-47 years, had attempted to become pregnant for 3.5 years on average (range 1-8 years) before study entry. Amenorrhea, known tubal occlusion and severe male factor had been excluded. An additional seven women, who had initially been recruited, became pregnant during the cycle immediately prior to Sensiplan training: this is taken to be the spontaneous pregnancy rate per cycle in the cohort in the absence of fertility awareness training. *Results:* The cumulative pregnancy rate of subfertile couples after fertility awareness training was 38% (95% CI 27-49%; 58 pregnancies) after eight observation months, which is significantly higher than the estimated basic pregnancy rate of 21.6% in untrained couples in the same cohort. For couples who had been seeking to become pregnant for 1-2 years, the pregnancy rate increased to 56% after 8 months. A female age above 35 (cumulative pregnancy rate 25%, $p=0.06$), couples who had attempted to become pregnant for more than 2 years (cumulative pregnancy rate 17%, $p<0.01$), all significantly reduce the chances of conceiving naturally at some point. *Conclusions*: Training women to identify their fertile window in the menstrual cycle seems to be a reasonable first-line therapy in the management of subfertility.

Expert Opinions on Drug Safety

S. Harrison Farber et al., **The safety of available immunotherapy for the treatment of glioblastoma**, *Expert Opin Drug Saf* 16.3 (March 2017): 277–287, doi: 10.1080/14740338.2017.1273898 • *Introduction:* Glioblastoma (GBM) is the most common malignant primary brain tumor in adults. Current standard of care involves maximal surgical resection combined with adjuvant chemoradiation. Growing support exists for a role of immunotherapy in treating these tumors with the goal of targeted cytotoxicity. Here we review data on the safety for current immunotherapies being tested in GBM. *Areas covered:* Safety data from published clinical trials, including ongoing clinical trials were reviewed. Immunotherapeutic classes currently under investigation in GBM include various vaccination strategies, adoptive T cell immunotherapy, immune checkpoint blockade, monoclonal antibodies, and cytokine therapies. Trials include children, adolescents, and adults with either primary or recurrent GBM. *Expert opinion:* Based on the reviewed clinical trials, the current immunotherapies targeting GBM are safe and well-tolerated with minimal toxicities which should be noted. However, the gains in patient survival have been modest. A safe and well-tolerated combinatory immunotherapeutic approach may be essential for optimal efficacy towards GBM.

Expert Review of Pharmacoeconomics and Outcomes Research

Nathalie Largeron et al., **An estimate of the public health impact and cost-effectiveness of universal vaccination with a 9-valent HPV vaccine in Germany**, *Exp Rev Pharmacoecon Outcomes Res* 17.1 (2017): 85–98, doi: 10.1080/14737167.2016.1208087 • *Introduction:* Since 2007, the German Standing Vaccination Committee recommends HPV vaccination for girls aged 12-17 with a 2- (Cervarix) or 4-valent (Gardasil) vaccine. A 9-valent vaccine (Gardasil 9) recently received a European market authorization

in 2015. *Methods:* A dynamic transmission model was calibrated to the German setting and used to estimate costs and QALYs associated with vaccination strategies. *Results*: Compared to the current vaccination program, the 9-valent vaccine extended to boys shows further reductions of 24% in the incidence of cervical cancer, 30% and 14% in anal cancer for males and females, as well as over a million cases of genital warts avoided after 100 years. The new strategy is associated with an ICER of 22,987€ per QALY gained, decreasing to 329€ when considering the vaccine switch for girls-only. *Conclusion*: Universal vaccination with the 9-valent vaccine can yield significant health benefits when compared to the current program.

Frontiers in Public Health

Matthias Unseld et al., **Use of natural family planning (NFP) and its effect on couple relationships and sexual satisfaction: a multi-country survey of NFP users from US and Europe**, *Front. Public Health*, e-pub March 13, 2017, doi: 10.3389/fpubh.2017.00042 • *Purpose:* Birth control is a persistent global health concern. Natural family planning (NFP) comprises methods to achieve or avoid pregnancy independent of mechanical or pharmacological intervention. The sympto-thermal method (STM) of NFP employs daily observation of cervical fluids and measurement of basal body temperature. This multi-country study was undertaken to describe the characteristics of STM users, understand their perceptions of NFP, and its perceived impact on relationships. *Methods and results:* Questionnaires for women and men were developed in German and translated to English, Polish, Italian, Czech, and Slovak by native speakers. A total of 2,560 respondents completed the online questionnaire (37.4% response). Participants were married (89%) and well educated, and their self-perceived financial status was described as "good" or "very good" by 65% of the respondents. Forty-seven percent had previously used contraceptives. Ninety-five percent of women and 55% of men said using NFP has helped them to know their body better. Large majorities of men (74%) and women (64%) felt NFP helped to improve their relationship while <10% felt use of NFP had harmed their relationship. Most women (53%) and men (63%) felt using NFP improved their sex life while 32% of women and 24% of men felt it was unchanged from before they used NFP. Seventy-five percent of women and 73% of men said they are either "satisfied" or "very satisfied" with their frequency of sexual intercourse. *Conclusion*: This survey demonstrates STM of NFP is a well-accepted approach to family planning across several Western cultures. It is consistently viewed as being beneficial to couples' self-knowledge, their relationship, and satisfaction with frequency of sexual intercourse.

JAMA

Hope S. Rugo et al., **Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)–positive metastatic breast cancer: a randomized clinical trial**, *JAMA* 317.1 (January 3, 2017): 37–47, doi: 10.1001/jama.2016.18305 • *Importance:* Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab and chemotherapy significantly improves outcome in patients with ERBB2 (HER2)-positive metastatic breast cancer; a clinically effective biosimilar may help increase access to this therapy. *Objective:* To compare the overall response rate and assess the safety of a proposed trastuzumab biosimilar plus a taxane or trastuzumab plus a taxane in patients without prior treatment for ERBB2-positive metastatic breast cancer. *Design, setting, and participants:* Multicenter, double-blind, randomized, parallel-group, phase 3 equivalence study in patients with metastatic breast cancer. From December 2012 to August 2015, 500 patients were randomized 1:1 to receive a proposed biosimilar or trastuzumab plus a taxane. Chemotherapy was administered for at least 24 weeks followed by antibody alone until unacceptable toxic effects or disease progression occurred. *Interventions:*

Proposed biosimilar (n=230) or trastuzumab (n=228) with a taxane. *Main outcomes and measures:* The primary outcome was week 24 overall response rate (ORR) defined as complete or partial response. Equivalence boundaries were 0.81 to 1.24 with a 90% CI for ORR ratio (proposed biosimilar/trastuzumab) and -15% to 15% with a 95% CI for ORR difference. Secondary outcome measures included time to tumor progression, progression-free and overall survival at week 48, and adverse events. *Results:* Among 500 women randomized, the intention-to-treat population included 458 women (mean [SD] age, 53.6 [11.11] years) and the safety population included 493 women. The ORR was 69.6% (95% CI, 63.62%-75.51%) for the proposed biosimilar vs 64.0% (95% CI, 57.81%-70.26%) for trastuzumab. The ORR ratio (1.09; 90% CI, 0.974-1.211) and ORR difference (5.53; 95% CI, -3.08 to 14.04) were within the equivalence boundaries. At week 48, there was no statistically significant difference with the proposed biosimilar vs trastuzumab for time to tumor progression (41.3% vs 43.0%; -1.7%; 95% CI, -11.1% to 6.9%), progression-free survival (44.3% vs 44.7%; -0.4%; 95% CI, -9.4% to 8.7%), or overall survival (89.1% vs 85.1%; 4.0%; 95% CI, -2.1% to 10.3%). In the proposed biosimilar and trastuzumab groups, 239 (98.6%) and 233 (94.7%) had at least 1 adverse event, the most common including neutropenia (57.5% vs 53.3%), peripheral neuropathy (23.1% vs 24.8%), and diarrhea (20.6% vs 20.7%). *Conclusions and relevance:* Among women with ERBB2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks. Further study is needed to assess safety and long-term clinical outcome. *Trial registration:* clinicaltrials.gov Identifier: NCT02472964; EudraCT Identifier: 2011-001965-42.

Suzanne Nielsen, Briony Larance, and Nicholas Lintzeris, **Opioid agonist treatment for patients with dependence on prescription opioids**, *JAMA* 317.9 (March 7, 2017): 967–687, doi: 10.1001/jama.2017.0001 • *Clinical question:* Are different opioid agonist treatments (eg, methadone vs buprenorphine) associated with differences in efficacy for treating prescription opioid dependence, and is long-term maintenance of opioid agonist treatment associated with differences in efficacy compared with opioid taper or psychological treatments alone? *Bottom line:* For patients who are dependent on prescription opioids, long-term maintenance of opioid agonists is associated with less prescription opioid use and better adherence to medication and psychological therapies for opioid dependence compared with opioid taper or psychological treatments alone. Methadone maintenance was not associated with differences in therapeutic efficacy compared with buprenorphine maintenance treatment. Evidence quality was low to moderate.

JAMA Oncology

Veena Shankaran, Richard J. LaFrance, and Scott D. Ramsey, **Drug price inflation and the cost of assisted death for terminally ill patients: death with indignity**, *JAMA Oncol* 3.1 (January 2017): 15–16, doi: 10.1001/jamaoncol.2016.3842 • The Washington State Death with Dignity (DWD) Act passed into law in November 2008 and allows terminally ill adults with a life expectancy of fewer than 6 months to request lethal doses of barbiturate medications to end their lives. Participants have cited concerns about loss of autonomy, dignity, and ability to engage in activities that make life enjoyable as reasons for participating in the program. Since 2009, the number of DWD prescriptions dispensed in Washington State has steadily increased, and the majority of patients (approximately 75% with cancer diagnoses) to whom the medications are dispensed will ingest them.The DWD program has generally been considered successful and patients have reported feeling grateful to have an option for physician-assisted death. Today, however, patients and their families are raising new concerns about the high cost of DWD medication and the unaffordability of ending their lives in this way.

Journal of Bioethical Inquiry

Thomas Blikshavn, Tonje Lossius Husum, and Morten Magelssen, **Four reasons why assisted dying should not be offered for depression**, *J Bioeth Inq* 14.1 (March 2017): 151–157, doi: 10.1007/s11673-016-9759-4 • Recently, several authors have argued that assisted dying may be ethically appropriate when requested by a person who suffers from serious depression unresponsive to treatment. We here present four arguments to the contrary. First, the arguments made by proponents of assisted dying rely on notions of "treatment-resistant depression" that are problematic. Second, an individual patient suffering from depression may not be justified in believing that chances of recovery are minimal. Third, the therapeutic significance of hope must be acknowledged; when mental healthcare opens up the door to admitting hopelessness, there is a danger of a self-fulfilling prophecy. Finally, proponents of assisted dying in mental healthcare overlook the dangers posed to mental-health services by the institutionalization of assisted dying.

Journal of Immunology Research

Boyuan Huang et al., **Advances in immunotherapy for glioblastoma multiforme**, *J Immunol Res* 2017 (February 19, 2017): 1–11, doi: 10.1155/2017/3597613 • Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults. Patients with GBM have poor outcomes, even with the current gold-standard first-line treatment: maximal safe resection combined with radiotherapy and temozolomide chemotherapy. Accumulating evidence suggests that advances in antigen-specific cancer vaccines and immune checkpoint blockade in other advanced tumors may provide an appealing promise for immunotherapy in glioma. The future of therapy for GBM will likely incorporate a combinatorial, personalized approach, including current conventional treatments, active immunotherapeutics, plus agents targeting immunosuppressive checkpoints.

Journal of Medical Ethics

E. Stolz et al., **Attitudes towards end-of-life decisions in case of long-term care dependency: a survey among the older population in Austria**, *J. Med. Ethics*, e-pub February 25, 2017, doi: 10.1136/medethics-2016-103731 • *Background*: Research on attitudes towards end-of-life decisions (ELDs) contextually most often refers to the very end of life, that is, to situations of terminally ill patients or severe pain, but it is rarely applied to the broader context of long-term care dependency in old age. *Methods*: In a representative survey among older Austrians (50+, n=968), respondents were asked about their approval of assisted suicide and euthanasia (EUT) when requested by an older, severely care-dependent person. The influence of sociodemographics, care-related experiences and expectations, religiosity, trust, locus of control and concerns regarding constrictions of old age on the approval of both these ELDs was assessed through logistic regression analyses. *Results*: 42% and 34% of the respondents approved assisted suicide and EUT, respectively, in case of care dependency. Non-religious individuals, less trusting respondents and those concerned about constrictions associated with old age were more likely to approve both these ELDs. *Conclusions*: Widespread concerns regarding long-term care dependency in old age should be addressed in information campaigns, and public discourse about ELDs should pay more attention to situations of long-term care dependency.

Journal of Palliative Medicine

Liliana De Lima et al, **International Association for Hospice and Palliative Care position statement: euthanasia and physician-assisted suicide**, *J Palliat Med* 20.1 (January 2017): 8–14, doi:10.1089/jpm.2016.0290 • *Background:* Reports about regulations and laws on Euthanasia and Physician Assisted Suicide (PAS) are becoming increasingly common in the media. Many groups have expressed opposition to

euthanasia and PAS while those in favor argue that severely chronically ill and debilitated patients have a right to control the timing and manner of their death. Others argue that both PAS and euthanasia are ethically legitimate in rare and exceptional cases. Given that these discussions as well as the new and proposed laws and regulations may have a powerful impact on patients, caregivers, and health care providers, the International Association for Hospice and Palliative Care (IAHPC) has prepared this statement. *Purpose:* To describe the position of the IAHPC regarding Euthanasia and PAS. *Method:* The IAHPC formed a working group (WG) of seven board members and two staff officers who volunteered to participate in this process. An online search was performed using the terms "position statement", "euthanasia", "assisted suicide", "PAS" to identify existing position statements from health professional organizations. Only statements from national or pan-national associations were included. Statements from seven general medical and nursing associations and statements from seven palliative care organizations were identified. A working document including a summary of the different position statements was prepared and based on these, an initial draft was prepared. Online discussions among the members of the WG took place for a period of three months. The differences were reconciled by email discussions. The resulting draft was shared with the full board. Additional comments and suggestions were incorporated. This document represents the final version approved by the IAHPC Board of Directors. *Result:* IAHPC believes that no country or state should consider the legalization of euthanasia or PAS until it ensures universal access to palliative care services and to appropriate medications, including opioids for pain and dyspnea. *Conclusion:* In countries and states where euthanasia and/or PAS are legal, IAHPC agrees that palliative care units should not be responsible for overseeing or administering these practices. The law or policies should include provisions so that any health professional who objects must be allowed to deny participating.

New England Journal of Medicine

Sheila Isanaka et al., **Efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger**, *N Engl J Med* 376.12 (March 23, 2017): 1121–1130, doi: 10.1056/NEJMoa1609462 • *Background:* Each year, rotavirus gastroenteritis is responsible for about 37% of deaths from diarrhea among children younger than 5 years of age worldwide, with a disproportionate effect in sub-Saharan Africa. *Methods:* We conducted a randomized, placebo-controlled trial in Niger to evaluate the efficacy of a live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India) to prevent severe rotavirus gastroenteritis. Healthy infants received three doses of the vaccine or placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis were assessed through active and passive surveillance and were graded on the basis of the score on the Vesikari scale (which ranges from 0 to 20, with higher scores indicating more severe disease). The primary end point was the efficacy of three doses of vaccine as compared with placebo against a first episode of laboratory-confirmed severe rotavirus gastroenteritis (Vesikari score, ≥11) beginning 28 days after dose 3. *Results:* Among the 3508 infants who were included in the per-protocol efficacy analysis, there were 31 cases of severe rotavirus gastroenteritis in the vaccine group and 87 cases in the placebo group (2.14 and 6.44 cases per 100 person-years, respectively), for a vaccine efficacy of 66.7% (95% confidence interval [CI], 49.9 to 77.9). Similar efficacy was seen in the intention-to-treat analyses, which showed a vaccine efficacy of 69.1% (95% CI, 55.0 to 78.7). There was no significant between-group difference in the risk of adverse events, which were reported in 68.7% of the infants in the vaccine group and in 67.2% of those in the placebo group, or in the risk of serious adverse events (in 8.3% in the vaccine group and in 9.1% in the placebo group); there were 27 deaths in the vaccine group and 22 in the placebo group. None of the infants had confirmed intussusception. *Conclusions:* Three doses of BRV-PV, an oral rotavirus vaccine, had an efficacy of 66.7%

against severe rotavirus gastroenteritis among infants in Niger. (Funded by Médecins sans Frontières Operational Center and the Kavli Foundation; ClinicalTrials.gov number, NCT02145000.).

Practical Radiation Oncology

Randy L. Wei et al., **Attitudes of radiation oncologists toward palliative and supportive care in the United States: report on national membership survey by the American Society for Radiation Oncology (ASTRO)**, *Pract Radiat Oncol* 7.2 (March–April 2017): 113–119, doi: 10.1016/j.prro.2016.08.017 • *Purpose:* Radiation oncologists are frequently involved in providing palliative and supportive care (PSC) for patients with advanced cancers through delivery of palliative radiation. Whether they are confident in their ability to assess and initiate treatments for pain, nonpain, and psychosocial distress is unknown. The American Society for Radiation Oncology surveyed its practicing members in the United States on self-assessment of their primary PSC skills and access to continuing medical education on PSC. *Methods:* We electronically surveyed 4093 practicing radiation oncologists in the United States. The survey consisted of 16-questions in 5 sections: demographics, PSC training, domains of PSC, perceived barriers as a radiation oncologist to initiate advanced care planning, and discussion of prognosis. *Results:* The survey was e-mailed to 4093 American Society for Radiation Oncology members, and 649 responses were received (response rate 16%). The majority (91%) of radiation oncologists surveyed believe PSC is an important competency for radiation oncologists. Most radiation oncologists reported that they are moderately confident in their ability to assess and manage pain and gastrointestinal symptoms, but less confident in their ability to manage anorexia, anxiety, and depression. Despite areas of decreased confidence, a large number (42%) of radiation oncologists do not receive any additional PSC education beyond their residency training. Lastly, a perceived fear of upsetting referring medical oncologists and lack of clinic time are concerns for radiation oncologists who may want to initiate goals of care/advance care planning discussions with patients and their families. *Conclusion:* Radiation oncologists are more confident in their ability to assess and manage pain than in their ability to manage depression, anxiety, anorexia, and fatigue. There is a need for increasing continuing medical educational efforts in PSC for practicing radiation oncologists, and strengthening PSC training in residency programs.