

New laws in a post-*Roe* America declaring that life begins at conception may have additional ramifications. In vitro fertilization (IVF) did not exist before *Roe*. Since its development in 1978, use of IVF has grown, and 2% of all U.S. births now result from assisted reproductive technology, most commonly IVF.⁸ IVF procedures usually result in numerous oocytes ovulated per cycle, and fertilization frequently creates numerous embryos. Because modern IVF practice favors single-embryo transfers whenever possible, to reduce risks of multiple gestation and attendant complications, unused embryos are generally frozen for potential future transfer. Nationwide, there are tens of thousands of human embryos cryopreserved in IVF laboratories. While “adoption” programs exist to allow persons to donate their unused embryos to others who would like to implant them, many people are uncomfortable with this option, and unused embryos are often destroyed. If these embryos are declared human lives by the stroke of a governor’s pen, their destruction may be outlawed. What will be the fate of abandoned embryos, of the people who “abandon” them, and more broadly of IVF centers in these jurisdictions?

For nearly 50 years, Americans have lived under the protection of *Roe v. Wade*, free to determine their own reproductive destinies. At a time when dozens of other countries around the world are codifying protections for reproductive decision making for their citizens, we are turning the clock backward to take these rights away from our citizens. As has been pointed out by others,⁹⁻¹¹ the most privileged members of U.S. society will always be able to work around restrictive laws and find abortion care in jurisdictions that permit it. Currently proposed changes in our laws will be most burdensome and unfair to the low-income persons and persons of color

who are least able to overcome the impediments placed in their paths. These changes will inevitably exacerbate our already vast disparities in wealth and health.

By abolishing longstanding legal protections, the U.S. Supreme Court’s reversal of *Roe v. Wade* serves American families poorly, putting their health, safety, finances, and futures at risk. In view of these predictable consequences, the editors of the *New England Journal of Medicine* strongly condemn the U.S. Supreme Court’s decision.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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1. Melbye M, Wohlfahrt J, Olsen JH, et al. Induced abortion and the risk of breast cancer. *N Engl J Med* 1997;336:81-5.
2. Munk-Olsen T, Laursen TM, Pedersen CB, Lidegaard Ø, Mortensen PB. Induced first-trimester abortion and risk of mental disorder. *N Engl J Med* 2011;364:332-9.
3. Kortsmits K, Mandel MG, Reeves JA, et al. Abortion surveillance — United States, 2019. *MMWR Surveill Summ* 2021;70:1-29.
4. Hoyert DL. Maternal mortality rates in the United States, 2020. NCHS Health E-Stats, February 23, 2022 (<https://dx.doi.org/10.15620/cdc.113967>).
5. Panich-Linsman I, Kelley L. Before *Roe*. *New York Times*, January 21, 2022 (<https://www.nytimes.com/interactive/2022/01/21/opinion/roe-v-wade-abortion-history.html>).
6. Harris LH, Grossman D. Complications of unsafe and self-managed abortion. *N Engl J Med* 2020;382:1029-40.
7. Wilcox AJ, Dunson DB, Weinberg CR, Trussell J, Baird DD. Likelihood of conception with a single act of intercourse: providing benchmark rates for assessment of post-coital contraceptives. *Contraception* 2001;63:211-5.
8. Centers for Disease Control and Prevention. State-specific assisted reproductive technology surveillance (<https://www.cdc.gov/art/state-specific-surveillance/index.html>).
9. The Lancet. Why *Roe v. Wade* must be defended. *Lancet* 2022;399:1845.
10. The US Supreme Court is wrong to disregard evidence on the harm of banning abortion. *Nature* 2022;605:193-4.
11. Foster DG. The court is ignoring science. *Science* 2022;376:779.

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VITAL Findings — A Decisive Verdict on Vitamin D Supplementation

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An estimated one third or more of U.S. adults 60 years of age or older take vitamin D supplements, not including those who take multivita-

mins or other compounds containing vitamin D.¹ Yet controversy continues about its overall benefits. In this issue of the *Journal*, LeBoff and

colleagues² report findings from an ancillary study of the Vitamin D and Omega-3 Trial (VITAL),³ which extend the results of that trial; taken together, VITAL and this ancillary study show that vitamin supplements do not have important health benefits in the general population of older adults, even in those with low 25-hydroxyvitamin D levels.

VITAL grew from the landmark 2011 Institute of Medicine (IOM) report that established recommended dietary allowances for vitamin D of 600 to 800 IU per day to meet the bone health needs of 97.5% of the general population.⁴ The IOM report also recommended that large clinical trials of vitamin D be undertaken to determine the role of supplementation for the prevention or treatment of common diseases. VITAL has been the largest, most prolific, and most definitive trial to date. In a two-by-two factorial design, VITAL randomly assigned 25,871 U.S. men 50 years of age or older and women 55 years of age or older to one of four groups: vitamin D₃ (cholecalciferol, 2000 IU per day) plus n-3 fatty acids (1 g per day), vitamin D₃ plus placebo, n-3 fatty acids plus placebo, or double placebo.³ Notably, 20% of the participants were Black, although only a small proportion of the participants were Hispanic. Baseline blood samples were obtained from nearly 17,000 participants. Annual questionnaires collected information about numerous health outcomes. Results of analyses from VITAL published in peer-reviewed journals have shown that vitamin D supplementation did not prevent cancer or cardiovascular disease, prevent falls, improve cognitive function, reduce atrial fibrillation, change body composition, reduce migraine frequency, improve stroke outcomes, decrease age-related macular degeneration, or reduce knee pain.⁵⁻⁸

In the ancillary study published in this issue of the *Journal*, LeBoff and colleagues report that, contrary to expectations, vitamin D₃ did not reduce the risk of fractures over a median follow-up of 5.3 years, even in the 20% of the participants taking supplemental calcium at a dose of up to 1200 mg per day. 25-Hydroxyvitamin D is essential for the absorption of calcium in the gut and is produced by nonenzymatic skin conversion of previtamin D with activation of the pro-hormone by liver and renal hydroxylation. Virtually every tissue in the body has vitamin D receptors, a finding that has engendered consid-

erable interest in the potential benefits of vitamin D for multiple health conditions.

The skeleton is one of the most prominent targets of vitamin D actions through the vitamin D receptors, directly by stimulating bone remodeling and indirectly through induction by parathyroid hormone. More than a century ago, nutritional rickets, a devastating and disfiguring skeletal disease in infants and children, was noted to be cured by artificial ultraviolet light, irradiation of food, or supplementation with phytosterol. Hence, it was logical to presume that a deficiency of vitamin D could lead to osteoporosis. Observational studies showed that low vitamin D levels were associated with osteoporosis and other health conditions, but these were at least partially confounded by covariation with its vitamin D-binding protein. Critically, randomized, placebo-controlled trials remain the reference standard of evidence. Recently, a trial of vitamin D that used high-resolution computed tomography showed that bone mineral density and structure did not differ significantly between participants who received vitamin D and those who received placebo.⁹ The long-anticipated results of VITAL now clearly demonstrate that daily supplementation with 2000 IU of vitamin D₃ does not reduce the risk of total, hip, or non-vertebral fractures. Subgroup analyses showed a similar lack of effect on fracture risk according to sex, age, race or ethnic group, body-mass index, and other characteristics.

More than 10 million serum 25-hydroxyvitamin D tests are performed annually in the United States. Results from these tests often include the classification of vitamin D “insufficiency” (<30 ng per milliliter) and “deficiency” (<20 ng per milliliter), prompting vitamin D supplementation. In this ancillary study and other VITAL studies, no subgroups defined according to baseline 25-hydroxyvitamin D level, even below 20 ng per milliliter, benefited from supplements.^{2,3,7} Thus, there is no justification for measuring 25-hydroxyvitamin D in the general population or treating to a target serum level. A 25-hydroxyvitamin D level might be a useful diagnostic test for some patients with conditions that may be due to or that may cause severe deficiency. For example, persons living in residential settings with little or no sunlight exposure or malabsorption or those receiving treatments for osteoporosis that might cause

hypocalcemia may benefit from vitamin D supplementation; the need for measuring serum 25-hydroxyvitamin D levels in these groups remains uncertain. Otherwise, the use of the terms vitamin D “insufficiency” and “deficiency” should now be reconsidered.

What are the implications of VITAL? The fact that vitamin D had no effect on fractures should put to rest any notion of an important benefit of vitamin D alone to prevent fractures in the larger population. Adding those findings to previous reports from VITAL and other trials showing the lack of an effect for preventing numerous conditions suggests that providers should stop screening for 25-hydroxyvitamin D levels or recommending vitamin D supplements, and people should stop taking vitamin D supplements to prevent major diseases or extend life.

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1. Mishra S, Stierman B, Gahche JJ, Potischman N. Dietary supplement use among adults: United States, 2017–2018. *NCHS Data Brief* 2021;399:1-8.

2. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. *N Engl J Med* 2022;387:299-309.

3. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and Omega-3 Trial (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012;33:159-71.

4. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press, 2011.

5. Manson JE, Bassuk SS, Buring JE; VITAL Research Group. Principal results of the VITamin D and Omega-3 Trial (VITAL) and updated meta-analyses of relevant vitamin D trials. *J Steroid Biochem Mol Biol* 2020;198:105522.

6. Rist PM, Buring JE, Cook NR, Manson JE, Rexrode KM. Effect of vitamin D and/or omega-3 fatty acid supplementation on stroke outcomes: a randomized trial. *Eur J Neurol* 2021;28:809-15.

7. LeBoff MS, Murata EM, Cook NR, et al. VITamin D and Omega-3 Trial (VITAL): effects of vitamin D supplements on risk of falls in the US population. *J Clin Endocrinol Metab* 2020;105:2929-38.

8. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019;380:23-32.

9. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA* 2019;322:736-45.

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A Better Treatment for Advanced-Stage Hodgkin’s Lymphoma?

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Treatment for patients with Hodgkin’s lymphoma is one of the success stories of modern medicine. A once uniformly fatal disorder is now curable, even in an advanced stage, in the great majority of patients. In fact, particularly in limited-stage Hodgkin’s lymphoma, much of the therapeutic focus is on maintaining the high probability of cure while reducing the incidence of toxic effects. How little therapy can we give without losing efficacy?

For patients with advanced-stage, high-risk disease, debates regarding the best currently available approach have centered on the “old standard” ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen,¹ the very intensive escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen,² and risk-adapted approaches that use interim

positron-emission tomographic (PET) scans (usually after two cycles of therapy) as the basis of either intensifying or deescalating therapy.³ The clearance of a positive PET scan after the second cycle of therapy (PET2-negative status) is thought to carry an excellent prognosis and can serve to limit the extent of treatment; often, patients with PET2-negative status can stop therapy after two additional cycles of treatment. The introduction of the anti-CD30 antibody–drug conjugate brentuximab vedotin and its high response rate as a salvage treatment, including durable responses in some patients,⁴ offers a new approach. The hope has been that brentuximab vedotin, when substituted for bleomycin in the ABVD regimen, would lead to better survival when used as primary therapy, without the serious toxic effects that are associated with escalated BEACOPP.