

What's Next for Real-World Evidence in Oncology?

MICHAEL VASCONCELLES, MD; AND BRAD JORDAN, PHD



Michael Vasconcelles, MD, chief medical officer, head of the Medical and Scientific Organization, Flatiron Health



Brad Jordan, PhD, senior director, Regulatory Affairs Policy, Flatiron Health

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Why is it that the impact of RWD is growing and the convergence of clinical care and research is accelerating? Cancers are biologically complex and genetically heterogeneous. The ability to obtain optimal cancer care is impacted by social determinants within each patient's environment, and today, access to care is uneven.¹ Despite our recognition of these factors, the tools at our disposal to address each of them, be they diagnostic, therapeutic, or data and technologic, have been historically inadequate. These limitations have been compounded by well-intentioned social, health care, and regulatory policies that are incremental as measured against the scope of the challenge. For example, the bulk of what we've learned about how to treat cancer and the tremendous treatment advances over the last few decades are based on evidence generated from clinical trials centralized within academic medical centers and clinical research-focused practices and health systems. However, a minority of cancer care in the United States is actually delivered in these settings.² We know that patients who receive care in these centers may not be fully representative of the broader population of patients with cancer, which may, in some cases, limit the generalizability of these data. The result may be barriers to enrollment in clinical trials of novel and potentially lifesaving cancer treatments and access to the resulting advanced diagnostics, therapies, or other interventions once they are approved.

A recent example of how real-world data have contributed to improved care in the form of updated product labeling is the approval of a new dosing regimen for cetuximab, for use in certain patients with metastatic colorectal cancer or squamous cell carcinoma of the head and neck.

These constraints on our ability to discover and learn about how our treatments and other interventions affect patient outcomes, and to do so with the confidence in the generalizability of our data, are disintegrating now at an accelerating pace, breadth, and depth. We are in the midst of a period of dramatic change. The remarkable speed with which scientific inquiry into cancer biology and host response mechanisms to cancer has transformed the therapeutic landscape is also being replicated in cancer diagnostics. The digitalization of health care data is driving the ability to generate observations that may inform novel hypotheses or, at a minimum, provide deeper insights across ever-expanding patient populations. Coincident with this remarkable expansion of our therapeutic, diagnostic, and digital tool kit, our deepening societal commitment to health equity is institutionalizing the expectation that access to equitable health care, regardless of an individual's racial or sociodemographic profile, must be an integral element of our social contract.

In the United States, the digitalization of health care data accelerated in earnest more than 12 years ago with the passage of 2 critical pieces of federal legislation in short succession, the Health Information Technology for Economic and Clinical Health (HiTECH) Act and the Affordable Care Act (ACA), both of which encouraged the meaningful use of electronic health records (EHRs).^{3,4} With the proliferation of EHRs designed to meet the requirements mandated within these statutes, the potential opportunities for broad uses of RWD were readily apparent. One example within oncology is Flatiron Health's aggregation of deidentified real-world data sets derived from the medical records of more than 3 million US patients with cancer. Real-world use cases with these Flatiron Health data have included comparative effectiveness and outcomes research questions that contribute to improving our understanding of care delivery and its quality, the natural history of specific patient cohorts, use patterns, effectiveness, and adverse events of cancer medicines, among many others. The curation of both structured and unstructured data from EHRs involves a multifunctional team of clinical and technical experts, employing both human and machine-assisted components. These systems work together to create a deeply annotated research data set enhanced by the addition of composite or derived variables that can be linked to other data (eg, genomic and/or medical claims) to develop a highly comprehensive real-world data set.

A recent example of how RWD have contributed to improved care in the form of updated product labeling is the approval of a new dosing regimen for cetuximab, for use in certain patients with metastatic colorectal cancer (CRC) or squamous cell carcinoma of the head and neck (SCCHN). In April 2021, the FDA approved a biweekly dosing regimen for cetuximab as an alternative to the previously approved weekly regimen.⁵ Real-world evidence (RWE) generated from RWD from patients receiving either the weekly or biweekly dosing regimen, including patient survival outcomes, supported the results of the population pharmacokinetic modeling analyses in the supplemental submission. The sponsor's application was also supported by pooled analyses of overall response rates, progression-free survival, and overall survival from published literature focusing on patients with CRC and SCCHN.⁵ An alternative, less-frequent cetuximab dosing regimen allows scheduling alongside other biweekly treatments, significantly reducing patient visit frequency to infusion centers. Time is a precious commodity for all of us, and even more so for patients with advanced cancer; every moment saved not traveling to and from the clinic, or being in the clinic, is a moment saved for living life.

This recent regulatory approval decision is one of several using RWD to provide evidence in the postapproval setting in support of regulatory decision-making, potentially obviating the need for expensive, difficult-to-accrue, and/or time-consuming clinical trials.

This is only one recent example of how RWD and RWE can help drive progress in cancer treatments and have an impact on patient care. The effect that RWE can have in improving patients' lives, such as the example with cetuximab above, is substantial, and in this fast-evolving field will be one of many in short order. However, innovations such as those that have facilitated the use of digital health care data to improve care require policies that

support and incentivize continued investment. The rapid pace of legislative initiatives with key digital health components, like the Prescription Drug User Fee Act VII reauthorization⁶ and the 21st Century Cures Acts (ie, Cures 1.0 and proposed 2.0),⁷ and the steady drumbeat of RWD/E-focused FDA Draft Guidance documents released since September 2021⁸ are critical examples of how we're meeting this need.

Flatiron Health, along with our colleagues in the RWE Alliance,⁹ commends the FDA for its efforts to advance the use of RWD/E for regulatory decision-making. For example, recent FDA Draft Guidance focusing on characterization of EHR data for use in developing RWE for regulatory decision-making is foundational to progressing toward more widespread generation and use of relevant, and reliable, RWE. We also welcome the provision in the proposed Cures 2.0 legislation for creation of an RWE Task Force to develop recommendations that encourage patients to participate in generating RWE, such as by joining postapproval clinical trials. These kinds of initiatives can help define ways that RWE can illuminate the effectiveness of drugs in the real world. This is important work, and it is critical that health technology and data companies, leaders in the RWE field for years, add their expertise to this evolution toward the wider use of RWD for smarter, more efficient health care that meets the individual needs of each patient. It's time to develop new mechanisms by which health tech and data companies can work directly with regulators to address a broad range of topics that fall outside of a specific drug development program. Being smarter means not having to keep reinventing the wheel every time a sponsor takes RWD to the FDA.

The future demands a broader vision that builds on the already growing sources of health care information to capture and integrate a larger quantity of data from a wider variety of sources—initiatives such as the Flatiron Health – Foundation Medicine Clinico-Genomic Database; augmenting EHR data with medical and prescription claims data; and incorporating medical imaging into integrated, multisource RWD. RWD are helping to identify patients who may be good matches for clinical trials. They are also changing the design and conduct of clinical research, with the prospect of, for example, new EHR software that facilitates intentional data capture aimed at answering a specific research question.

Growing the footprint of clinical research beyond academic centers into the community oncology settings where most US patients with cancer are treated will help drive greater representativeness in the evidence used for important high-quality research, and for regulatory and treatment decisions. With this infrastructure and new tools that the field is working to put in place, it will be possible to use RWD to assess real-world effectiveness. Some of this proof-of-concept work is already being done with Health Technology Assessment bodies in Europe.

RWD and RWE are here to stay and have enormous potential to accelerate the development of new drugs and improve cancer treatment and outcomes. We all need to work together to ensure that the infrastructure is in place to keep supporting and incentivizing continued innovation. Patients are counting on us. ♦

AUTHOR INFORMATION

The authors are affiliated with Flatiron Health, a health care technology and services company focused on accelerating cancer research and

improving care. Michael Vasconcelles, MD, is chief medical officer and head of the Medical and Scientific Organization at Flatiron Health.

Brad Jordan, PhD, is senior director of Regulatory Affairs Policy at Flatiron Health and leads the company's efforts to ensure an optimal regulatory environment in order to advance the use of real-world evidence.

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