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THE PRESENT AND FUTURE

TECHNOLOGY CORNER

Data Sharing and Cardiology

Platforms and Possibilities

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ABSTRACT

Sharing deidentified patient-level research data presents immense opportunities to all stakeholders involved in cardiology research and practice. Sharing data encourages the use of existing data for knowledge generation to improve practice, while also allowing for validation of disseminated research. In this review, we discuss key initiatives and platforms that have helped to accelerate progress toward greater sharing of data. These efforts are being prompted by government, universities, philanthropic sponsors of research, major industry players, and collaborations among some of these entities. As data sharing becomes a more common expectation, policy changes will be required to encourage and assist data generators with the process of sharing the data they create. Patients also will need access to their own data and to be empowered to share those data with researchers. Although medicine still lags behind other fields in achieving data sharing's full potential, cardiology research has the potential to lead the way. (J Am Coll Cardiol 2017;70:3018–25)

Data sharing in cardiology has progressed markedly in recent years. A 2016 study found patient-level data from 1 in 4 large cardiovascular trials conducted by major pharmaceutical companies to be available for sharing with outside investigators (1). In this paper, we examine the rationale for sharing clinical research data and discuss the major data sharing initiatives and platforms that are influencing cardiology research. We also present examples of how data sharing fits into the broader open-science movement and ultimately affects clinical care. This is particularly

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important in cardiology, given its history of generating evidence for knowledge creation and secondary data analysis.

BACKGROUND

Several articles have argued that medicine would benefit from greater data sharing (2–5). Two central observations set the rationale for this new research paradigm.

1. Much data generated in clinical trials are kept out of public view. A recent study showed that nonpublication of clinical trials hovers around 50% across major academic institutions in the United States (6). The studies are not missing at random. Research shows that trials are more likely to be published if they yield positive or statistically significant outcomes (7). Withholding data, positive or negative, can cause harm. In a famous example, Merck held unpublished data showing that Vioxx (rofecoxib) likely increased the risk of acute myocardial infarction; it nevertheless took years for the drug to be withdrawn from the market, exposing numerous patients to potentially unnecessary risk (2).
2. Clinical trial data are often used inefficiently, with little opportunity for independent validation. Even when clinical trial results are published, the underlying patient-level data often remain unavailable. Many questions that could be asked using the data remain unaddressed, including secondary research questions and examination of rare outcomes not reported in the main publications. As a result, the expense and effort of creating the data resource may produce suboptimal yield (8). In addition, when independent scientists cannot view and analyze the data, they cannot verify and replicate the results (9).

Data sharing in medicine lags behind that found in other scientific disciplines. Physicists can access shared data from the Large Hadron Collider, astronomers from the Hubble Space Telescope, and geneticists from the Human Genome Project (10). In contrast, clinician-researchers often cannot answer investigative questions because they lack access to existing clinical trial data.

To address this concern, the Institute of Medicine (now the National Academy of Medicine) in 2015 called for researchers to share the "full analyzable data set with metadata" within 18 months of finishing a study, thereby fostering a culture in which data sharing is the standard (11). Senator Elizabeth Warren has called for making data sharing "a condition of publication in major medical journals" (12). Former Vice President Joe Biden endorsed data sharing in the Cancer Moonshot initiative, and the 21st Century Cures Act, which funds the Moonshot, empowers the Director of the National Institutes of Health (NIH) to require sharing of data from NIH-supported research (13,14). Through groups such as the Academic Research Organization Consortium for Continuing Evaluation of Scientific Studies–Cardiovascular, trialists are coming together in advocacy of sharing and are calling for standards (15). Thus, the move toward the sharing of clinical trial data is advancing.

INITIATIVES FOR DATA SHARING AND REPORTING OF RESULTS

Several organizations have sought to promote clinical trial data sharing, even to require it as a condition for funding. The reporting of results is also increasingly being encouraged. We explain these processes and highlight notable examples in the following section.

RESULTS REPORTING: FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007 AND NIH. Unlike full data sharing, which involves releasing the underlying deidentified patient-level data, results reporting refers to releasing summary results from clinical trials. The Food and Drug Administration (FDA) Amendments Act increased the scope of requirements for clinical trial sponsors of FDA-regulated products to register studies and report results at ClinicalTrials.gov (16). The Department of Health and Human Services Final Ruling on the FDA Amendments Act, effective January 2017, includes (among other features) a results-reporting requirement for phase II and phase III trials of products that have not gained approval (17).

This policy regarding FDA-regulated products complements new guidance from the NIH. As of January 2017, the NIH expects all trials that it partly or fully funds to be registered and to report summary results at ClinicalTrials.gov (18). Because many trial results previously went unreported, this new policy clarifies existing statutory ambiguities so that researchers and funders know what specific information to submit for compliance (16). The NIH will also withhold funding for clinical trials from institutions that fail to meet registry and reporting requirements, with an option to subject researchers and trial sponsors to monetary penalties (19). The new NIH policy requires results reporting for clinical trials at all stages, including phase I safety trials, and submission of original protocols and statistical analysis plans (17).

ABBREVIATIONS AND ACRONYMS

BioLINCC = Biologic Specimen and Data Repository Information Coordinating Center

EHR = electronic health record

FDA = Food and Drug Administration

ICMJE = International Committee of Medical Journal Editors

NHLBI = National Heart, Lung, and Blood Institute

NIH = National Institutes of Health

PCORI = Patient-Centered Outcomes Research Institute

PMI = Precision Medicine Initiative

S4S = Sync for Science

YODA = Yale University Open Data Access

DATA SHARING: NIH AND OTHER MAJOR FUNDERS. The NIH requires data sharing plans from investigators who request >$500,000 in any year of a proposal and allows researchers to request funds as a part of grant applications to support data sharing (20,21). However, individual NIH institutes, including the National Institute of Mental Health, have started to implement patient-level data sharing requirements (22). The National Heart, Lung, and Blood Institute (NHLBI), the NIH institute primarily responsible for funding cardiology research, strongly encourages all grant applicants to prepare a plan for data sharing or explain why sharing is not possible (23). Although the NHLBI allows multiple approaches to sharing data, it prefers that data be submitted to its data repository, managed by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) (20).

Some philanthropic funders of medical research now require data sharing. In 2014, the Bill & Melinda Gates Foundation made data sharing a requirement for entities that seek its funding (24). The foundation covers the costs of publishing in a journal, on open-access terms, under a Creative Commons Attribution 4.0 Generic License that allows others to copy and build on the research for any purpose (25). Similarly, the Wellcome Trust encourages researchers to make anonymized patient-level clinical trial data available and mandates the publication of all results, including negative findings, from clinical trials (26).

The Patient-Centered Outcomes Research Institute (PCORI) will soon implement data sharing and data management requirements for investigators who receive support for patient-centered comparative clinical effectiveness research (27). According to proposals in the PCORI draft "Policy for Data Access and Data Sharing," researchers, depending on their type of PCORI funding, must either deposit their full data packages into established repositories or maintain the full data packages at their own institutions for at least 7 years, during which PCORI reserves the right to request that the data be placed in a repository. PCORI's draft policy commits to covering the financial costs of sharing data with an established repository (28).

DATA SHARING: JOURNAL EDITORS. The International Committee of Medical Journal Editors (ICMJE), a group of leading medical journal editors that produces widely followed recommendations for publishing in medical journals, has argued for an "ethical obligation to responsibly share data" from clinical trials (29). The organization has previously advocated for mandatory registration of clinical trials before patient enrollment (30,31). Under new guidelines, manuscripts submitted to ICMJE journals after July 1, 2018 that report clinical trial results must contain data sharing statements (32). Clinical trials that enroll patients starting January 1, 2019 must include data sharing plans when the trials are registered. Data sharing statements must explain whether and when data will be shared and how access to shared data will be controlled. The ICMJE does not require data sharing, but ICMJE member journals may consider data sharing statements in evaluating manuscripts for publication, and some ICMJE journals have stricter data sharing requirements. The ICMJE aims to make data sharing a standard practice and is exploring additional ways to encourage it (32).

DATA SHARING: PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AND THE EUROPEAN FEDERATION OF PHARMACEUTICAL INDUSTRIES AND ASSOCIATIONS. In 2013, the consortium of firms in the Pharmaceutical Research and Manufacturers of America and European Federation of Pharmaceutical Industries and Associations committed to data sharing (33). The companies promised to make available to researchers study- and patient-level clinical trial data, the protocols used to conduct the trials, and full clinical study reports for drugs approved in the United States and Europe. The Yale University Open Data Access (YODA) Project and Clinical Study Data Request (discussed in a subsequent section) illustrate how these companies have followed through on their commitments.

DATA SHARING PLATFORMS

As organizations and funders have embraced data sharing, platforms for sharing these research data have been created. These platforms post individual trials and other data, but have not harmonized formats. We highlight some of them here.

GOVERNMENT-CREATED PLATFORM. In 2000, the NHLBI started a data repository for deidentified, patient-level data to facilitate data sharing with the broader scientific community. After an approximately 2-year proprietary-use period, researchers conducting NHLBI-funded clinical trials and observational studies store their data in the BioLINCC repository (34). An NHLBI study analyzing the use of the data repository from January 2000 to May 2016 found that the number of requests for data increased over time and that 72% of requests were for secondary analyses of new questions (34). A survey of investigators who used clinical research data from BioLINCC from 2007 to 2014 found that the vast majority used the shared data for independent research rather than replication of previous studies (35).

INDUSTRY-SUPPORTED PLATFORM. Clinical Study Data Request, an online sharing platform for industry-sponsored clinical trial data launched in 2013, now lists deidentified patient-level clinical trial data from more than a dozen major pharmaceutical companies, including Roche, Novartis, Bayer, and GlaxoSmith-Kline (36). Researchers interested in the data submit proposals that are evaluated by an independent review panel run by the Wellcome Trust (37). The panel has the responsibility of filtering out requests from researchers with conflicts of interest, nonexperts aiming to perform reanalysis studies, and proposals from researchers who do not intend to share their study findings publicly. It does not, however, evaluate scientific merit in the manner of a journal's peer-review system, preferring instead to accept as many proposals as possible (38). As of March 31, 2017, >300 research proposals had been submitted, of which only 23 were rejected or advised to resubmit (36).

UNIVERSITY- AND NONPROFIT-BASED PLATFORMS. The YODA Project is a data sharing model launched in 2011 by several authors of this review (10). The project uses a "trusted intermediary" system to create a layer of separation between the trial sponsor and the data requestor, ensuring independence, so that the manufacturer of a drug or medical device may not unilaterally veto requests from researchers who might find something negative about the product. Instead, YODA Project scientists, aided by a scientific advisory committee if needed, independently evaluate data access proposals on the basis of scientific merit and the potential contribution to scientific knowledge and public health. The YODA Project has full jurisdiction over the decision to provide data access. To date, the YODA Project has received 73 requests to access shared data, and none has been denied (39). Since 2014, Johnson & Johnson has shared clinical trial data from pharmaceutical products through the YODA Project, with expansion to medical devices in 2015 and consumer products in 2017. The YODA Project simultaneously accelerates scientific research, improves transparency, and provides industry with an impartial mechanism to demonstrate product safety and efficacy (10,40).

Two other data sharing platforms have emerged through collaborations between academia and industry. In 2014, Bristol-Myers Squibb and the Duke Clinical Research Institute announced a partnership called Supporting Open Access for Researchers to share clinical trial information, including protocols and deidentified patient-level data, for drugs approved in the United States or Europe (41,42). Notably, data from closed trials also will be shared under the partnership 2 years after termination. As with Clinical Study Data Request and the YODA Project, faculty from the Duke Clinical Research Institute, rather than employees of Bristol-Myers Squibb, will serve on the independent review panel and make final decisions about requests for access to the shared data.

Vivli, a project established in 2016 at Brigham and Women's Hospital and Harvard University, aims to "coordinate existing platforms and servers and provide a basic platform to enable more data generators to share their trial data" (43). Although it has yet to make data available for sharing, Vivli aims to host clinical trial data and other types of health-related data, including epidemiology and genomic data.

DATA SHARING EXAMPLES

Although many data sharing platforms are new, data sharing itself has already influenced clinical practice. The reanalysis of data from the clinical trial of digoxin, a heart failure drug, illustrates the real-world importance of data sharing (44). In 1997, the Digitalis Investigation Group published results showing that digoxin reduced the risks of hospitalization for worsening heart failure and overall hospitalization during a 3-year follow-up (45). Clinical guidelines recommended digoxin for both sexes, even though heart failure is known to have different risks, causes, and prognoses in men and women, and only 22.3% of trial participants were women (44,46). A few years after the results were published, independent researchers requested a public-use copy of the underlying trial data from the NHLBI. In a post hoc subgroup analysis comparing the effects of digoxin between men and women, digoxin was associated with a higher risk of death, and a smaller reduction in the rate of hospitalization for worsening heart failure, in women (44). This study was one of many to use the database produced from the Digitalis Investigation Group's clinical trial. Recent research into the results of sharing this data found that the research productivity of the trial database essentially doubled after outside investigators were allowed access to it, and that the journals in which outside investigators published their results rivaled, in impact factor, the journals in which the original trialists published their own research (47).

A recent example of data sharing comes from the Systolic Blood Pressure Intervention Trial (SPRINT) (48). Leading up to the *New England Journal of Medicine*'s April 2017 summit on "Aligning Incentives for Sharing Clinical Trial Data," the journal hosted the SPRINT Data Analysis Challenge, which shared the underlying SPRINT data to encourage researchers to submit novel analyses (49). Of note was an abstract

that found incorrectly calculated data for the Framingham 10-year cardiovascular risk score regression model. The originally published SPRINT results erroneously suggested, on the basis of the baseline data, that 61% of the study population had a 10-year cardiovascular risk ≥15%, not the 76% figure that the correctly applied formula would have yielded. The SPRINT team was alerted to this by an outside researcher participating in the SPRINT Data Analysis Challenge. A notification was subsequently made about the error in coding involving the reversal of the equation coefficients for treated versus untreated systolic blood pressure (50).

Data sharing has led journals to correct previously published papers when independent investigators detect errors. In the case of a 2014 *Journal of the American Heart Association* article summarizing results from a clinical trial on antibiotic resistance in intensive care units, an independent researcher calculated results that differed from those in the paper and then contacted the authors (51). Upon rechecking the analysis, the original investigators found that the 2 interventions had been miscoded in 1 intensive care unit and informed the *Journal of the American Heart Association* of the error, leading to a retraction and replacement (51,52). Reflecting on the retraction process, the last author wrote that the lesson was to "always let others use your original data for new (or just the same) analyses (53)."

THE FUTURE OF OPEN DATA IN CARDIOLOGY

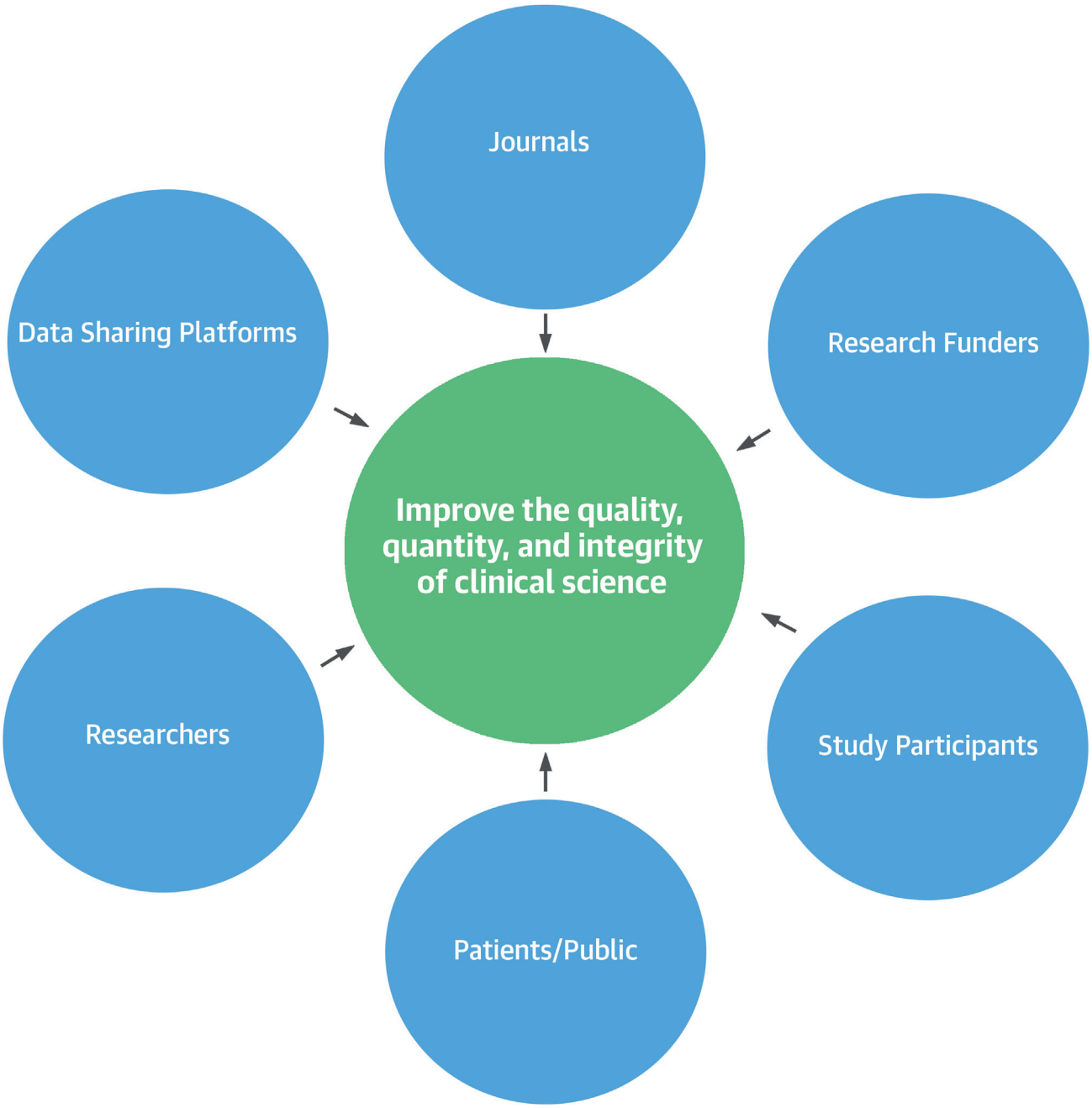
NEW INCENTIVES. Some have observed that data sharing may encourage researchers to capitalize on the productivity of others rather than create original data (54). Thus, new incentive structures will be necessary to accelerate and reward data creation, such as acknowledging the original producers of shared data in publications, providing funding for sharing, giving credit for data sharing and its downstream use in academic promotions, and reimbursing health systems that share data with patients and researchers (3,55). Another proposal suggests creating a standardized recognition system for data generators, a "data authorship" system distinct from the current system used for authors of peer-reviewed journal articles (56). Within this new structure, the best datasets and data generators will likely increase in prominence as it becomes more common to track the production (not just the analysis) of data (56).

SYNC FOR SCIENCE. The sharing of clinical data by patients with researchers also holds much potential. The Sync for Science (S4S) program of the NIH enables individuals to share their clinical data to support research through the Precision Medicine Initiative (PMI) (57). An application of big data analytics in medical research, the *All of Us* Research Program (formerly known as the PMI Cohort Program) aims to enroll >1 million patients who will donate health data in an electronic format (58). Using electronic health records (EHRs) limits the time and resources needed to support data requests because data flow from EHRs to researchers through the patient portal system. As S4S expands, researchers will be able to receive clinical data from patients, who thereby help contribute to scientific research. The PMI Working Group stated in 2015 that for S4S to incorporate updated clinical data as new events occur, EHR systems would need to allow S4S participants to "transmit and store their preference for automated data updates to be sent" to the S4S Coordinating Center (59).

S4S depends on patients having access to all of their records, including clinicians' notes. Patient groups and advocates, who are among the most vigorous in calling for data sharing, have created organizations including Genetic Alliance, Get My Health Data, and Free the Data to promote patient access to data (60,61). The OpenNotes movement, a voluntary effort to promote patient access to clinicians' notes, which are often absent from the available record, is gaining momentum. In the United States, >14 million patients in 37 states can now access the notes taken by their physicians during office and hospital visits, and at least 20 health systems plan to start open notes systems in 2017 (62,63). Evidence suggests that patients strongly support having access to notes and that most physicians find little change to their practice styles after a transition period (64,65). Questions remain regarding whether physicians should be allowed to keep some notes private and how to operate open notes systems in inpatient settings, where the existence of multiple clinicians and frequently changing plans complicate the process of granting access. Given that major medical systems, including the M.D. Anderson Cancer Center, the Veterans Health Administration, and the Mayo Clinic, have served as successful models for open notes systems, the OpenNotes movement appears poised to play a key role in the open data ecosystem and in making S4S a reality (66).

Returning data to patients, or "syncing back," represents another possibility for direct patient involvement. Recently, the Return of Individual Results workgroup at the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard articulated principles to guide the return of individual results, including routine results, individual endpoints, and exploratory findings, to patients (67). The workgroup argued that this practice not only

CENTRAL ILLUSTRATION **The New Data Sharing Ecosystem: Improving Research and Clinical Practice**



Dey, P. et al. J Am Coll Cardiol. 2017;70(24):3018–25.

The emerging health data ecosystem aligns the incentives of all stakeholders in the health care and research system to increase the pool of shared data available to generate new knowledge.

honors trial participants' contributions and enhances transparency, but also helps them become "actively involved in research and the generation of new scientific knowledge" (68). The principles emphasize returning results responsibly, using ordinary language, and engaging participants in a broader conversation (starting with informed consent) about their option to receive their data.

CONCLUSIONS

The revolution in data sharing that has transformed domains ranging from physics to genetics is just beginning for clinical medicine. Accelerated by new initiatives, encouraged by funder support, and enabled by new platforms, data sharing has started to transform research and practice in cardiology, even as the question of who should bear the costs of sharing remains controversial and the costs themselves are a potential impediment to sharing (**Central Illustration**). Resolving the cost issue will be central to achieving a culture of sharing. As we move toward a world of open data, cardiology has the opportunity to lead and, in so doing, to serve as a model for all of medicine.

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