NEWDIGS

LEAPS

Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation

Downstream Innovation
Part II: Real-World Discovery LEAPS to Life!
December 2019 marked the transition from the LEAPS two-year design and feasibility assessment phase to the rollout of the rheumatoid arthritis in Massachusetts (RA MA) Pilot. Some important themes surrounding Downstream Innovation emerged that have helped us define next steps in implementation. These include:

DISEASED-FOCUSED LEARNING
Growing recognition of the need to augment product-focused learning with disease-focused learning in order to optimize therapeutic regimens.

COLLABORATION TO ENHANCE VALUE
Collaborate on RWE production with competitors and other stakeholder organizations where the time and cost efficiencies outweigh any proprietary risk.

EXPANDING "FIT FOR PURPOSE"
With Downstream Innovation, LEAPS can help broaden the lens of "fit for purpose" RWE to meet the decision-making needs for payers (i.e., access to therapeutics), providers and patients (i.e., use of therapeutics), rather than focusing primarily, or even solely, on meeting regulatory standards.

TIMELY USE OF RWE
There is well-founded concern that even if high-quality RWE is produced, it may not be used in a timely fashion, or at all, by downstream decision-makers. Hence, evidence generation platforms must be designed with end-user inputs.

AGGREGATE EVIDENCE, NOT DATA
In order to drive the robustness and scale of collective intelligence without the risk of patient-level data sharing, knowledge will be gleaned from the analysis of aggregated evidence.

A TWO-PART SERIES

The MIT NEWDIGS "LEAPS Project" is advancing sustainable, patient-centered biomedical innovation through a new collaborative systems approach to the planning, production, and use of real-world evidence.

This two-part Research Brief Series introduces the concept of "Downstream Innovation" as a critical enabler of biomedical innovation. Part I outlined the concept of Downstream Innovation and described strategic perspectives.

ESTABLISHING A CURRENT STATE
RA is rich with anecdotes and slim on data-driven insights. A better understanding of the current state of this disease as baseline for the pilot is critical in order to identify specific priorities to impact.

IDENTIFY PATIENT JOURNEYS
Identifying and characterizing patterns of variability in patient experiences with RA treatments over time into "archetypes" of patient journeys may help to improve decisions and outcomes.
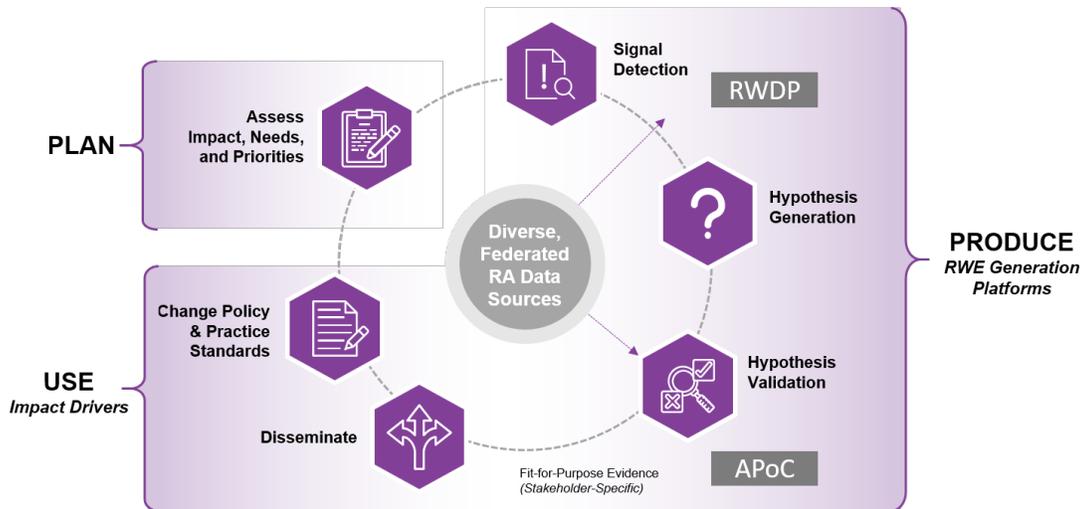
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Figure 1: LEAPS Learning Lifecycle: Transforming How We Plan, Produce, and Use RWE to Optimize Regimens for a Target Disease

LEARNING LIFECYCLE: TRANSFORMING RWE TO OPTIMIZE REGIMENS FOR A TARGET DISEASE

Two core evidence generation platforms are being developed for the RA MA pilot, each with the aim of creating a scalable, connected, virtual infrastructure for disease-focused learning. This connected learning system ensures that evidence is planned and produced for real-world impact. The platforms are designed through a structured, multi-stakeholder collaboration process using the LEAPS "Learning Lifecycle" framework (Fig 1). The first of these platforms, the Real-World Discovery Platform (RWDP) is currently being rolled out.

THE REAL-WORLD DISCOVERY PLATFORM – HUMAN EXPERTISE MEETS ARTIFICIAL INTELLIGENCE

The RWDP marries human expertise with artificial intelligence and machine learning, and applies it to diverse, distributed, retrospective real-world data sets (i.e., administrative claims, clinical, registry, socioeconomic, patient generated, and potentially others) to discover insights for informing decisions about use of therapeutics. The RWDP is a virtual infrastructure that can be scaled and used across a variety of data sources to develop smarter evidence that can fill gaps and address biases.

The role of the RWDP is to generate hypotheses that, if validated, would have significant impact on clinical decisions and outcomes. Hypotheses that emerge from the RWDP, that are also deemed promising by a governance team/process, will advance for validation into a separate but connected platform – the Adaptive Point of Care (APoC) platform (now under development).

APoC

The Adaptive Point of Care (APoC) platform integrates adaptive clinical trial principles and platform trial mechanics into a prospective point of care study design for continuous learning, embedded in clinical decision-making. APoC assesses not only therapeutic comparative effectiveness but also the relative benefits of regimens that vary the order, combination, switching criteria and patient sub-populations of medicines.

REAL-WORLD DISCOVERY LEAPS TO LIFE IN 2020: THREE INITIAL WORKSTREAMS

RWE platforms in LEAPS are designed to enable a comprehensive program of research, both generating and investigating multiple questions from different stakeholder perspectives. Accordingly, in this "proof of concept" phase of the first LEAPS pilot, efforts associated with the RWDP will be organized into three workstreams, each addressing different, but related, needs.
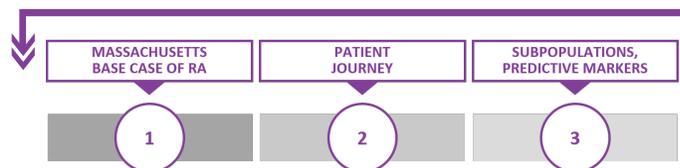

Figure 2: The Three Initial RWDP Workstreams

1. Massachusetts base case of RA

The first workstream will develop a baseline profile for the RA patient population and care utilization. Quantifying the heterogeneity of patient demographic characteristics and care will likely suggest opportunities for improvements as well as provide a basis for future comparison. Beginning with more than 5 years of MA data from its All Payer Claims Database (APCD), the LEAPS Integrated Knowledge Team based at MIT will create cross-sectional profiles to examine not only average statistics but also the trends, variability and clusters of those characteristics. For example, characterizing the population by its medicine switching rates by demographic or clinical sub-populations (such as severity or co-morbidities) might suggest opportunities for improved therapy selection, sequencing and/or patient monitoring and support. This workstream will also prototype the RWDP processes to guide the analysis with multi-stakeholder priorities and, perhaps most importantly, to invite other groups to replicate the analysis, compare their results and refine the evidence to generate stronger concepts to explore and test in the other workstreams.

2. Patient journey

LEAPS is exploring the potential to identify patterns of variability in the response of patients to different therapeutics over time. These patterns may lead to Patient Journey "archetypes" which may prove to be valuable for improving clinical decisions about therapies, especially when combined with predictive markers that may emerge from the next workstream in the RWDP. In addition, Patient Journeys may be a useful way to begin segmenting the natural history of RA, and, when linked to genomic and other biologic ('omic) markers data, could eventually illuminate underlying mechanistically distinct diseases.

Initial activities in this workstream focus on the following:
1. Build on the experiences of patients and the observations of clinicians to illuminate a set of qualitative descriptions of Patient Journeys on a continuum from mild to aggressive.
2. Identify cohorts of RA patients on specific classes of therapeutic products in different real-world data sets and analyze their disease trajectories over time.

Patient Journey:
Sequence of disease-specific health care events which mark a patient's clinical and life experience over the course of a disease, including diagnosis, treatments used, testing, changes in treatments, quality of life, co-morbidities, etc.

3. Subpopulations / predictive markers

While a number of 'omic markers have been identified in RA, none have been clinically validated. The working hypothesis in LEAPS is that through the RWDP, clinical/socioeconomic markers can be identified that, when combined with 'omic markers, enhance the ability for predictive decision-making, i.e., deciding which treatments to use for which patients when. This hypothesis will be evaluated on cohorts of patients receiving different product classes, with an initial focus on a single data type (claims), with the intent of broadening to other data types over time. The LEAPS Integrated Knowledge Team will start by identifying responders and non-responders to a product class in the Massachusetts APCD using an existing validated algorithm[1]. Subsequently, sub-populations of responders and non-responders will be identified based on characteristics with potential predictive value for decision-making, for development of a Feature Selection Profile v1.0 to be applied across a distributed network of collaborating organizations.

While the claims data are being analyzed first within the RWDP, attention is already being placed on broadening next to include the analysis of EHR data. Since there is currently no validated algorithm for identifying responders and non-responders in EHR data, discussions are now underway on how to leverage the LEAPS distributed network to accelerate progress on this.

	Workstream I: Base Case	Workstream II: Patient Journey	Workstream III: Sub-populations & Predictive Markers
Concept, Objectives	✓	✓	✓
Analytic Enablers	• Analysis plan v1.0 – initially developed for APCD	• Initial patient journey profiles v1.0 (descriptive, vetted) • Analysis plan v1.0 – patient cohorts	• Validated algorithms (data type specific) for identifying responders vs non-responders to product class • Feature selection profile v1.0
Reporting Template	✓	✓	✓

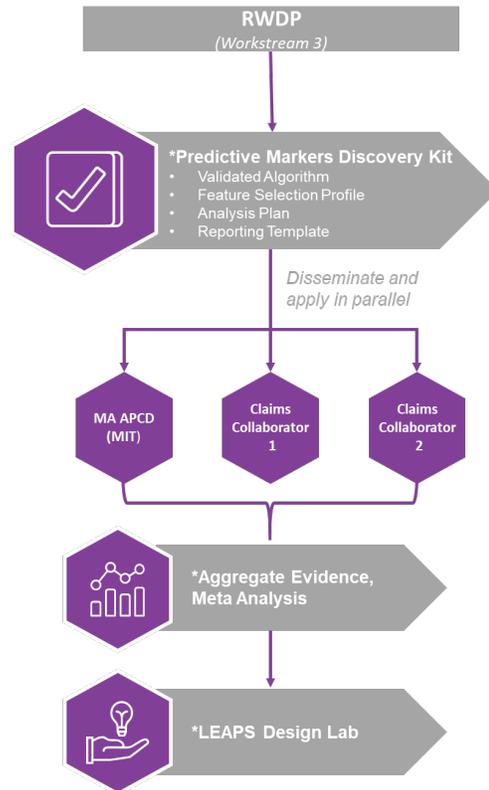Figure 3: Real-World Discovery Kits

STRUCTURING WORK AND COLLABORATIONS FOR SUCCESS AND FUTURE SCALING

A key differentiator of the LEAPS RWDP is that it leverages a network of distributed collaborators and federated real-world data sources to produce actionable evidence to improve decisions and outcomes for a target disease (RA). It builds on elements of other successful initiatives involving federated data sources, such as the FDA's Sentinel System, but differs in that RWDP will be used for generating new hypotheses, rather than addressing a specific type of query. In addition, the RWDP will not require data partners to use a common data model. Rather, the alignment of efforts will be guided by the shared development and use of common analytic protocols, open algorithms, and streamlined evidence sharing processes. [2]

FDA Sentinel System:
The U.S. Food and Drug Administration's (FDA) Sentinel System is a long-term effort to improve the FDA's ability to identify and assess medical product safety issues. The Sentinel System is an active surveillance system that uses routine querying tools and pre-existing electronic healthcare data from multiple sources to monitor the safety of regulated medical products.

For each of the three workstreams, a virtual team of collaborators develops the Workstream Plan that sets forth the goals/objectives and approach (methods, processes, etc.). Implementation planning includes the development and iterative enrichment of a *Real-World Discovery Kit*, customized for the particular workstream. The kits incorporate enablers for organizations within the LEAPS network who want to participate as an evidence production site for the associated workstream and streamlines evidence sharing through a standardized Reporting Template. The team will aggregate and analyze evidence from participating sites for evaluation and planning at multi-stakeholder LEAPS Design Labs.

Figure 5: Success Drivers in Downstream Innovation: Fit-for-Purpose System Designs

*Activities led by the MIT Integrated Knowledge Team

Figure 4: Workstream 3 Illustrates How Platform Strategies and Decision-Making Needs Underpin Distributed Evidence Generation In RWDP. A Similar Process Applies to Other Workstreams.

Findings at these events will be viewed within the framework of the LEAPS Learning Lifecyle to determine not only the next steps in Production (e.g., advancement to APoC for validation), but also to ensure strategic coordination with evolving Plan & Use priorities for RA regimen optimization.

As discussed in Part I of the research brief, Downstream Innovation system design centers around RWE generation platforms and their associated environments, shaped by governance and incentives models. Accordingly, the LEAPS team is currently working through the technical and operational details of the RWDP "proof of concept" phase (as described above), in addition to its environment, including:

- **Incentives** to motivate participation including contributing data, and technical and functional expertise
- **Governance** to ensure performance excellence such as transparency, structured decision-making processes, accountability, and other elements critical to ensuring the trust of all participants, as well as the credibility that will be important to drive industry-wide acceptance and impact of findings and recommendations
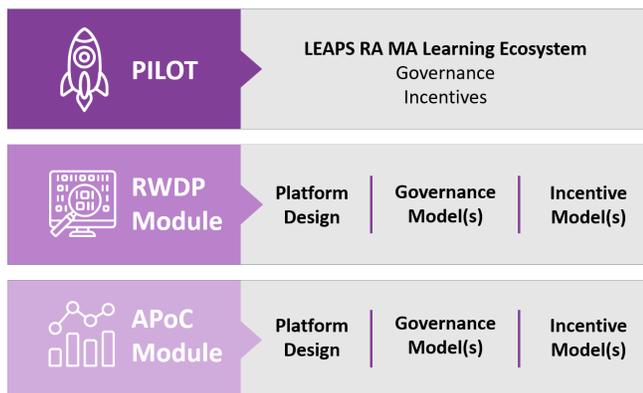
NEXT STEPS – GET INVOLVED IN 2020 AND BEYOND

Throughout 2020, there will be an iterative rollout of the RWDP workstreams, as well as modeling and simulation focused on the design of the APoC platform (details to follow in coming research briefs). While a number of collaborator organizations are currently involved in this project, additional partners will be warmly welcomed to broaden perspectives, enrich data sources, and accelerate value for all stakeholders – especially patients.

If you are interested in transforming the way we plan, produce and use RWE, please contact us at newdigs@mit.edu to become a partner organization.

REFERENCES

[1] Curtis et al.: Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis. Arthritis Research & Therapy 2011 13: R155. 9

[2] Keith A. Marsolo, Jeffrey S. Brown, Adrian F. Hernandez, Bradley G. Hammill, Sudha R. Raman, Beth Syat, Richard Platt, Lesley H. Curtis: Considerations for using distributed research networks to conduct aspects of randomized trials. Contemporary Clinical Trials Communications, Vol 17, 2020. https://doi.org/10.1016/j.conctc.2019.100515.

ABOUT LEAPS

The LEAPS Project (Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation) is advancing the mission of the MIT NEWDIGS consortium—to deliver more value from biomedical innovation faster to patients, in ways that work for all stakeholders—through a new collaborative systems approach to the planning, generation, and use of evidence across R&D and healthcare delivery. A model system for Rheumatoid Arthritis is now being piloted in Massachusetts and will inform related efforts in other diseases and geographies. Success in LEAPS targets better patient outcomes while also reducing waste and inefficiency across the system.

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