lost, these tenets can still be upheld by using advance directives or by respecting the choices of surrogate decision makers.[5] However, this analysis suggests that a majority of US states restrict the health care options available to decisionally incapacitated women during pregnancy and do not disclose these restrictions in advance directive forms.

Although states have an obligation to be transparent about pregnancy restrictions, the heterogeneity among state laws and the justification for these restrictions warrant further ethical and legal scrutiny. Neither the frequency with which these statutes are encountered nor their effect on clinical practice is known. It is unclear whether the current legal framework achieves an ethical balance between the state's interest in preserving fetal life and the interests incapacitated women may have in forgoing life-sustaining treatments.[6]

**Erin S. DeMartino, MD**
**Beau P. Sperry, BA**
**Cavan K. Doyle, JD, LLM**
**Julie Chor, MD, MPH**
**Daniel B. Kramer, MD, MPH**
**David M. Dudzinski, MD, JD**
**Paul S. Mueller, MD, MPH**

**Author Affiliations:** Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota (DeMartino); Biomedical Ethics Research Program, Mayo Clinic, Rochester, Minnesota (Sperry); Neiswanger Institute for Bioethics, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois (Doyle); Department of Obstetrics and Gynecology, University of Chicago, Chicago, Illinois (Chor); Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Kramer); Department of Cardiology, Massachusetts General Hospital, Boston (Dudzinski); General Internal Medicine, Mayo Clinic Health System, La Crosse, Wisconsin (Mueller).

**Accepted for Publication:** February 27, 2019.

**Corresponding Author:** Erin S. DeMartino, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (demartino.erin@mayo.edu).

**Author Contributions:** Dr DeMartino had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* DeMartino, Sperry, Doyle, Kramer, Dudzinski, Mueller.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* DeMartino, Sperry, Mueller.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Sperry, Doyle.
*Administrative, technical, or material support:* DeMartino, Sperry, Doyle.
*Supervision:* DeMartino, Sperry, Kramer, Mueller.

**Conflict of Interest Disclosures:** Dr Kramer reported grant funding from Greenwall Foundation. Dr Mueller reported receiving consulting fees from the Boston Scientific Patient Safety Advisory Board and personal fees from NEJM Journal Watch and American College of Physicians. No other disclosures were reported.

**Additional Contributions:** We thank Mark Siegler, MD, Department of Medicine, MacLean Center for Clinical Medical Ethics, University of Chicago, and Daniel P. Sulmasy, MD, PhD, Departments of Medicine and Philosophy, Pellegrino Center for Clinical Bioethics, Georgetown University, for contributions to the analysis and writing of the manuscript and Sei Unno, BA, Beazley Institute for Health Law and Policy, Loyola University Chicago School of Law, for contributions to data collection and analysis. No compensation was received.

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## COMMENT & RESPONSE

### Post Hoc Bayesian Analyses

**To the Editor** Dr Goligher and colleagues[1] used a Bayesian approach to reanalyze the negative ECMO [extracorporeal membrane oxygenation] to Rescue Lung Injury in Severe ARDS [acute respiratory distress syndrome] (EOLIA) trial. I believe this reanalysis is an example of confirmation bias[2] and illustrates the common criticisms of Bayesian methodology.

An unplanned Bayesian reanalysis would probably not have been performed if the EOLIA trial results had been marginally positive (eg, $P = .03$), especially if known prior information about the efficacy of ECMO was unfavorable. To the contrary, the data showing a $P$ value of .09 in the EOLIA trial needed only a small boost to cross a significance threshold in reanalysis. The authors used prior probability distributions that were not impartial to the analytical result. The severely skeptical prior placed the relative risk (RR) at 1.0 rather than a higher number that would reflect the possibility that some therapies initially shown to be beneficial are found to be harmful in larger replication trials.[3] Excluding the noninformative prior, the remainder of the priors were likewise generous. Using the ARDS Network tidal volume trial[4] as a reference for the prior distributions is biased because it is one of the few positive trials in ARDS with a favorable RR and is an outlier among unselected ARDS trials.[5] A cohort of all randomized clinical trials of therapies for ARDS would likely show a reduced aggregate effect that would be more narrowly distributed around an RR of 1.0, compared with the distributions shown in Figure 1 in the article.[1]

The results of the Bayesian analysis underscore the subjective nature of Bayesian methods for the analysis of trial data and the latitude and flexibility to perform unplanned (and unregistered) analyses using data known to the authors at the outset, thus increasing type I error rates. A simpler approach would be to advise practitioners that if the results of a trial approach significance, they should just enlist their beliefs. This would obviate formal Bayesian analyses with their arrays of prior probability distributions, yet it would yield the same result—a biased estimate of treatment effect driven as much by beliefs as by evidence.

**Scott K. Aberegg, MD, MPH**

**Author Affiliation:** University of Utah School of Medicine, Salt Lake City.

**Corresponding Author:** Scott K. Aberegg, MD, MPH, University of Utah School of Medicine, 1321 S 600 E, Salt Lake City, UT 84105 (scottaberegg@gmail.com).

**Conflict of Interest Disclosures:** None reported.

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**To the Editor** The article by Dr Goligher and colleagues[1] reported a post hoc Bayesian analysis of a randomized clinical trial assessing the effects of ECMO for ARDS on mortality. The new analysis of the trial evaluated an important clinical issue using an appropriate methodology, but we would like to suggest that this analysis be completed with another tool of Bayesian methods.

Goligher and colleagues computed the posterior probability that the ECMO effect would exceed a certain value. However, the authors did not consider the sequential aspects of the EOLIA trial,[2] which was stopped early for futility. We believe that the calculation of predictive probabilities, to "determine the degree of belief" in these posterior probabilities computed on the basis of an intermediate analysis, was missing.

Interim high posterior probabilities are not necessarily associated with good prediction of the clinical effect derived from the final results with a larger sample size.[3] These interim posterior probabilities must be interpreted with predictive probabilities. Bayesian predictive probabilities measure the credibility of the hypothesis of superiority based on interim data and allow for termination of the study if predefined bounds are crossed. The predictive probability of superiority is then the probability to conclude superiority by the end of the study, considering all the possible future data. Predictive probabilities open the way to early trial stopping for futility or efficacy. If a stopping rule is defined before the beginning of the study, based on a predefined lower bound (for futility) and a predefined upper bound (for efficacy), the study can be discontinued if the predictive probability is above or below these boundaries. If the predictive probability is between these 2 predefined values, the accrual continues to the next interim analysis and to the next computation of the predictive probability of superiority.

The EOLIA trial concluded after the inclusion of 249 of 331 planned patients, during the fourth sequential interim analysis. If a predictive probability was calculated at this point, it is likely that the trial would have been continued and would have had a chance of being positive in favor of ECMO.

**David Ferreira, MD**
**Nicolas Meyer, MD, PhD**

**Author Affiliations:** Anesthesiology and Intensive Care Department, University Hospital of Besançon, Besançon, France (Ferreira); Public Health Department, University Hospital of Strasbourg, Strasbourg, France (Meyer).

**Corresponding Author**: David Ferreira, MD, Département d'Anesthésie et de Reanimation, CHU Jean Minjoz, 3 Boulevard A, Fleming, 25030 Besançon Cedex, France (dferreira@chu-besancon.fr).

**Conflict of Interest Disclosures:** None reported.

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**In Reply** Dr Aberegg raises several important issues about our Bayesian reanalysis of the EOLIA trial.[1]

First, in raising the specter of confirmation bias, the author describes exactly the kind of intuitive Bayesian analysis that clinicians perform regularly, combining a hypothetical prior consistent with treatment harm and a hypothetical marginally "significant" trial result to imagine a posterior consistent with treatment harm. He may or may not be correct in speculating that such a result would not have been met by a Bayesian reanalysis; a prior for harm might have motivated this. Nevertheless, his concern about confirmation bias is not an argument against Bayesian analysis as such, but rather that these analyses should be performed consistently regardless of the anticipated result and specified as part of the design, a contention that we fully support.

Second, we disagree with the statement regarding the strongly skeptical prior. While it was centered on a RR of 1.0, it specifies a 50% probability that early ECMO increases mortality and only a small chance (<5%) that the true benefit of ECMO could equal or exceed the effect observed in the ARDS Network low tidal volume trial (RR, 0.78). Given that this prior is equivalent to having data from a hypothetical trial larger than EOLIA (n = 264) finding no benefit, it seems difficult to justify greater skepticism from available evidence.

Third, priors are not used to "boost" the result; priors can also function to temper unrealistically large observed effects. We specified the priors to represent the range of beliefs about ECMO among the clinical community prior to EOLIA. We also used data-driven priors from recently published randomized clinical trials and observational studies with similar results. The resulting posterior probability of benefit was also consistent with the observed effect of early ECMO on many secondary outcomes in EOLIA.[2]

Fourth, the critique draws a false dichotomy between evidence and belief. The goal of science is not to exclude belief but rather to form beliefs appropriately warranted by evidence. Bayesian analysis helps physicians understand the extent to which a trial should inform their beliefs about the benefit of therapy and whether there is sufficient confidence to support action. Overreliance on *P* values derived

from frequentist analysis isolated from all other prior information leads to a high risk of misguided beliefs about treatment effect.[3]

Fifth, regarding subjectivity in Bayesian analysis, judgment plays an inescapable role in scientific inference. Interpreting data requires the judgment of properly trained minds, not merely a robotic response to arbitrarily significant *P* values. Such judgments are subjective only in the sense that they reflect a personal or community weighting of various relevant considerations. Bayesian analysis makes such judgments explicit and is therefore more transparent and informative.

Drs Ferreira and Meyer raise the important issue of early stopping. The authors point out that decisions by the data and safety monitoring board may have been very different had the trial been designed in accordance with Bayesian principles. This important point strongly supports consideration of Bayesian trial design principles for future trials.

**Ewan C. Goligher, MD, PhD**
**George Tomlinson, PhD**
**Arthur S. Slutsky, MD**

**Author Affiliations:** Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada (Goligher, Slutsky); Department of Medicine, University Health Network, Toronto, Ontario, Canada (Tomlinson).

**Corresponding Author:** Ewan C. Goligher, MD, PhD, Toronto General Hospital, 585 University Ave, Peter Munk Bldg, 11th Floor, Room 192, Toronto, ON M5G 2N2, Canada (ewan.goligher@utoronto.ca).

**Conflict of Interest Disclosures:** Dr Goligher reported receiving travel reimbursement and speaking honoraria from Getinge. Dr Slutsky reported being a consultant to Baxter Critical Care, Maquet Critical Care, and Novalung/Xenios. No other disclosures were reported.

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## Patient-Physician Relationship in the Age of Expanded Access to Information

**To the Editor** Drs Kilbride and Joffe discussed how expanded access to medical information and services will change the nature of the patient-physician relationship by enhancing patient autonomy and diminishing the physician's role as the gatekeeper to medical information, tests, and interventions.[1] They concluded that the physician will cede power to the patient and shift into the role of an advisor with increased focus on downstream care coordination.[1] This characterization is incomplete; increased access to information does not necessarily foster meaningful autonomy or independence.

Insofar as ideal autonomy requires understanding relevant information and having access to an appropriate array of valuable choices,[2] factors that limit information or eliminate options impair the capacity to choose and thus diminish a patient's autonomy. Accordingly, readily available online medical resources and direct-to-consumer testing may enhance a patient's autonomy by improving access to information and removing barriers to certain health services.

However, for a patient to use these services to meaningfully improve medical decisions requires making sense of the variety of data these services provide; ie, understanding their meaning and significance and applying the lessons to a patient's own health. This capacity to gather and interpret health information to make meaningful health decisions is defined as health literacy.[3]

Interpreting medical information from online sources and direct-to-consumer tests requires applying data gathered from "complex graphs, tables, or other health-related texts or documents."[4] This requires intermediate health literacy according to the US Department of Education.[4] Yet, in a national US survey, only 53% had intermediate health literacy, and 36% fell below this level.[4]

Therefore, merely increasing the availability of health information or direct-to-consumer testing will do little to empower the more than one-third of all patients who cannot make use of this information. The assumption that increasing access to information alone enhances autonomy must be discarded; information must be paired with the ability to interpret and apply it.

What does this mean for physicians? The physician must rise above the role of gatekeeper or advisor. Physicians should acknowledge any disparity in health literacy, tailor the conversation to the patient's level of understanding, and guide them toward a thoughtful, meaningful choice in accordance with their values. When faced with a patient who requests a subspecialty referral based on results from a direct-to-consumer test, the physician should inquire further. Doing so can address the limits of health literacy and enhance autonomy; this is the essence of shared decision making.

**Eric Weinlander, MD**

**Author Affiliation:** Kellogg Eye Center, University of Michigan, Ann Arbor.

**Corresponding Author:** Eric Weinlander, MD, Kellogg Eye Center, University of Michigan, 1000 Wall St, Ann Arbor, MI 48105 (weinland@med.umich.edu).

**Conflict of Interest Disclosures:** None reported.

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**In Reply** Dr Weinlander argues that the characterization of the modern patient-physician relationship in our Viewpoint[1] was incomplete. Specifically, he contends that patients' decreasing dependence on physicians for access to information and health care resources does not, as we asserted, enhance patient autonomy.