Medicine

Lord, thou hast been our dwelling place in all generations.

— Psalms 90[89]:1

As I prepared this column on recent progress in medicine and clinical research, I reflected on Psalm 90, a prayer of Moses the man of God. The recent US election has been divisive and has raised concerns about the future of health care, immigration, and the poor. One issue of special concern is the potential repeal and replacement of the Affordable Care Act, which provides health coverage to an estimated 16.4 million Americans.[1] Thanks to the ACA, many measures of health access inequality have steeply declined, especially for minorities and women. In all, the Congressional Budget Office estimates that 32 million people could lose coverage in the coming years because of the repeal of the ACA.[2] I hope that all of our leaders will reflect on the Golden Rule (Matt. 7:12) as they enact law, formulate policy, or govern by implementing policy.

The world celebrated the first feast of St. Teresa of Calcutta, who was a universal symbol of God's merciful love for the poor, on September 5, 2016, the day after her canonization by Pope Francis in Saint Peter's Square. I have found the example of this Nobel Prize–winning nun to be a beacon of hope, especially in these politically turbulent times. During the divisive US election, I was reminded that politics at its worst pits the interests of one group against another's; instead it should focus on meeting the universal needs of the human family and achieving the common good.

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1. Assistant Secretary for Public Affairs, "The Affordable Care Act Is Working," US Department of Health and Human Services (HHS), June 24, 2015, https://www.hhs.gov/.

2. Kate Fritzsche and Sarah Masi, "How Repealing Portions of the Affordable Care Act Would Affect Health Insurance Coverage and Premiums," Congressional Budget Office, January 2017, https://www.cbo.gov/.

Our leaders should heed Teresa's words: "Life is not worth living unless it is lived for others."[3]

Courageous efforts are being made to improve the human condition on a daily basis through science and medicine. Let us pray that some of the challenges reflected in the literature, especially those that affect the most vulnerable in society, will be addressed not only at the policy level, but by the physicians and allied professionals on the front line of health care who follow the example of St. Teresa of Calcutta on a daily basis.

Vaccines

On September 15, the *New England Journal of Medicine* reported the results of a phase III trial of a vaccine aimed at the prevention of shingles in adults older than seventy (ZOE-70).[4] The ZOE-70 study was sponsored by GlaxoSmithKline. Currently, individuals are immunized against zoster with a live attenuated herpes zoster vaccine (Zostavax, Merck) approved for use in adults fifty years of age or older but recommended for adults sixty years of age or older. The ground-breaking Shingles Prevention Study established that vaccination with Zostavax reduced the incidence of herpes zoster by more than 50 percent in the study population.[5] The present study investigated a potentially safer and more effective recombinant subunit vaccine containing VZV glycoprotein E and the AS01B adjuvant system (HZ/su, GlaxoSmithKline). This alternative to the live attenuated vaccine may be suitable for persons with suppressed immune responses, because it eliminates the risk of virus replication. It may also afford more effective protection from herpes zoster because of its specific immunogenicity. Although the immunologic basis for the HZ/su vaccine is not known, it is believed to induce T-helper cells (CD4 cells) with strong glycoprotein E–specific immune responses capable of directing the immune response when they detect zoster infection.[6]

Shingles is caused by the varicella zoster virus, which is also responsible for chickenpox. It is a member of the Herpesviridae family, along with the viruses that cause cold sores and genital herpes, and for this reason it is known as herpes zoster. Anyone who has had chickenpox may later develop shingles, because zoster, like other

3. Amy Ruth, *Mother Teresa* (Minneapolis, MN: Lerner Publications, 1999), 96.

4. Anthony L. Cunningham et al., "Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older," *New England Journal of Medicine* 375.11 (September 15, 2016): 1019–1032, doi: 10.1056/NEJMoa1603800. See also GlaxoSmithKline, "Study to Evaluate Efficacy, Safety and Immunogenicity of GlaxoSmithKline (GSK) Biologicals Herpes Zoster (HZ) Vaccine GSK1437173A in Adults Aged 70 Years or Older," NCT01165229 (July 15, 2010; updated June 29, 2016), https://clinicaltrials.gov/.

5. S.K. Tyring et al., "Safety and Tolerability of a High-Potency Zoster Vaccine in Adults ≥ 50 Years of Age," *Vaccine* 25.10 (February 26, 2007): 1877–1883, doi: 10.1016/j.vaccine.2006.10.027.

6. Ann M. Arvin, "Humoral and Cellular Immunity to Varicella-Zoster Virus: An Overview," *Journal of Infectious Diseases* 197 suppl 2 (March 1, 2008): S58–S60, doi: 10.1086/522123.

viruses in this family, has the ability to enter the nervous system and lie dormant for years, most often within the cell bodies of sensory neurons. The eventual reactivation of the virus manifests as shingles. Although shingles can occur anywhere on the body, it most often appears as a painful strip of blisters that wraps around either the left or the right side of the torso and follows the distribution of the affected nerve endings.[7] As an eye doctor, I often have to deal with the consequences of reactivation on the head and neck—sometimes an infection can even directly involve the tissues of the eye. The reason for the reactivation of the latent virus is unclear, but it may be due to lowered immunity, stress, or even local, minor trauma. Importantly, shingles is more common as we age. A majority of those affected by it are over the age of sixty. Vaccination with the currently approved live attenuated herpes zoster vaccine affords some protection, but this decreases within the first five years after vaccination; for this reason adults receiving the vaccine before age sixty might not be protected when their risk for shingles and its complications are greatest.[8] While shingles is not ordinarily a life-threatening condition, it can be very painful and leaves in its wake postherpetic neuralgia, a chronic painful hypersensitivity in the involved nerve endings. Furthermore, a person with shingles can pass the virus to anyone who is not immune to chickenpox. This is of special concern for anyone who has a weak immune system, such as newborns, pregnant women, and the immunocompromised, for example, individuals who are infected with HIV or undergoing cancer treatment. In most cases, an individual is no longer contagious once the blisters dry up and scab over.

A previous trial of zoster efficacy in adults fifty years of age or older (the ZOE-50 study) showed that the HZ/su has a vaccine efficacy against herpes zoster of 97.2 percent.[9] The ZOE-70 study expanded the data for adults who are seventy years of age or older and estimates the vaccine's efficacy against postherpetic neuralgia. The ZOE-70 study demonstrates mean vaccine efficacy against herpes zoster of 89.8 percent (95%CI, 84.2–93.7; $P<0.001$). While the Shingles Prevention Study demonstrated 67 percent vaccine efficacy against postherpetic neuralgia,[10] the ZOE-70 study demonstrated even greater protection against this long-term complication: 88.8 percent vaccine efficacy against postherpetic neuralgia in the pooled population of adults who were seventy years of age or older from the ZOE-50 and ZOE-70 studies. The long-term durability of this protection has yet to be reported. The mean follow-up of patients in the study was 3.7 years. The vaccine efficacy against herpes zoster remained 87.9 percent in the fourth year after vaccination, an insignificant decline.

7. Additional signs and symptoms of shingles may include pain, burning, itching, numbness or tingling, sensitivity to touch, a red rash followed by fluid-filled blisters that break open and crust over, and, in some people, fever, fatigue and headache.

8. "What Everyone Should Know about Shingles Vaccine," Centers for Disease Control and Prevention (CDC), November 22, 2016, https://www.cdc.gov/.

9. Himal Lal et al., "Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults," *New England Journal of Medicine* 372.22 (May 28, 2015):2087–2096, doi: 10.1056/NEJMoa1501184.

10. Tyring et al., "Safety and Tolerability of a High-Potency Zoster Vaccine," 1877–1883.

"Additional follow-up is required to assess the persistence of HZ/su-induced protection over a longer period," but the results are very promising.[11]

Nearly 80 million Americans—about one in four people—are currently infected with human papillomavirus (HPV).[12] Persistent infection with one of the high-risk serotypes of HPV is a key step in the pathogenesis of cervical cancer; at least 70 percent of cervical cancer cases and a majority of high-grade cervical intraepithelial neoplasia (CIN) are caused by HPV types 16 and 18, included in HPV vaccines.[13] Almost ten years of data indicate that the vaccines effectively prevent high-risk HPV infections.[14] With this knowledge, HPV vaccination programs have been implemented in many countries, and more than 175 million doses have been administered worldwide.[15] If prophylactic vaccination confers timely and lasting immunity, many cases of cervical cancer could be prevented and the lives of countless women saved.

A study of the effectiveness of the quadrivalent HPV vaccine in preventing high-grade cervical lesions was recently published in the *International Journal of Cancer*.[16] A team from the Karolinska Institutet in Stockholm and the Public Health Agency of Sweden's Department of Monitoring collected data from all pap smears administered in Sweden. They examined the effectiveness of the vaccination in the prevention of CIN based on the age at which the girls and women first received the vaccine, which is usually given as a series of three shots at least six months apart. The study stratified the data by the age at which the girls and young women received vaccination: (1) on or before their seventeenth birthday, (2) between ages seventeen and nineteen, or (3) between ages twenty and twenty-nine. This stratification roughly coincides with the age at which girls and women first become sexually active. Exposure to HPV is common and may even occur following sexual activity with the first

11. Injection-site and systemic reactions were mild to moderate in intensity, and their severity did not appear to increase significantly after the second dose.

12. "Human Papillomavirus (HPV)," CDC, last updated January 25, 2017, https://www.cdc.gov/hpv/.

13. F.X. Bosch et al., "Epidemiology and Natural History of Human Papillomavirus Infections and Type-Specific Implications in Cervical Neoplasia," *Vaccine* 26 suppl 10 (August 19, 2008): K1–K16, doi: 10.1016/j.vaccine.2008.05.064.

14. Cecilia M. Roteli-Martins et al., "Sustained Immunogenicity and Efficacy of the HPV-16/18 AS04-Adjuvanted Vaccine: Up to 8.4 Years of Follow-Up," *Human Vaccines and Immunotherapeutics* 8.3 (March 2012): 390–397, doi: 10.4161/hv.18865; and Paul S. Naud et al., "Sustained Efficacy, Immunogenicity, and Safety of the HPV-16/18 AS04-Adjuvanted Vaccine: Final Analysis of a Long-Term Follow-Up Study Up to 9.4 Years Post-Vaccination," *Human Vaccines and Immunotherapeutics* 10.8 (August 2014): 2147–2162, doi: 10.4161/hv.29532.

15. The vaccines were licensed in 2006. World Health Organization, "Global Advisory Committee on Vaccine Safety, 11–12 December 2013," *Weekly Epidemiological Record* 89.7 (February 14, 2014): 58.

16. Eva Herweijer et al., "Quadrivalent HPV Vaccine Effectiveness against High-Grade Cervical Lesions by Age at Vaccination: A Population-Based Study," *International Journal of Cancer* 138.12 (June 15, 2016): 2867–2874, doi: 10.1002/ijc.30035.

male sex partner.[17] Prevention of CIN should therefore be strongest if vaccination is given before the age at which sexual activity commences. In Sweden this averages around age sixteen.[18] This retrospective analysis shows that there is a reduction of approximately 75 percent in CIN (grades 2 or 3) if girls are vaccinated before age seventeen, compared to a 50 percent or 25 percent reduction for those initiating vaccination at ages seventeen through nineteen or at ages twenty through twenty-nine, respectively. These results argue strongly that prophylactic vaccination should be advocated in younger girls and women. The Swedish HPV "vaccination register is not totally complete and thus a small proportion of vaccinated individuals might have been misclassified as unvaccinated—potentially resulting in [an] underestimation of vaccine effectiveness." A highly effective vaccine may also contribute to herd immunity with a less-than-complete two- or three-dose series.

The sensitive nature by which a primary risk factor for cervical cancer is transmitted makes conversations about this particular vaccine especially difficult for some parents. On a policy level, stressing that the HPV vaccination is part of a universal and routine immunization schedule can remove much of the stigma that may follow from a vaccination related to a common and silent sexually transmitted infection. In October, the US Centers for Disease Control and Prevention (CDC) revised its recommendation so that eleven- and twelve-year-olds should only receive two doses of the HPV vaccine at least six months apart instead of the previously recommended three doses; older teens and adults who start the series later will continue to receive three doses.[19] The new guidelines from the CDC have also been endorsed by the American Cancer Society, which recommends that the vaccination be offered to both boys and girls between the ages of eleven and twelve, because HPV causes penile, anal, oropharyngeal, and other types of cancers.[20] Targeted communication strategies are needed to effectively address HPV vaccine hesitancy by focusing less on HPV exposure and more on the importance and effectiveness of routine cancer prevention.[21] Let us pray that through routine vaccination, as well as efforts to increase abstinence and reduce high-risk sexual behavior, we will be able to free the next generation from HPV infection and the associated risks of cancer.

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17. Rachel L. Winer et al., "Risk of Female Human Papillomavirus Acquisition Associated with First Male Sex Partner," *Journal of Infectious Diseases* 197.2 (January 15, 2008): 279–282, doi: 10.1086/524875.

18. Kirsten Egebjerg Jensen et al., "Women's Sexual Behavior. Population-Based Study among 65 000 Women from Four Nordic Countries before Introduction of Human Papillomavirus Vaccination," *Acta Obstetricia et Gynecologica Scandinavica* 90.5 (May 2011): 459–467, doi: 10.1111/j.1600-0412.2010.01066.x.

19. "CDC Recommends Only Two HPV Shots for Younger Adolescents," CDC, October 19, 2016, https://www.cdc.gov/.

20. Debbie Saslow et al., "Human Papillomavirus Vaccination Guideline Update: American Cancer Society Guideline Endorsement," *CA: Cancer Journal for Clinicians* 66.5 (September–October 2016): 375–385, doi: 10.3322/caac.21355.

21. Melissa B. Gilkey et al., "Parents Who Refuse or Delay HPV Vaccine: Differences in Vaccination Behavior, Beliefs, and Clinical Communication Preferences," *Human Vaccines and Immunotherapeutics*, e-pub October 20, 2016, doi: 10.1080/21645515.2016.1247134.

Health care workers ranging from doctors to orderlies have a higher annual rate of influenza infection compared to other working adults in the population (4.8 versus 3 percent).[22] Health care workers might not call in sick when infected with influenza, increasing the risk to patients, especially those in hospitals and long-term care institutions. Vaccination against influenza may reduce the duration and severity of infection, thereby decreasing its complications, such as lower respiratory tract infections, hospitalizations, and even death. In July 2102, the Joint Commission established an infection control requirement that all accredited organizations must operate an annual influenza vaccination program for their employees, including licensed independent practitioners and nonclinical staff.[23] However, the voluntary uptake of influenza vaccination among health care workers is generally low; increasingly, vaccination is a requirement imposed on them out of an actual or perceived duty to protect the patients under their care.[24] However, little evidence exists that this commonsense measure actually leads to better patient outcomes.

A systematic review of the evidence for influenza vaccination among health care workers who care for people aged sixty or older in long-stay hospital wards and nursing homes was recently published by the Cochrane Group.[25] The review did not find any conclusive evidence that health-care-worker vaccination programs confer benefits on people over the age of sixty who live in long-term care institutions in terms of specific outcomes of laboratory-proven influenza, its complications, or all causes of mortality. The study did not evaluate the potential confounding role of co-interventions, such as "hand-washing, face masks, early detection of laboratory-proven influenza, quarantine, avoiding admissions, antivirals and asking health care workers with influenza or influenza-like illness" to absent themselves from the workplace. By blunting the severity of influenza infection, it is also possible that some cases of flu among vaccinated health care workers were missed, or that vaccinated workers remained on the job with subclinical infections, thereby abrogating some of the benefits of their vaccination. In summary, there is no high-quality, level-I evidence that vaccinating health care workers benefits individuals who live in long-term care institutions. By contrast, vaccinating residents of long-stay hospital wards and nursing homes is a well-established practice producing positive results.[26] Nevertheless, the

22. Stefan P. Kuster et al., "Incidence of Influenza in Healthy Adults and Healthcare Workers: A Systematic Review and Meta-Analysis," *PLoS One* 6.10 (October 18, 2011), e26239, doi: 10.1371/journal.pone.0026239.

23. Joint Commission, "Influenza Vaccination for Licensed Independent Practitioners and Staff," *R3 Report*, May 30, 2012, http://www.jointcommission.org/.

24. J. J. M. van Delden et al., "The Ethics of Mandatory Vaccination against Influenza for Health Care Workers," *Vaccine* 26.44 (October 16, 2008): 5562–5566, doi: 10.1016/j .vaccine.2008.08.002.

25. R. E. Thomas, T. Jefferson, and T. J. Lasserson, "Influenza Vaccination for Healthcare Workers Who Care for People Aged 60 or Older Living in Long-Term Care Institutions," *Cochrane Database of Systematic Reviews* 6 (June 2, 2016): CD005187, doi: 10.1002/14651858.CD005187.pub5.

26. Aurora Pop-Vicas et al., "Estimating the Effect of Influenza Vaccination on Nursing Home Residents' Morbidity and Mortality," *Journal of the American Geriatrics Society* 63.9

reduced morbidity associated with influenza infection among vaccinated health care workers, as well as the reduction in worker productivity, may justify this intervention. Health care workers should also set a good example for their patients by availing themselves of the influenza vaccine when possible.

Newborn Screening and Laboratory Medicine

In August, *JAMA* published a preliminary report on the utility of RNA biosignatures for detecting serious and potentially life-threatening bacterial infections in febrile infants.[27] From December 2008 to December 2010, a cohort comprising babies sixty days of age or younger was selected from twenty-two emergency departments, evaluated for fever (temperature > 38° C), and subjected to laboratory evaluations, including blood cultures. Consent was given by the parents to allow the investigators to perform microarray analyses of RNA expressed by blood leukocytes present in the blood drawn at the time of evaluation. The parents of 2,820 febrile infants were approached, and roughly two-thirds gave consent to participate in the study. Of these, fewer than one hundred samples from patients with culture-proven bacterial infections were included in the present analysis (thirty-three infants with bacteremia and fifty-eight with urinary tract infections). These results were compared to around two hundred children without bacterial infection, more than half of whom had enteroviral or influenza infections. Twenty-five healthy afebrile infants were also enrolled as controls. Bioinformatics tools were used to characterize the RNA gene expression patterns, generating biosignatures that classified the febrile infants by infection type.

The expression of sixty-six genes were identified that distinguished infants with and without bacterial infections (87 percent sensitivity and 89 percent specificity), and a further ten genes distinguished infants with bacteremia from those without bacterial infections (94 percent sensitivity and 95 percent specificity). Notably, the RNA biosignature was far more predictive of bacterial infection than clinical examination was. Compared to the Yale Observation Scale (YOS) for prediction of bacteremia in febrile children, a commonly used observational tool by pediatrician and emergency departments, the RNA biosignature had a concordance statistic of 0.89 compared to 0.53 for the YOS.[28] Furthermore, the RNA biosignature is far more specific for actual bacterial infection than the YOS is, which must be interpreted with caution because of a host of external influences that can worsen the overall clinical appearance of a febrile child.

(September 2015): 1798–1804, doi: 10.1111/jgs.13617.

27. Prashant Mahajan et al., "Association of RNA Biosignatures with Bacterial Infections in Febrile Infants Aged 60 Days or Younger," *JAMA* 316.8 (August 23, 2016): 846–857, doi: 10.1001/jama.2016.9207.

28. Paul L. McCarthy et al., "Observation Scales to Identify Serious Illness in Febrile Children," *Pediatrics* 70.5 (November 1982): 802–209. The Yale Observation Scale (YOS) for prediction of bacteremia in febrile children consists of six observational items that have been validated to detect serious illness in young children (<24 months) with fevers. It is simple, quick, easy to apply, and cost-effective, as it does not contain investigational items. The C (concordance) statistic is a measure of goodness of fit for a binary outcome in a logistic regression model.

The authors have demonstrated a proof of concept that RNA biosignatures are capable of identifying children who present with fevers caused by bacterial infections. However, many limitations need to be considered before this new technology can be implemented in clinical practice. The large number of samples collected compared to the number presented in the preliminary analysis suggests that there are many laboratory and logistical limitations to the use of this tool. At present, it takes at least twenty-four hours to process an RNA biosignature sample. In an emergency setting, this turnaround is not likely to be fast enough to obviate the need for empiric antibiotic treatment of a very sick child. Handling RNA, a very fragile substrate, is far more difficult than processing a specimen for routine culture, which is the gold standard for detecting a bacterial infection. The cost of operating a molecular biology diagnostic laboratory, in terms of both resources and personnel, is not insignificant. Although frozen samples can be processed off site, this technique will most likely be limited to the best-equipped medical centers, which can afford to operate a fully automated facility on site. Furthermore, patients who screen negative with this test may still have cultures sent at the time of evaluation, and for those who screen positive, culture results would remain just as important for clinicians to properly adjust antimicrobial therapy. As this technology matures, perhaps even allowing for the rapid identification of the pathogen based on host response, molecular diagnostic approaches may find their way into clinical medicine.

Another study looking at the application of RNA biosignatures was published in the June 2016 issue of *Lancet*.[29] A multinational group in the field of infectious disease looked at whole blood RNA expression patterns to detect signals that could predict which patients were likely to convert from latent *Mycobacterium tuberculosis* infection to active tuberculosis (TB). Although a third of the world's population is infected with *M. tuberculosis,* a majority of infected individuals remain healthy, with little or no risk of transmitting the disease; only a small percentage develop TB during their lifetimes.[30] The risk of progression is associated with aging, comorbid diseases, such as diabetes mellitus or HIV, depressed socioeconomic status, institutionalization or incarceration, and nutritional compromise.[31] Current assays for detecting *M. tuberculosis* infection, such as interferon gamma release assay or tuberculin skin test, cannot predict which infected individuals will develop active TB. Clinical monitoring of infected individuals is imperfect, and delayed detection may lead to increased morbidity, mortality, and the spread of the disease.

The *Lancet* study was a large prospective cohort study that included adolescents aged twelve through eighteen years from the South African Adolescent Cohort

29. Daniel E. Zak et al., "A Blood RNA Signature for Tuberculosis Disease Risk: A Prospective Cohort Study," Lancet 387.10035 (June 4, 2016): 2312–2322, doi: 10.1016/S0140-6736.

30. "Global Tuberculosis Report 2016," World Health Organization, accessed January 20, 2017, http://www.who.int/.

31. Rupak Shivakoti et al., "Association of HIV Infection with Extrapulmonary Tuberculosis: A Systematic Review," Infection, e-pub November 9, 2016, doi: 10.1007/s15010-016-0960-5.

Study (ACS). The research was funded by the Bill and Melinda Gates Foundation, the US National Institutes of Health, the South African Medical Research Council, and others. Blood samples from adolescents infected with *M. tuberculosis* were taken at six-month intervals for a period of two years. All adolescents gave their assent to enroll in the trial, and parents or legal guardians provided written informed consent. RNA sequencing data compared participants who developed TB (progressors) with those who remained healthy (matched controls) in a 2:1 ratio. TB was defined as intrathoracic disease, with either two sputum smears positive for acid-fast bacilli or one sputum culture confirmed as positive for *M. tuberculosis* complex.

The expression of a sixteen-gene signature of risk was identified in whole blood RNA within the twelve months preceding diagnosis with TB. The predictive value of this pattern of gene expression was assessed by using an independent cohort sample obtained from the Grand Challenges 6-74 Study—a group of HIV-negative individuals aged ten through sixty years who had household exposure to an adult with sputum smear positive for tuberculosis—as well as from additional cases in the ACS not included in the development of the RNA biosignature profile. The resulting assay had a sensitivity of 66.1 percent and specificity of 80.6 percent for identifying TB in the twelve months preceding diagnosis. These results suggest that RNA biosignatures could be used to enhance clinical surveillance. Additional prospective research is needed to determine if a positive screening result can be used by clinicians to initiate treatment to prevent TB among the highest-risk individuals and settings. Furthermore, as RNA expression levels may be influenced by numerous host factors, any RNA biosignature approach would need to be validated for each population-based application.

Preventive Health

The US Preventive Services Task Force recently published guidelines for the use of lipid screening in children and adolescents.[32] Cholesterol and triglyceride levels are checked primarily to identify abnormalities that if addressed might reduce primarily cardiovascular outcomes, such as the rate of heart attack or stroke, though other benefits may also follow. The authors conclude that "the diagnostic yield of lipid screening varies by age and body mass index. No direct evidence was identified for benefits or harms of childhood screening or treatment on outcomes in adulthood."[33] Apart from children with inherited disorders related to blood lipid levels and specific conditions in which blood lipid levels have been shown to play a role in morbidity and mortality, such as diabetes, the screening of younger individuals is of questionable benefit. The authors provide an extensive review of the literature and identify several studies that highlight the limited role of lipid screening for adolescents. One of these studies is the Dietary Intervention Study in Children, randomized clinical trial in 663 children aged eight to ten years with mild to moderate dyslipidemia (LDL-C

32. Paul Lozano et al., "Lipid Screening in Childhood and Adolescence for Detection of Multifactorial Dyslipidemia: Evidence Report and Systematic Review for the US Preventive Services Task Force," *JAMA* 16.6 (August 9, 2016): 634–644, doi: 10.1001/jama.2016.6423.

33. Ibid., 634.

between the eightieth and ninety-eighth percentiles for age and sex).[34] This multiyear study shows that short-term, intensive dietary interventions can reduce blood lipid levels without affecting nutritional status, growth, and development in these age groups. However, the clinical significance of any changes was indeterminate, and the effect of the dietary intervention dissipated by year five of the study. The authors also highlight an observational study based on data from the National Health and Nutrition Examination Survey in children and young adults aged twelve to thirty-nine years (n=9,245), which found that blood lipid levels had no association with death before age fifty-five.[35] The US Preventive Services Task Force is relatively conservative when it comes to making recommendations and therefore does not suggest that clinicians routinely offer such screening to their patients.

Adult Stem Cell Therapy

Heart failure occurs when the heart muscle cannot pump blood as well as it should. Nearly 5.7 million adults in the United States are currently living with congestive heart failure (CHF), and about half of people who develop heart failure die within five years of diagnosis.[36] CHF affects people of all ages, from children and young adults to the middle aged and the elderly. CHF has many causes, including high blood pressure and coronary artery disease, but unexpected cardiotoxicity from medications has become an increasing concern. Despite strict FDA guidelines for studies that evaluate potential cardiac toxicity ahead of drug approval, many medications enter the market but are later labeled with warnings or withdrawn outright owing to cardiac toxicity. This accounts for almost a third of drug withdrawals.[37] Developing better preclinical assays could help to protect patients and reduce overall drug development costs.

Cardiomyocytes derived from human pluripotent stem cells (hPSC-CMs) are one of the most promising mechanisms for treating CHF and predicting cardiotoxicity. However, the ability of hPSC-CMs to recapitulate the effects of drugs in vivo "contrasts from failure to almost total success." One of the bottlenecks in this new era of safety pharmacology is the ability to differentiate hPSCs-CMs. An important article by Chris Denning and his colleagues in the United Kingdom reviews the advances in differentiating and characterizing hPSCs-CMs.[38]

34. "National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents," *Pediatrics* 89.3 (March 1992): 495–501.

35. Sharon Saydah et al., Cardiometabolic Risk Factors among US Adolescents and Young Adults and Risk of Early Mortality," *Pediatrics* 131.3 (March 2013): e679–e689, doi: 10.1542/peds.2012-2583.

36. "Heart Failure Fact Sheet," CDC, updated June 16, 2016, https://www.cdc.gov/.

37. Judith K. Gwathmey, Ktya Tsaioun, and Roger J. Hajjar, "Cardionomics: A New Integrative Approach for Screening Cardiotoxicity of Drug Candidates," *Expert Opinion on Drug Metabolism and Toxicology* 5.6 (June 2009): 647–660, doi: 10.1517/17425250902932915.

38. Chris Denning et al., "Cardiomyocytes from Human Pluripotent Stem Cells: From Laboratory Curiosity to Industrial Biomedical Platform," *Biochimica et Biophysica Acta* 1863.7 pt B (July 2016): 1728–1748, doi: 10.1016/j.bbamcr.2015.10.014.

Organ Donation and Transplantation

One of the great successes of modern medicine has been the development of organ transplantation for the treatment of human disease. Nobel Laureate Joseph Murray performed the first successful kidney transplant in Boston in 1954; now more than thirty thousand transplants are now performed every year in the United States.[39] Remaining in the shadow of this success are the numerous lives that could be saved if there were not such an acute shortage of organs. In the United States alone, more than 119,000 people are on transplant waiting lists, and twenty-two people die each day, waiting for an organ.[40] Efforts to increase the number of available organs include live donation, split-organ donation, and the use of paired donor exchanges,[41] but the failure of more individuals to register as donors remains one of the greatest limitations. Although about 95 percent of Americans support organ donation, less than half have actually signed up as donors. Each donor can greatly improve the frequency of life-saving transplants and affect up to eight lives. More successful transplants are being performed today, in fact, despite a lower number of donors.[42]

Although the organ shortage affects all ethnic groups, it is more pronounced in minority populations. An article in the June issue of *Progress in Transplantation* highlights the potential for community engagement to enhance new organ donor registrations in a predominantly Spanish-speaking, Hispanic community.[43] There is a growing appreciation that prospective donors require not only an immediate and complete registration opportunity (ICRO) but motivational information, focused engagement, and favorable activation (IIFF) to encourage registration. A majority of registrations occur through a state's department of motor vehicles, and frustrating experiences at the DMV may result in significantly fewer enrollments.[44]

The present study staged registration interventions at two Mexican consulates in New Mexico. The results show that when all four components of the IIFF model are present, there is a substantial increase in the number of new organ donor registrations: approximately four registrations per day compared to approximately one registration

39. Dr. Murray shared the 1990 Nobel Prize in Physiology or Medicine with Donnall Thomas for their work in cell and organ transplantation.

40. "Organ Donation Statistics," HHS, accessed January 23, 2017, https://www.organdonor.gov/.

41. A better match can greatly enhance the outcome of a transplantation, and organ donor exchanges allow for optimal matching of available organs with those in need of transplants. In 2012, Alvin Roth and Lloyd Shapley shared the Nobel Prize in economics for their work in market design and matching theory, which has been instrumental in the success of these exchanges.

42. "Organ Donation Statistics," HHS.

43. Jason T. Siegel et al., "The Potential (F)utility of a Passive Organ Donor Registration Opportunity: A Conceptual Replication," *Progress in Transplantation* 26.2 (June 2016): 103–108, doi: 10.1177/1526924816641814.

44. Jason T. Siegel et al., "Anger, Frustration, Boredom and the Department of Motor Vehicles: Can Negative Emotions Impede Organ Donor Registration?" *Social Science and Medicine* 153 (March 2016): 174–181, doi: 10.1016/j.socscimed.2016.02.013.

every fifteen days when only an ICRO was present. Adding a health educator and providing Spanish-language information designed to dispel common myths about the donation process led to significantly greater engagement and follow-through in the target population.

Each year the number of people on transplant waiting lists continues to grow more rapidly than the numbers of donors and transplants. I myself am a registered organ donor, and I encourage readers to register as organ donors as well. Many states and the District of Columbia allow individuals to sign up online or in person at a local DMV office.[45]

Another article in the June issue of *Progress in Transplantation*, by Kathleen Gali and her colleagues, highlights the effects of smoking status on mortality among people on the waiting list for heart transplantation.[46] Heart transplantation is considered the gold standard treatment for advanced heart failure, but it is available for only a minority of patients because of the paucity of donor hearts. The number of transplant centers has increased, and the criteria for transplant recipients have been broadened—to include patients sixty-five years of age or older, those with a body mass index greater than thirty, and those with more comorbid conditions, such as diabetes mellitus and a history of smoking—but the number of hearts available for transplant has not kept pace.[47]

There is a clear survival benefit from transplantation for patients listed for heart transplantation in the United States,[48] and medical urgency is the primary determinant for the allocation of solid organs.[49] Perhaps not surprisingly, the article by Gali et al. shows that smoking at the time of listing may increase a person's risk of mortality during the waiting period, and "the relationship between smoking and mortality risk appeared to follow a dose-dependent pattern."[50] Although smoking cessation is required prior to listing for cardiac transplantation, some patients begin smoking again after recovery. In one study, in fact, more than a quarter of patients tested positive for active smoking at some point after cardiac transplant.[51] Although improved strategies for achieving smoking cessation as early as possible before

45. "Sign Up to Be an Organ Donor," HHS, accessed January 23, 2017, https://www.organdonor.gov/.

46. Kathleen Gali et al., "Smoking Status at Time of Listing for a Heart Transplant Predicts Mortality on the Waiting List: A Multicenter Prospective Observational Study," *Progress in Transplantation* 26.2 (June 2016): 117–121, doi: 10.1177/1526924816640687.

47. Lynne Warner Stevenson, "Crisis Awaiting Heart Transplantation: Sinking the Lifeboat," *JAMA Internal Medicine* 175.8 (August 2015): 1406–1409, doi: 10.1001/jamainternmed.2015.2203.

48. Tajinder P. Singh et al., "Survival Benefit from Transplantation in Patients Listed for Heart Transplantation in the United States," *Journal of the American College of Cardiology* 63.12 (April 1, 2014): 1169–1178, doi: 10.1016/j.jacc.2013.11.045.

49. HHS, "Organ Procurement and Transplantation Network," 42 CFR §121 (2011).

50. Gali et al., "Smoking Status at Time of Listing," 117.

51. P. Botha et al., "Smoking after Cardiac Transplantation," *American Journal of Transplantation* 8.4 (April 2008): 866–871, doi: 10.1111/j.1600-6143.2007.02119.x.

heart transplantation could reduce the morbidity and mortality associated with this behavior, the high incidence of relapse among smokers remains a concern, and the expanding eligibility criteria may disadvantage long-term nonsmokers, whose projected survival exceeds that of recipients who resume smoking after transplantation.

Fertility and Reproduction

More than 1 percent of all babies born in the United States are conceived with some form of assisted reproductive technology, as are nearly 2 to 5 percent of all babies born in Europe.[52] Fertility treatments may be linked to certain forms of cancer in the mother because of hormone exposures—a logical concern given that it is well established that estrogen and progesterone can increase the risk of some cancers, including breast cancer.[53]

In the July issue of *JAMA*, a large historic cohort study compared the risk of breast cancer in the general population and in a large cohort of nearly twenty thousand women who underwent fertility treatment in the Netherlands between 1980 and 1995.[54] Breast cancer risk did not differ significantly between the general population and the women who used IVF. The findings of this study contrast with those of other large cohort studies—for example, one performed by Marte Reigstad et al. of women who underwent IVF in Norway between 1983 and 2010.[55] Strengths of the *JAMA* study include the large cohort and the population-based follow-up provided by access to the Netherlands Cancer Registry. An important limitation pointed out by the authors is that the IVF regimens used before 1995 differ from those currently in use in the Netherlands. Future studies should examine a more recent cohort to determine whether modern IVF techniques carry a similar level of risk.

David J. Ramsey, MD

52. A. P. Ferraretti et al., "Assisted Reproductive Technology in Europe, 2009: Results Generated from European Registers by ESHRE," *Human Reproduction* 28.9 (September 2013): 2313–2331, doi: 10.1093/humrep/det278.

53. "Carcinogenicity of Combined Hormonal Contraceptives and Combined Menopausal Treatment," UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), September 2005, http://www.who.int/.

54. Alexandra W. van den Belt-Dusebout et al., "Ovarian Stimulation for In Vitro Fertilization and Long-Term Risk of Breast Cancer," *JAMA* 316.3 (July 19, 2016): 300, doi: 10.1001/jama.2016.9389.

55. Marte Myhre Reigstad et al., "Risk of Breast Cancer following Fertility Treatment: A Registry-Based Cohort Study of Parous Women in Norway," *International Journal of Cancer* 136.5 (March 1, 2015): 1140–1148, doi: 10.1002/ijc.29069.

Medicine Abstracts

AIDS Care

D. B. Garfinkel et al., **Predictors of HIV-related risk perception and PrEP acceptability among young adult female family planning patients,** *AIDS Care*, e-pub September 29, 2016, 1–8, doi: 10.1080/09540121.2016.1234679 • HIV pre-exposure prophylaxis (PrEP) presents new opportunities for HIV prevention. While women comprise approximately 20% of new HIV infections in the US, significant questions remain about how to most effectively facilitate PrEP uptake for this population. Family planning clinics are a dominant source of health care for young women and support an estimated 4.5 million women annually. We explore characteristics associated with HIV risk perception and PrEP acceptability among young adult women seeking reproductive health services in a high-prevalence setting. A cross-sectional, clinic-based survey was conducted with women ages 18-35 (n = 146) seeking health care at two family planning clinics in the greater Baltimore, Maryland area, from January to April 2014. An estimated 22% of women reported being worried about HIV risk, and 60% reported they would consider taking a pill daily to prevent HIV. In adjusted models, HIV-related worry was associated with having no college education, being single or dating more than one person, practicing consistent condom use during vaginal sex, and having ever traded sex. PrEP acceptability was significantly associated with being Black (71% vs. 49%, AOR 2.23, CI: 1.89-2.64) and having ever traded sex (83% vs. 58%, AOR 4.94, CI: 2.00-12.22). For women with a history of intimate partner violence (IPV), PrEP acceptability was significantly lower (57% vs. 62%, AOR .71, CI: .59-.85) relative to their non-abused counterparts. Results suggest that family planning clinics may be a natural setting for PrEP discussion and roll-out. They should be considered in the context of integrating HIV prevention with reproductive health services. Women with a trauma history may need additional support for implementing HIV prevention in the form of PrEP.

Biochimica et Biophysica Acta

C. Denning et al., **Cardiomyocytes from human pluripotent stem cells: From laboratory curiosity to industrial biomedical platform**, *Biochim Biophys Acta* 1863.7 pt B (July 2016): 1728–1748, doi: 10.1016/j.bbamcr.2015.10.014 • Cardiomyocytes from human pluripotent stem cells (hPSCs-CMs) could revolutionise biomedicine. Global burden of heart failure will soon reach USD $90bn, while unexpected cardiotoxicity underlies 28% of drug withdrawals. Advances in hPSC isolation, Cas9/CRISPR genome engineering and hPSC-CM differentiation have improved patient care, progressed drugs to clinic and opened a new era in safety pharmacology. Nevertheless, predictive cardiotoxicity using hPSC-CMs contrasts from failure to almost total success. Since this likely relates to cell immaturity, efforts are underway to use biochemical and biophysical cues to improve many of the ~30 structural and functional properties of hPSC-CMs towards those seen in adult CMs. Other developments needed for widespread hPSC-CM utility include subtype specification, cost reduction of large scale differentiation and elimination of the phenotyping bottleneck. This review will consider these factors in the evolution of hPSC-CM technologies, as well as their integration into high content industrial platforms that assess structure, mitochondrial function, electrophysiology, calcium transients and contractility. This article is part of a Special Issue entitled: *Cardiomyocyte Biology: Integration of Developmental and Environmental Cues in the Heart* edited by Marcus Schaub and Hughes Abriel.

Cochrane Database of Systematic Reviews

R.E. Thomas, T. Jefferson, and T.J. Lasserson, **Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions,** *Cochrane Database Syst Rev* 6 (June 2, 2016): CD005187, doi: 10.1002/14651858.CD005187.pub5 • *Background:* A systematic review found that 3% of working adults who had received influenza vaccine and 5% of those who were unvaccinated had laboratory-proven influenza per season; in healthcare workers (HCWs) these percentages were 5% and 8% respectively. Healthcare workers may transmit influenza to patients. *Objectives:* To identify all randomised controlled trials (RCTs) and non-RCTs assessing the effects of vaccinating healthcare workers on the incidence of laboratory-proven influenza, pneumonia, death from pneumonia and admission to hospital for respiratory illness in those aged 60 years or older resident in long-term care institutions (LTCIs). *Search methods:* We searched CENTRAL (2015, Issue 9), MEDLINE (1966 to October week 3, 2015), EMBASE (1974 to October 2015) and Web of Science (2006 to October 2015), but Biological Abstracts only from 1969 to March 2013 and Science Citation Index-Expanded from 1974 to March 2013 due to lack of institutional access in 2015. *Selection criteria:* Randomised controlled trials (RCTs) and non-RCTs of influenza vaccination of healthcare workers caring for individuals aged 60 years or older in LTCIs and the incidence of laboratory-proven influenza and its complications (lower respiratory tract infection, or hospitalisation or death due to lower respiratory tract infection) in individuals aged 60 years or older in LTCIs. *Data collection and analysis:* Two authors independently extracted data and assessed risk of bias. Effects on dichotomous outcomes were measured as risk differences (RDs) with 95% confidence intervals (CIs). We assessed the quality of evidence with GRADE. *Main results:* We identified four cluster-RCTs and one cohort study (n = 12,742) of influenza vaccination for HCWs caring for individuals ≥ 60 years in LTCIs. Four cluster RCTs (5896 residents) provided outcome data that addressed the objectives of our review. The studies were comparable in their study populations, intervention and outcome measures. The studies did not report adverse events. The principal sources of bias in the studies related to attrition, lack of blinding, contamination in the control groups and low rates of vaccination coverage in the intervention arms, leading us to downgrade the quality of evidence for all outcomes due to serious risk of bias. Offering influenza vaccination to HCWs based in long term care homes may have little or no effect on the number of residents who develop laboratory-proven influenza compared with those living in care homes where no vaccination is offered (RD 0 (95% CI -0.03 to 0.03), two studies with samples taken from 752 participants; low quality evidence). HCW vaccination probably leads to a reduction in lower respiratory tract infection in residents from 6% to 4% (RD -0.02 (95% CI -0.04 to 0.01), one study of 3400 people; moderate quality evidence). HCW vaccination programmes may have little or no effect on the number of residents admitted to hospital for respiratory illness (RD 0 (95% CI -0.02 to 0.02, one study of 1059 people; low quality evidence). We decided not to combine data on deaths from lower respiratory tract infection (two studies of 4459 people) or all cause deaths (four studies of 8468 people). The direction and size of difference in risk varied between the studies. We are uncertain as to the effect of vaccination on these outcomes due to the very low quality of evidence. Adjusted analyses, which took into account the cluster design, did not differ substantively from the pooled analysis with unadjusted data. *Authors' conclusions:* Our review findings have not identified conclusive evidence of benefit of HCW vaccination programmes on specific outcomes of laboratory-proven influenza, its complications (lower respiratory tract infection, hospitalisation or death due to lower respiratory tract illness), or all cause mortality in people over the age of 60 who live in care institutions. This review did not find information on co-interventions with healthcare worker vaccination: hand-washing, face

masks, early detection of laboratory-proven influenza, quarantine, avoiding admissions, antivirals and asking healthcare workers with influenza or influenza-like illness (ILI) not to work. This review does not provide reasonable evidence to support the vaccination of healthcare workers to prevent influenza in those aged 60 years or older resident in LTCIs. High quality RCTs are required to avoid the risks of bias in methodology and conduct identified by this review and to test further these interventions in combination.

European Journal of Contraception and Reproductive Health Care

E. Berglund Scherwitzl et al., **Fertility awareness-based mobile application for contraception,** *Eur J Contracept Reprod Health Care* 21.3 (June 2016): 234–241, doi: 10.3109/13625187.2016.1154143 • *Objectives:* The aim of the study was to retrospectively evaluate the effectiveness of a fertility awareness-based method supported by a mobile-based application to prevent unwanted pregnancies as a method of natural birth control. *Methods:* In a retrospective analysis, the application's efficiency as a contraceptive method was examined on data from 4054 women who used the application as contraception for a total of 2085 woman-years. *Results:* The number of identified unplanned pregnancies was 143 during 2053 woman-years, giving a Pearl Index of 7.0 for typical use. Ten of the pregnancies were due to the application falsely attributing a safe day within the fertile window, producing a perfect-use Pearl Index of 0.5. Calculating the cumulative pregnancy probability by life-table analysis resulted in a pregnancy rate of 7.5% per year (95% confidence interval 5.9%, 9.1% per year). *Conclusions:* The application appears to improve the effectiveness of fertility awareness-based methods and can be used to prevent pregnancies if couples consistently protect themselves on fertile days.

International Journal of Cancer

E. Herweijer et al., **Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study,** *Int J Cancer* 138.12 (June 15, 2016): 2867–2874, doi: 10.1002/ijc.30035 • Human papillomavirus (HPV) types 16/18, included in HPV vaccines, contribute to the majority of cervical cancer, and a substantial proportion of cervical intraepithelial neoplasia (CIN) grades 2/3 or worse (CIN2+/CIN3+) including adenocarcinoma in situ or worse. The aim of this study was to quantify the effect of quadrivalent HPV (qHPV) vaccination on incidence of CIN2+ and CIN3+. A nationwide cohort of girls and young women resident in Sweden 2006–2013 and aged 13–29 (n=1,333,691) was followed for vaccination and histologically confirmed high-grade cervical lesions. Data were collected using the Swedish nationwide healthcare registers. Poisson regression was used to calculate incidence rate ratios (IRRs) and vaccine effectiveness [(1-IRR) x100%] comparing fully vaccinated with unvaccinated individuals. IRRs were adjusted for attained age and parental education, and stratified on vaccination initiation age. Effectiveness against CIN2+ was 75% (IRR=0.25, 95%CI=0.18–0.35) for those initiating vaccination before age 17, and 46% (IRR=0.54, 95%CI=0.46–0.64) and 22% (IRR=0.78, 95%CI=0.65–0.93) for those initiating vaccination at ages 17–19 and at ages 20–29, respectively. Vaccine effectiveness against CIN3+ was similar to vaccine effectiveness against CIN2+. Results were robust for both women participating to the organized screening program and for women at prescreening ages. We show high effectiveness of qHPV vaccination on CIN2+ and CIN3+ lesions, with greater effectiveness observed in girls younger at vaccination initiation. Continued monitoring of impact of HPV vaccination in the population is needed in order to evaluate both long-term vaccine effectiveness and to evaluate whether the vaccination program achieves anticipated effects in prevention of invasive cervical cancer.

JAMA

S.S. Carson et al., **Effect of palliative care-led meetings for families of patients with chronic critical illness: A randomized clinical trial,** *JAMA* 316.1 (July 5, 2016): 51–62,

doi: 10.1001/jama.2016.8474 • *Importance:* Family caregivers of patients with chronic critical illness experience significant psychological distress. *Objective:* To determine whether family informational and emotional support meetings led by palliative care clinicians improve family anxiety and depression. *Design, setting, and participants:* A multicenter randomized clinical trial conducted from October 2010 through November 2014 in 4 medical intensive care units (ICUs). Adult patients (aged ≥21 years) requiring 7 days of mechanical ventilation were randomized and their family surrogate decision makers were enrolled in the study. Observers were blinded to group allocation for the measurement of the primary outcomes. *Interventions:* At least 2 structured family meetings led by palliative care specialists and provision of an informational brochure (intervention) compared with provision of an informational brochure and routine family meetings conducted by ICU teams (control). There were 130 patients with 184 family surrogate decision makers in the intervention group and 126 patients with 181 family surrogate decision makers in the control group. *Main outcomes and measures:* The primary outcome was Hospital Anxiety and Depression Scale symptom score (HADS; score range, 0 [best] to 42 [worst]; minimal clinically important difference, 1.5) obtained during 3-month follow-up interviews with the surrogate decision makers. Secondary outcomes included posttraumatic stress disorder experienced by the family and measured by the Impact of Events Scale-Revised (IES-R; total score range, 0 [best] to 88 [worst]), discussion of patient preferences, hospital length of stay, and 90-day survival. *Results:* Among 365 family surrogate decision makers (mean age, 51 years; 71% female), 312 completed the study. At 3 months, there was no significant difference in anxiety and depression symptoms between surrogate decision makers in the intervention group and the control group (adjusted mean HADS score, 12.2 vs 11.4, respectively; between-group difference, 0.8 [95% CI, -0.9 to 2.6]; P=.34). Posttraumatic stress disorder symptoms were higher in the intervention group (adjusted mean IES-R score, 25.9) compared with the control group (adjusted mean IES-R score, 21.3) (between-group difference, 4.60 [95% CI, 0.01 to 9.10]; P=.0495). There was no difference between groups regarding the discussion of patient preferences (intervention, 75%; control, 83%; odds ratio, 0.63 [95% CI, 0.34 to 1.16; P=.14]). The median number of hospital days for patients in the intervention vs the control group (19 days vs 23 days, respectively; between-group difference, -4 days [95% CI, -6 to 3 days]; P=.51) and 90-day survival (hazard ratio, 0.95 [95% CI, 0.65 to 1.38], P=.96) were not significantly different. *Conclusions and relevance:* Among families of patients with chronic critical illness, the use of palliative care-led informational and emotional support meetings compared with usual care did not reduce anxiety or depression symptoms and may have increased posttraumatic stress disorder symptoms. These findings do not support routine or mandatory palliative care-led discussion of goals of care for all families of patients with chronic critical illness. *Trial registration:* clinicaltrials.gov identifier: NCT01230099.

P. Lozano et al., **Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: Evidence report and systematic review for the US Preventive Services Task Force,** *JAMA* 316.6 (August 9, 2016): 634–644, doi: 10.1001/jama.2016.6423 • *Importance:* Multifactorial dyslipidemia, characterized by elevated total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), is associated with dyslipidemia and markers of atherosclerosis in young adulthood. Screening for dyslipidemia in childhood could delay or reduce cardiovascular events in adulthood. *Objective:* To systematically review the evidence on benefits and harms of screening adolescents and children for multifactorial dyslipidemia for the US Preventive Services Task Force (USPSTF). *Data sources:* MEDLINE, Cochrane Central Register of Controlled Trials, and PubMed were searched for studies published between January 1, 2005, and June 2, 2015; studies included in a previous USPSTF evidence report and reference lists of relevant studies

and ongoing trials were also searched. Surveillance was conducted through April 9, 2016. *Study selection:* Fair- and good-quality studies in English with participants 0 to 20 years of age. *Data extraction and synthesis:* Two investigators independently reviewed abstracts and full-text articles and extracted data into evidence tables. Results were qualitatively summarized. *Main outcomes and measures:* Outcomes included dyslipidemia (TC ≥ 200 mg/dL or LDL-C ≥ 130 mg/dL) and atherosclerosis in childhood; myocardial infarction and ischemic stroke in adulthood; diagnostic yield (number of confirmed cases per children screened); and harms of screening or treatment. Simulated diagnostic yield was calculated as initial screening yield × positive predictive value from a study with confirmatory testing. *Results:* Screening of children for multifactorial dyslipidemia has not been evaluated in randomized clinical trials. Based on 1 observational study (n = 6500) and nationally representative prevalence estimates, the simulated diagnostic yield of screening for elevated TC varies between 4.8% and 12.3% (higher in obese children [12.3%] and at the ages when TC naturally peaks, 7.2% at age 9–11 years and 7.2% at age 16–19 years). One good-quality randomized clinical trial (n = 663) found a modest effect of intensive dietary counseling for a low-fat, low-cholesterol diet on lipid levels at 1 year in children aged 8 to 10 years with mild to moderate dyslipidemia; mean between-group difference in TC change from baseline was -6.1 mg/dL (95% CI, -9.1 to -3.2 mg/dL; P < .001). Between-group differences dissipated by year 5. The intervention did not adversely affect nutritional status, growth, or development over the 18-year study period. One observational study (n = 9245) found that TC concentration at age 12 to 39 years was not associated with death before age 55 years. *Conclusions and relevance:* The diagnostic yield of lipid screening varies by age and body mass index. No direct evidence was identified for benefits or harms of childhood screening or treatment on outcomes in adulthood. Intensive dietary interventions may be safe, with modest short-term benefit of uncertain clinical significance.

P. Mahajan et al., Pediatric Emergency Care Applied Research Network (PECARN), **Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger,** *JAMA* 316.8 (August 23, 2016): 846–857, doi: 10.1001/jama.2016.9207 • *Importance:* Young febrile infants are at substantial risk of serious bacterial infections; however, the current culture-based diagnosis has limitations. Analysis of host expression patterns ("RNA biosignatures") in response to infections may provide an alternative diagnostic approach. *Objective:* To assess whether RNA biosignatures can distinguish febrile infants aged 60 days or younger with and without serious bacterial infections. *Design, setting, and participants:* Prospective observational study involving a convenience sample of febrile infants 60 days or younger evaluated for fever (temperature > 38° C) in 22 emergency departments from December 2008 to December 2010 who underwent laboratory evaluations including blood cultures. A random sample of infants with and without bacterial infections was selected for RNA biosignature analysis. Afebrile healthy infants served as controls. Blood samples were collected for cultures and RNA biosignatures. Bioinformatics tools were applied to define RNA biosignatures to classify febrile infants by infection type. *Exposure:* RNA biosignatures compared with cultures for discriminating febrile infants with and without bacterial infections and infants with bacteremia from those without bacterial infections. *Main outcomes and measures:* Bacterial infection confirmed by culture. Performance of RNA biosignatures was compared with routine laboratory screening tests and Yale Observation Scale (YOS) scores. *Results:* Of 1883 febrile infants (median age, 37 days; 55.7% boys), RNA biosignatures were measured in 279 randomly selected infants (89 with bacterial infections—including 32 with bacteremia and 15 with urinary tract infections—and 190 without bacterial infections), and 19 afebrile healthy infants. Sixty-six classifier genes were identified that distinguished infants with and without bacterial infections in the test set with 87% (95% CI, 73%–95%) sensitivity and 89% (95% CI, 81%–93%) specificity. Ten classifier

genes distinguished infants with bacteremia from those without bacterial infections in the test set with 94% (95% CI, 70%–100%) sensitivity and 95% (95% CI, 88%–98%) specificity. The incremental C statistic for the RNA biosignatures over the YOS score was 0.37 (95% CI, 0.30–0.43). *Conclusions and relevance:* In this preliminary study, RNA biosignatures were defined to distinguish febrile infants aged 60 days or younger with vs without bacterial infections. Further research with larger populations is needed to refine and validate the estimates of test accuracy and to assess the clinical utility of RNA biosignatures in practice.

A. W. van den Belt-Dusebout et al., **Ovarian stimulation for in vitro fertilization and long-term risk of breast cancer,** *JAMA* 316.3 (July 19, 2016): 300–312, doi: 10.1001/jama.2016.9389 • *Importance:* Previous studies of breast cancer risk after in vitro fertilization (IVF) treatment were inconclusive due to limited follow-up. *Objective:* To assess long-term risk of breast cancer after ovarian stimulation for IVF. *Design, setting, and participants:* Historical cohort (OMEGA study) with complete follow-up through December 2013 for 96% of the cohort. The cohort included 19,158 women who started IVF treatment between 1983 and 1995 (IVF group) and 5950 women starting other fertility treatments between 1980 and 1995 (non-IVF group) from all 12 IVF clinics in the Netherlands. The median age at end of follow-up was 53.8 years for the IVF group and 55.3 years for the non-IVF group. *Exposures:* Information on ovarian stimulation for IVF, other fertility treatments, and potential confounders was collected from medical records and through mailed questionnaires. *Main outcomes and measures:* Incidence of invasive and in situ breast cancers in women who underwent fertility treatments was obtained through linkage with the Netherlands Cancer Registry (1989–2013). Breast cancer risk in the IVF group was compared with risks in the general population (standardized incidence ratios [SIRs]) and the non-IVF group (hazard ratios [HRs]). *Results:* Among 25,108 women (mean age at baseline, 32.8 years; mean number of IVF cycles, 3.6), 839 cases of invasive breast cancer and 109 cases of in situ breast cancer occurred after a median follow-up of 21.1 years. Breast cancer risk in IVF-treated women was not significantly different from that in the general population (SIR, 1.01 [95% CI, 0.93–1.09]) and from the risk in the non-IVF group (HR, 1.01 [95% CI, 0.86–1.19]). The cumulative incidences of breast cancer at age 55 were 3.0% for the IVF group and 2.9% for the non-IVF group (P=.85). The SIR did not increase with longer time since treatment (≥20 years) in the IVF group (0.92 [95% CI, 0.73–1.15]) or in the non-IVF group (1.03 [95% CI, 0.82–1.29]). Risk was significantly lower for those who underwent 7 or more IVF cycles (HR, 0.55 [95% CI, 0.39–0.77]) vs 1 to 2 IVF cycles and after poor response to the first IVF cycle (HR, 0.77 [95% CI, 0.61–0.96] for <4 vs ≥4 collected oocytes). *Conclusions and relevance:* Among women undergoing fertility treatment in the Netherlands between 1980 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years. Breast cancer risk among IVF-treated women was also not significantly different from that in the general population. These findings are consistent with absence of a significant increase in long-term risk of breast cancer among IVF-treated women.

Lancet

D. E. Zak et al., ACS and GC6-74 Cohort Study Groups, **A blood RNA signature for tuberculosis disease risk: A prospective cohort study,** *Lancet* 387.10035 (June 4, 2016): 2312–2322, doi: 10.1016/S0140-6736(15)01316-1 • *Background:* Identification of blood biomarkers that prospectively predict progression of Mycobacterium tuberculosis infection to tuberculosis disease might lead to interventions that combat the tuberculosis epidemic. We aimed to assess whether global gene expression measured in whole blood of healthy people allowed identification of prospective signatures of risk of active tuberculosis disease. *Methods:* In this prospective cohort study, we followed up healthy, South African adolescents aged 12–18 years from

the adolescent cohort study (ACS) who were infected with M tuberculosis for 2 years. We collected blood samples from study participants every 6 months and monitored the adolescents for progression to tuberculosis disease. A prospective signature of risk was derived from whole blood RNA sequencing data by comparing participants who developed active tuberculosis disease (progressors) with those who remained healthy (matched controls). After adaptation to multiplex quantitative real-time PCR (qRT-PCR), the signature was used to predict tuberculosis disease in untouched adolescent samples and in samples from independent cohorts of South African and Gambian adult progressors and controls. Participants of the independent cohorts were household contacts of adults with active pulmonary tuberculosis disease. *Findings:* Between July 6, 2005, and April 23, 2007, we enrolled 6363 participants from the ACS study and 4466 from independent South African and Gambian cohorts. 46 progressors and 107 matched controls were identified in the ACS cohort. A 16 gene signature of risk was identified. The signature predicted tuberculosis progression with a sensitivity of 66·1% (95% CI 63·2–68·9) and a specificity of 80·6% (79·2–82·0) in the 12 months preceding tuberculosis diagnosis. The risk signature was validated in an untouched group of adolescents (p=0·018 for RNA sequencing and p=0·0095 for qRT-PCR) and in the independent South African and Gambian cohorts (p values <0·0001 by qRT-PCR) with a sensitivity of 53·7% (42·6–64·3) and a specificity of 82·8% (76·7–86) in the 12 months preceding tuberculosis. *Interpretation:* The whole blood tuberculosis risk signature prospectively identified people at risk of developing active tuberculosis, opening the possibility for targeted intervention to prevent the disease.

Nature

L.A. Hyslop et al., **Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease,** *Nature* 534.7607 (June 8, 2016): 383–386, doi: 10.1038/nature18303 • Mitochondrial DNA (mtDNA) mutations are maternally inherited and are associated with a broad range of debilitating and fatal diseases. Reproductive technologies designed to uncouple the inheritance of mtDNA from nuclear DNA may enable affected women to have a genetically related child with a greatly reduced risk of mtDNA disease. Here we report the first preclinical studies on pronuclear transplantation (PNT). Surprisingly, techniques used in proof-of-concept studies involving abnormally fertilized human zygotes were not well tolerated by normally fertilized zygotes. We have therefore developed an alternative approach based on transplanting pronuclei shortly after completion of meiosis rather than shortly before the first mitotic division. This promotes efficient development to the blastocyst stage with no detectable effect on aneuploidy or gene expression. After optimization, mtDNA carryover was reduced to <2% in the majority (79%) of PNT blastocysts. The importance of reducing carryover to the lowest possible levels is highlighted by a progressive increase in heteroplasmy in a stem cell line derived from a PNT blastocyst with 4% mtDNA carryover. We conclude that PNT has the potential to reduce the risk of mtDNA disease, but it may not guarantee prevention.

R.A. Larocca et al., **Vaccine protection against Zika virus from Brazil,** *Nature* 536.7617 (August 25, 2016): 474–478, doi: 10.1038/nature18952 • Zika virus (ZIKV) is a flavivirus that is responsible for the current epidemic in Brazil and the Americas. ZIKV has been causally associated with fetal microcephaly, intrauterine growth restriction, and other birth defects in both humans and mice. The rapid development of a safe and effective ZIKV vaccine is a global health priority, but very little is currently known about ZIKV immunology and mechanisms of immune protection. Here we show that a single immunization with a plasmid DNA vaccine or a purified inactivated virus vaccine provides complete protection in susceptible mice against challenge with a strain of ZIKV involved in the outbreak in northeast Brazil. This ZIKV strain has recently been shown to cross the placenta and to induce fetal microcephaly and other congenital malformations in mice. We produced DNA vaccines expressing ZIKV premembrane and envelope (prM-Env), as well

as a series of deletion mutants. The prM-Env DNA vaccine, but not the deletion mutants, afforded complete protection against ZIKV, as measured by absence of detectable viraemia following challenge, and protective efficacy correlated with Env-specific antibody titers. Adoptive transfer of purified IgG from vaccinated mice conferred passive protection, and depletion of CD4 and CD8 T lymphocytes in vaccinated mice did not abrogate this protection. These data demonstrate that protection against ZIKV challenge can be achieved by single-shot subunit and inactivated virus vaccines in mice and that Env-specific antibody titers represent key immunologic correlates of protection. Our findings suggest that the development of a ZIKV vaccine for humans is likely to be achievable.

New England Journal of Medicine

A. L. Cunningham et al., ZOE-70 Study Group, **Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older,** *N Engl J Med* 375.11 (September 15, 2016):1019–1032, doi: 10.1056/NEJMoa1603800 • *Background:* A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella-zoster virus glycoprotein E and the AS01B adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70). *Methods:* This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50. *Results:* In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95%CI, 86.8 to 94.5; P < 0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95%CI, 68.7 to 97.1; P < 0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups. *Conclusions:* In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older.

Pediatric Blood and Cancer

K. Bona et al., **Impact of socioeconomic status on timing of relapse and overall survival for children treated on Dana-Farber Cancer Institute ALL Consortium protocols (2000–2010),** *Pediatr Blood Cancer*. 63.6 (June 2016):1012–1018, doi: 10.1002/pbc.25928 • *Background:* Population-based evidence suggests that lower socioeconomic status (SES) negatively impacts the overall survival (OS) of children with leukemia; however, the relationships between SES and treatment-related mortality, relapse, and timing of relapse remain unclear. *Procedure:* We examined OS, event-free survival (EFS) and cumulative incidence (CI) and timing of relapse by community-level poverty for 575 children aged 1–18 years with newly diagnosed acute lymphoblastic leukemia (ALL) treated on consecutive phase III multicenter Dana-Farber Cancer Institute ALL Consortium Protocols between 2000 and 2010. Children were categorized into high- and low-poverty areas for the analysis

using aggregate US Census data linked to zip code. *Results:* Children living in high-poverty areas experienced a 5-year OS of 85% as compared with 92% for those in low-poverty areas (P=0.02); poverty remained marginally significant (P=0.07) after adjustment for immunophenotype, age, and white blood cell count. There were no differences detected in EFS or CI relapse by poverty area. However, 92% of the relapses observed in children from high-poverty areas occurred <36 months from complete remission, compared to 48% of those in children from low-poverty areas (P=0.008). *Conclusions:* US children with ALL living in high-poverty areas have a higher risk of early relapse when compared with those living in low-poverty areas despite uniform treatment. This may in part explain decreased OS observed in these children. This finding highlights disparities in childhood cancer outcomes by SES despite uniform treatment. Further investigations of the mechanistic pathways underlying this finding are needed.

Progress in Transplantation

K. Gali et al., **Smoking status at time of listing for a heart transplant predicts mortality on the waiting list: A multicenter prospective observational study,** *Prog Transplant* 26.2 (June 2016): 117–121, doi: 10.1177/1526924816640687 • *Objective:* We examined the association of smoking status at time of listing with waitlist mortality among heart transplant (HTx) candidates. *Participants and design:* Data were analyzed from 316 participants (aged 53±11; 18% female) of the Waiting for a New Heart Study, a prospective observational study of patients newly listed for HTx at 17 hospitals. *Results:* During the study period (April 2005 to March 2010), 14% of those who never smoked died, 18% among former smokers died, and almost half (42%) died among those who reported smoking at time of wait listing. Multivariate Cox regression models controlling for age, sex, and disease severity revealed smoking at time of listing was associated with significantly higher risk of mortality compared to never smoking (hazard ratio [HR]=3.43; P=.03). The relationship between smoking and mortality risk appeared to follow a dose-dependent pattern: adjusted HRs were 1.80 for those who quit ≤1 year ago, 1.25 for those who quit >1 to 10 years ago, and 0.90 for those quit >10 years ago, compared to never smokers. Smoking at time of listing may increase risk of mortality during the waiting period, indicating the need for improved strategies to achieve smoking cessation as early as possible in the course of HTx.

J.T. Siegel et al., **The potential (f)utility of a passive organ donor registration opportunity: A conceptual replication,** *Prog Transplant* 26.2 (June 2016): 103–108, doi: 10.1177/1526924816641814 • *Context:* Approximately 22 people die each day in the United States as a result of the shortage of transplantable organs. This is particularly problematic among Spanish-dominant Hispanics. Increasing the number of registered organ donors can reduce this deficit. *Objective:* The goal of the current set of studies was to conceptually replicate a prior study indicating the lack of utility of a lone, immediate and complete registration opportunity (ICRO). *Design and setting:* The study, a quasi-experimental design involving a total of 4 waves of data collection, was conducted in 2 different Mexican consulates in the United States. Guided by the IIFF Model (ie, an ICRO, information, focused engagement, and favorable activation), each wave compared a lone ICRO to a condition that likewise included an ICRO but also included the 3 additional intervention components recommended by the model (ie, information, focused engagement, and favorable activation). *Participants:* Visitors to the Mexican consulates in Tucson, Arizona, and Albuquerque, New Mexico, constituted the participant pool. *Main outcome measure:* New organ donor registrations represented the dependent variable. *Results:* When all 4 components of the IIFF Model were present, approximately 4 registrations per day were recorded; the lone ICRO resulted in approximately 1 registration every 15 days. *Conclusion:* An ICRO, without the other components of the IIFF Model, is of minimal use in regard to garnering organ donor registrations. Future studies should use the IIFF Model to consider how the utility of ICROs can be maximized.