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Editorial Office

Journal of Law, Medicine & Ethics, 765 Commonwealth Avenue, Suite 1704, Boston, MA 02215 USA
Phone: 617-262-4990; Fax: 617-437-7596
E-mail: thutchinson@aslme.org

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C O N T E N T S

VOLUME 47:3 • FALL 2019

Symposium Articles

SYMPOSIUM

**Biomarker
Research and
Validation: Current
Challenges, Future
Opportunities**

Guest Edited by
Spencer Phillips Hey

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*Letter from
the Editor*

Cover image ©Getty Images

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**Challenges and Opportunities for
Biomarker Validation**

*Spencer Phillips Hey, Elvira D'Andrea,
Emily H. Jung, Frazer Tessema, Jing
Luo, Bishal Gyawali, and Aaron S.
Kesselheim*

Biomarkers can be powerful tools to guide diagnosis, treatment, and research. However, prudent use of biomarkers requires formal validation efforts. Although the data needed for biomarker validation has traditionally been hard to access, new research initiatives can ease this process.

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**Is Cancer Solvable? Towards Efficient
and Ethical Biomedical Science**

*Jeff Shrager, Mark Shapiro, and William
Hoos*

Global Cumulative Treatment Analysis (GCTA) is a novel clinical research model combining expert knowledge, and treatment coordination based upon global information-gain, to treat every patient optimally while efficiently searching the vast space that is the realm of cancer research.

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**How Clinical Trial Data Sharing
Platforms Can Advance the Study
of Biomarkers**

Rebecca Li and Ida Sim

Although data sharing platforms host diverse data types the features of these platforms are well-suited to facilitating biomarker research. Given the current state of biomarker discovery, an innovative paradigm to accelerate biomarker discovery is to utilize platforms such as Vivli to leverage researchers' abilities to integrate certain classes of biomarkers.

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**Cochrane's Linked Data Project:
How it Can Advance our Understanding
of Surrogate Endpoints**

*Chris Mavergames, Deirdre Beecher,
Lorne A. Becker, A. Last, and A. Ali*

Cochrane has developed a linked data infrastructure to make the evidence and data from its rich repositories more discoverable to facilitate evidence-based health decision-making. These annotated resources can enhance the study and understanding of biomarkers and surrogate endpoints.

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**Surrogate Endpoints and Drug
Regulation: What Is Needed to Clarify
the Evidence**

*Spencer Phillips Hey, William B.
Feldman, Emily H. Jung, Elvira
D'Andrea, and Aaron S. Kesselheim*

The FDA's new table of surrogate endpoints used for drug approvals is an important step forward for overseeing the use of biomarkers in clinical trials. Nevertheless, we present several ways in which the table can be improved.

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**Biomarker Validation: Context and
Complexities**

Lisa M. McShane

Validation of a biomarker-based medical product development tool or clinical test is an evidentiary process that must be tailored to the proposed use. Appropriate data and analyses are needed to demonstrate that the biomarker meets analytical and clinical performance criteria consistent with favorable benefit: risk balance.

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**Biomarkers as Surrogate Endpoints:
Ongoing Opportunities for Validation**

Audrey D. Zhang and Joseph S. Ross

Surrogate endpoints are a common application of biomarkers to estimate clinical benefit in clinical trials, despite questions about reliability. This article discusses ongoing opportunities for their validation, in the context of a regulatory environment in which they are increasingly championed.

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**Managing the Use and Dissemination of
Information about Biomarkers:
The Importance of Incentive Structures**

Ariel Dora Stern

The use of biomarkers holds great promise for the development of new therapeutics and the acceleration of clinical research. However, biomarkers must be validated — a complex and costly endeavor. Importantly, biomarker validation is meaningfully shaped by economic and policy-driven incentives.

Independent Articles

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**Prenatal Care for Undocumented
Immigrants: Professional Norms,
Ethical Tensions, and Practical
Workarounds**

Rachel E. Fabi and Holly A. Taylor

This paper examines the practice implications of various state policies that provide publicly funded prenatal care to undocumented immigrants for health care workers who see undocumented patients. Data were collected through in-depth interviews with purposively sampled health care workers at safety net clinics in California, Maryland, Nebraska, and New York. Health care workers were asked about the process through which undocumented patients receive prenatal care in their health center and the ethical tensions and frustrations they encounter when providing or facilitating this care under policy restrictions. Respondents discussed several professional practice norms as well as the ethical tensions they encountered when policy or institutional constraints prevented them from living up to professional norms. Using Nancy Berlinger's "workarounds" framework, this paper examines health care workers' responses to the misalignment of their professional norms and the policy restrictions in their state. These findings suggest that the prenatal policies in each state raise ethical and professional challenges for the health care workers who implement them.

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**Assessing National Public Health Law to
Prevent Infectious Disease Outbreaks:
Immunization Law as a Basis for Global
Health Security**

*Tsion Berhane Ghedamu and Benjamin
Mason Meier*

Immunization plays a crucial role in global health security, preventing public health emergencies of international concern and protecting individuals from infectious disease outbreaks, yet these critical public health benefits are dependent on immunization law. Where public health law has become central to preventing, detecting, and responding to infectious disease, public health law reform is seen as necessary to implement the Global Health Security Agenda (GHSA). This article examines national immunization laws as a basis to implement the GHSA and promote the public's health, analyzing the scope and content of these laws to prevent infectious disease across Sub-Saharan Africa. Undertaking policy surveillance of national immunization laws in 20 Sub-Saharan African countries, this study: (1) developed a legal framework to map the legal attributes relevant to immunization; (2) created an assessment tool to determine the presence of these attributes under national immunization law; and (3) applied this assessment tool to code national legal landscapes. An analysis of these coded laws highlights legal attributes that govern vaccine requirements, supply chains, vaccine administration standards, and medicines quality and manufacturer liability. Based upon this international policy surveillance, it will be crucial to undertake legal epidemiology research across countries, examining the influence of immunization law on vaccination rates and disease outbreaks.

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COMMENTARY

Alexandra L. Phelan and Rebecca Katz

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Patients' Knowledge of Key Messaging in Drug Safety Communications for Zolpidem and Eszopiclone: A National Survey

Aaron S. Kesselheim, Michael S. Sinha, Paula Rausch, Zhigang Lu, Frazer A. Tessema, Brian M. Lappin, Esther H. Zhou, Gerald J. Dal Pan, Lee Zwanziger, Amy Ramanadham, Anita Loughlin, Cheryl Enger, Jerry Avorn, and Eric G. Campbell

Drug Safety Communications (DSCs) are used by the Food and Drug Administration (FDA) to inform health care providers, patients, caregivers, and the general public about safety issues related to FDA-approved drugs. To assess patient knowledge of the messaging contained in DSCs related to the sleep aids zolpidem and eszopiclone, we conducted a large, cross-sectional patient survey of 1,982 commercially insured patients selected by stratified random sampling from the Optum Research Database who had filled at least two prescriptions for either zolpidem or eszopiclone between July 1, 2012 and June 30, 2013. Among the 594 respondents (32.7% response rate), two-thirds reported hearing generally about drug safety information prior to starting a new drug, with the remaining one-third "rarely" or "never" hearing such information. Providers and pharmacists were primary sources of drug safety information. Two-thirds of zolpidem users and half of eszopiclone users reported having heard about the related DSC messages, ability to accurately identify the major factual messages was limited (overall median 2 correct out of 5, with men and those reporting higher educational level scoring higher [2/5 vs. 1/5, $p=0.001$]). Respondents reacted to new drug safety information about their sleep aids by reporting that they would want to learn about alternative ways to help them sleep (70%) and seek out more information about the safety of their specific sleeping pill (59-78%). Opportunities may exist for the FDA to work with providers and pharmacies to help ensure the DSC information is more widely received and is more fully understood by those taking the affected medications.

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COMMENTARY

Barbara Mintzes

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The Law and Economics of Grindr: A Response to Carson

Jonathan Hardman

In the Winter 2017 edition of *JLME*, Dr. Carson outlined an economic approach to the epidemiology of HIV transmission within the gay community, with a special emphasis on mobile apps. His conclusion is that HIV transmission amongst the gay community constitutes a collective action problem, which is resolved by the social norm of using a condom. This article critiques Dr. Carson's approach from an economic perspective. By utilizing classic law and economic theory, this article will argue that HIV transmission may not, in fact, constitute a collective action problem in economic terms, and that instead condom use as a method of disease protection in theory can arise from purely rational, market driven actions. To do so, it borrows from transactional theory of information asymmetry to show the potential to alert counterparts as to serostatus. This conclusion provides an important supplement to Carson: rather than social norms being the core driver in condom usage to prevent HIV, instead condom use may arise solely as a result of rational, private decision making arising from market signaling. The article then critiques its own findings to demonstrate that it is unclear whether Carson's argument or the argument in this paper is, indeed, correct — which may represent a limitation in the analytical techniques advanced.

Symposium articles are solicited by the guest editor for the purposes of creating a comprehensive and definitive collection of articles on a topic relevant to the study of law, medicine and ethics. Each article is peer reviewed.

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Columns are written or edited by leaders in their fields and appear in each issue of JLME.

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Promise and
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Hoffmann

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*Stephanie R. Morain, Mary A. Majumder,
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*James G. Hodge, Leila Barraza, Michelle
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HEALTH POLICY PORTAL Lung Cancer Survival Gains: Contributions of Academia and Industry

*Bishal Gyawali, Gauthier Bouche, Pan
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