

## NEW DIGS

# LEAPS

Learning Ecosystems Accelerator for  
Patient-centered, Sustainable innovation

## RESEARCH BRIEF

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LEAPS Project  
November 2019

### Downstream Innovation

#### *Part I: Strategic Perspectives and the Case for LEAPS*

There is a growing recognition of the importance of augmenting product-focused learning with disease-focused learning, incorporating the value of advances in real-world evidence (RWE). Biopharmaceutical companies are creating internal data ecosystems fueled by aggregation and/or access to diverse real-world data (RWD) sources. However, most of these efforts are done in proprietary ways with substantial costs and duplication across companies. **In LEAPS, we aim to define the collaborative space for disease-focused RWE production.**

#### Introduction

As value-based healthcare evolves, the ability to deliver the right treatment to the right patient at the right time—“regimen optimization”—becomes an essential capability for the sustainability of biomedical innovation. Our inability to reliably deliver optimized regimens generates risks for all stakeholders, and is especially harmful for patients. Multiple, interdependent barriers prevent us from achieving this capability:



#### EVIDENCE GAPS

Massive, complex knowledge gaps undermine targeted clinical decision-making.



#### INEFFICIENT EVIDENCE GENERATION

The ways in which evidence is generated do not allow us to fully understand both the disease and patient journey.



#### MISALIGNED INCENTIVES

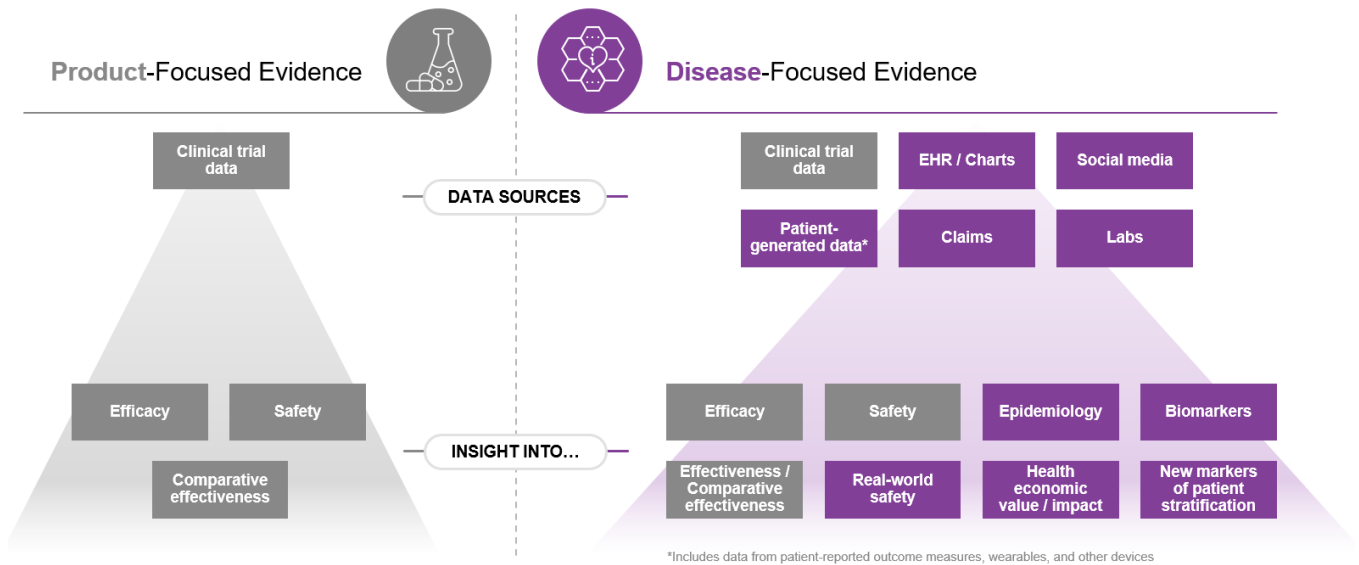
Flawed and misaligned incentives make it challenging to efficiently and effectively address real-world knowledge gaps.

#### A TWO-PART SERIES

The MIT NEWDIGS “LEAPS Project” is advancing sustainable, patient-centered biomedical innovation through a case-based approach to the design of new collaborative systems for disease-focused learning.

This two-part Research Brief Series introduces the concept of “Downstream Innovation” as a critical enabler of biomedical innovation. Part I outlines the concept of Downstream Innovation and describes strategic perspectives. Part II will apply the concepts of Downstream Innovation to the LEAPS case: a pilot for rheumatoid arthritis (RA) in Massachusetts (MA), the “RA MA” pilot.

**Figure 1: Product vs. Disease-Focused Evidence**



**PRODUCT-FOCUSED EVIDENCE ISN'T ENOUGH FOR DISEASE-FOCUSED STAKEHOLDERS**

Biomedical evidence is primarily produced by biopharmaceutical companies and is largely product-focused, driven by requirements for regulatory approval (Figure 1). However, product-focused evidence alone is insufficient to inform the decisions of downstream stakeholders (i.e., payers, providers, patients) (Figure 2). Shifting the paradigm to disease-focused evidence can enhance understanding of the disease and patients living with it, reduce uncertainties, and create profound improvements for treatment strategies and patient outcomes. *This need is illustrated by a fundamental uncertainty in RA—RA as currently understood phenotypically will most likely be characterized as multiple diseases mechanistically once underlying pathophysiological mechanisms are better understood.*

traditional clinical trial setting (efficacy) to a “real-world” setting (effectiveness).

Randomized clinical trials (RCTs) are necessarily conducted in very controlled settings with narrowly defined populations to isolate a therapeutic’s treatment effect in support of regulatory approval. Once on the market, the use of most therapeutics expands in multiple ways, often to a much broader patient population and more diverse treatment settings. As a result, many patient characteristics that may affect individual treatment response in real-world settings, e.g., disease stage, comorbid conditions, concomitant medication use, socioeconomic and demographic diversity, are excluded from RCTs and are not systematically studied. However, how these characteristics affect treatment response are critically important to downstream stakeholders when making treatment decisions.

**Figure 2: Upstream & Downstream Stakeholders**



**REAL-WORLD EVIDENCE GAPS: Individual Responses Matter**

A major uncertainty faced by downstream stakeholders is the change in a therapeutic’s benefit:risk profile from a

The lack of systematic learning from individual response differences in real-world use contributes to significant uncertainties for downstream stakeholders. *For example, in RA, among other disease areas, two relevant uncertainties include: 1) lack of clinically meaningful subpopulations, and 2) lack of clinically validated predictive biomarkers to guide treatment decisions. Currently, first-line biologics for RA only work for 20%-30% of patients after an inadequate response to methotrexate<sup>1</sup>—while they are on suboptimal treatments their disease is progressing in irreversible ways.*

In addition to its use in value-based healthcare, innovative areas such as precision medicine, also desperately need these types of deeper insights into individual responses. Without them, the development and implementation of novel therapies may be stalled or abandoned.

**INEFFICIENT EVIDENCE GENERATION:*****Narrow, Fragmented, Time Limited Evidence***

The knowledge needed to optimize treatment regimens is complex, dynamic, and multi-dimensional. It requires integration of multiple streams of evidence that together enhance our understanding of both the disease and the patients, as well as different patient experiences over the disease trajectory—“patient journeys.” However, the current state of evidence generation in biomedical innovation does not support this need. Biomedical evidence is generated in ways that are:

***Narrow***

Studies are too often designed to answer just one question, about one or two drugs, and for one stakeholder at a time. As such, they do not provide the insight needed to adequately inform decisions about the access and use of therapeutics in the real world.

***Fragmented***

Biomedical evidence is often generated within stakeholder siloes, at different points along a patient’s disease journey, and with inadequate contextual information, which limits the learning.

***Time-limited***

Biomedical evidence generation is time-limited with one-and-done, short duration studies for near-term conclusions and deliverables. The myopic, isolated research approach results in slow and costly systemic learning.

*And without the evidence that matters to them, payers may not provide coverage and reimbursement—regulatory approval is no longer synonymous with patient access and benefit.*

**FLAWED, MISALIGNED INCENTIVES:*****Behaviors that are Rewarded***

Traditionally, biopharmaceutical companies were incentivized to develop products with the largest possible market. They focused on fulfilling the requirements of regulators, funneling their resources into the generation of evidence centered around safety and efficacy in order to receive marketing authorization.

This model was acceptable when payment in healthcare was volume-based, but it does not work in a value-based healthcare system. Additional uncertainties vitally important to payers, such as cost effectiveness and real-world comparative effectiveness, cannot be adequately addressed by safety and efficacy evidence derived from RCTs. And without the evidence that matters to them, payers may not provide coverage and reimbursement—regulatory approval is no longer synonymous with patient access and benefit.

In value-based healthcare, there is an opportunity to modify and align incentives around patient-centered value, where RWE enables payers to provide coverage and reimbursement of therapeutics that work best for specific patient profiles or sub-populations.

Evolving models of value-based contracts between manufacturers and payers introduce a potentially powerful mechanism for aligning the incentives of all stakeholders in ways that fuel disease-focused learning. Currently, however, value assessment models lack strong RWE, which has inhibited the evolution of these models, so payers continue to base contracting on cost, not value. *For example, treatment choices are currently guided by strict step therapy programs, which generally requires that patients try the less expensive Drug A before they can take the more expensive Drug B.* Payer collaborators within LEAPS report that if they had better and more timely info, updated by high quality RWE, they would base contracting more on clinical value rather than just cost.

However, the evolution toward value-based payment models will continue to lag as long as downstream stakeholders persist in relying primarily on product-focused evidence supplied by pharma. If downstream stakeholders worked together in new ways to fill gaps in RWE in ways that are enabled in LEAPS, this evolution could be accelerated and we could expect incentives to align to favor patient-centered value. In addition, this RWE yields valuable insights not only for access to and use of products once on the market, but also for upstream Research and Development<sup>2</sup>.

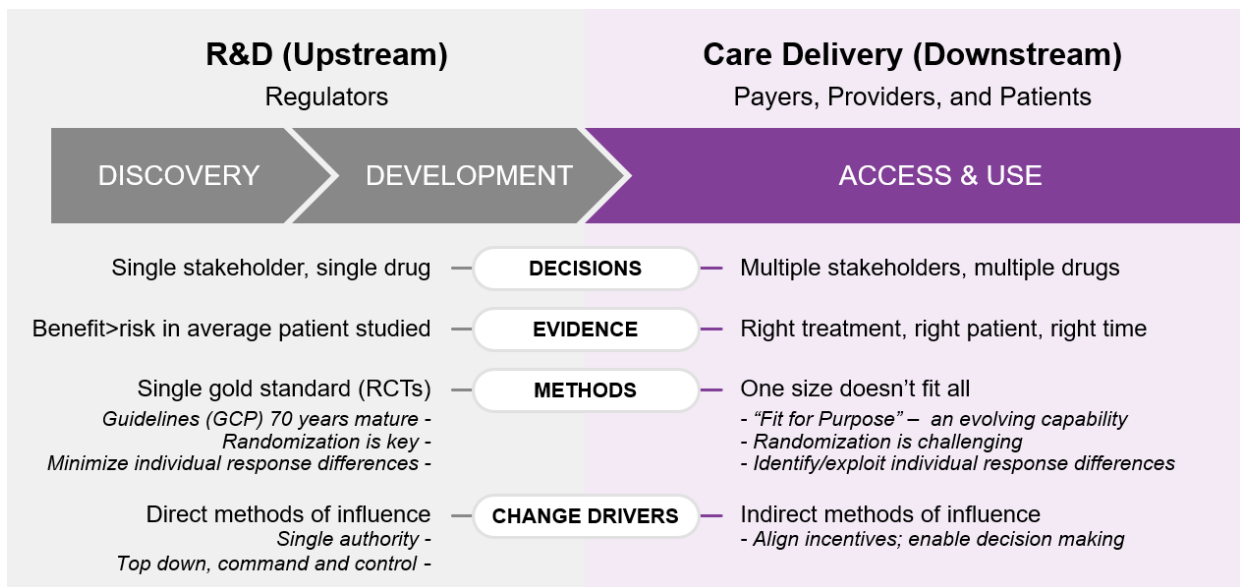
**THE DOWNSTREAM CHALLENGE**

Historically, most systematic learning about a therapeutic stops at the point of regulatory approval. Consequently, downstream stakeholders make their decisions with evidence primarily from RCTs, which is not always fit-for-purpose for their considerations. In value-based healthcare, it is critical that systematic learning continue into the real-world setting. However, effecting this change is more challenging than it sounds.

Several key distinctions between upstream (R&D) and downstream (care delivery) activities present challenges in tackling the complex RWE needs and addressing the critical knowledge gaps to enable evidence-based care (Figure 3).

Currently, downstream evidence is predominately generated by biopharmaceutical companies and primarily targets specific uncertainties related to safety and post-marketing regulatory commitments of a single drug or class of drugs. Additionally, downstream stakeholders hold much of the data necessary to produce RWE and inform real-world treatment decisions. *There is a need to embrace a broader view of RWE to extend systematic learning downstream.* However, evidence standards that must be met for regulatory decisions may not be possible, or necessary, for all RWE efforts. Requirements may vary by stakeholder, and acquiring a deeper understanding of these requirements will help identify areas of commonality and make it easier for stakeholders to work together to meet everyone’s needs.

**Figure 3: Reducing Uncertainty: What’s Different about “Upstream” vs. “Downstream” Activities**



## DESIGNING A DOWNSTREAM INNOVATION SYSTEM: A Preview

LEAPS is catalyzing the evolution of a biomedical innovation system in which post-market activities are fragmented, narrow, and time limited, to a system that utilizes greater coordination and results in increased efficiencies and impact for stakeholders—most importantly, a system that helps improve patient outcomes. Given the complexities of the downstream space, effecting this change will require the creation of a new Downstream Innovation System.

The goal for Downstream Innovation in LEAPS is to enhance the capacity of a disease ecosystem to optimize therapeutic regimens. Achieving this goal requires generating targeted evidence that meets the decision-making needs of each stakeholder in ways that are scalable, and with greater time and cost efficiencies.

Two key elements in the design of a Downstream Innovation System are:

1. **Infrastructures** to reduce knowledge uncertainties
2. **An environment** around the infrastructures to encourage conducive behaviors

The Downstream Innovation System is based on three foundational pillars: Platforms, Governance, and Incentives (Figure 4). All three pillars are critical to the success of the system and must be designed in tight coordination with the others, with input from all key stakeholders.

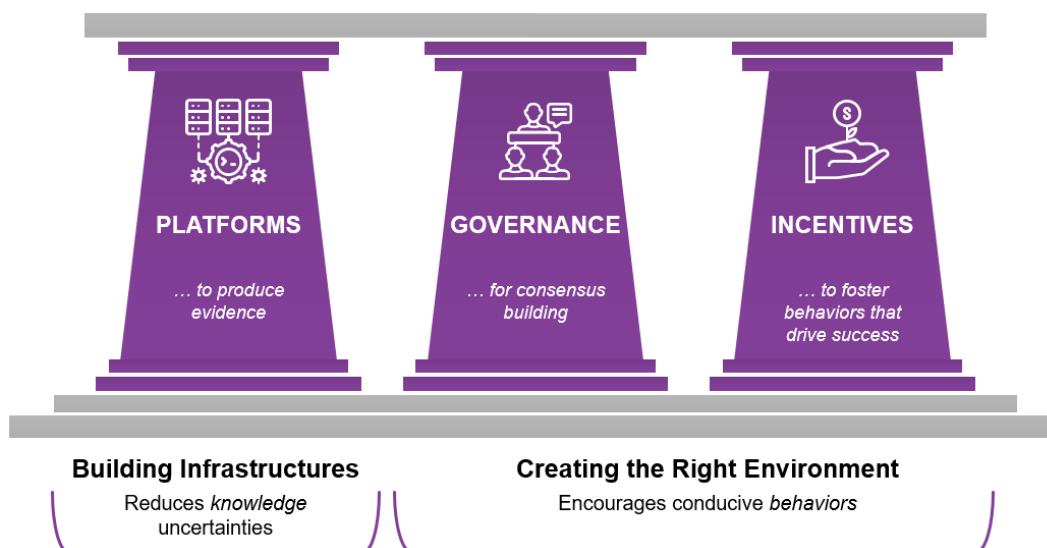
### INFRASTRUCTURES *for reducing knowledge uncertainties*

- **Platforms** will drive efficient generation of actionable knowledge. Designs will be tailored and will include access to relevant distributed data sources, as well as application of specific design and analysis methods to address evidence needs that are common to multiple stakeholders in a disease ecosystem.

### ENVIRONMENT *for encouraging conducive behaviors*

- **Governance** is necessary for consensus building and will require creation of a new distributed leadership entity. A governance model will involve multi-stakeholder representation and the cross-cutting technical expertise required to develop effective principles and decision-making processes that consider the needs and priorities of all stakeholders.
- **Incentives** foster behaviors that drive success. Innovative incentive models will be tailored to stakeholder behaviors that are important for the success of the system.

Figure 4: Pillars of a Downstream Innovation System



**DEFINING THE COLLABORATIVE SPACE FOR DISEASE-FOCUSED RWE PRODUCTION**

In LEAPS, we aim to define the collaborative space for disease-focused RWE production. That is, knowing when and how it is possible to drive more value to all stakeholders by working together rather than alone to generate the RWE necessary for disease-focused learning. Additionally, when such collaborative opportunities are identified, how can we make it easier to pursue them in ways that are timely and efficient? Insight into these key questions will be pursued through the LEAPS RA MA pilot.

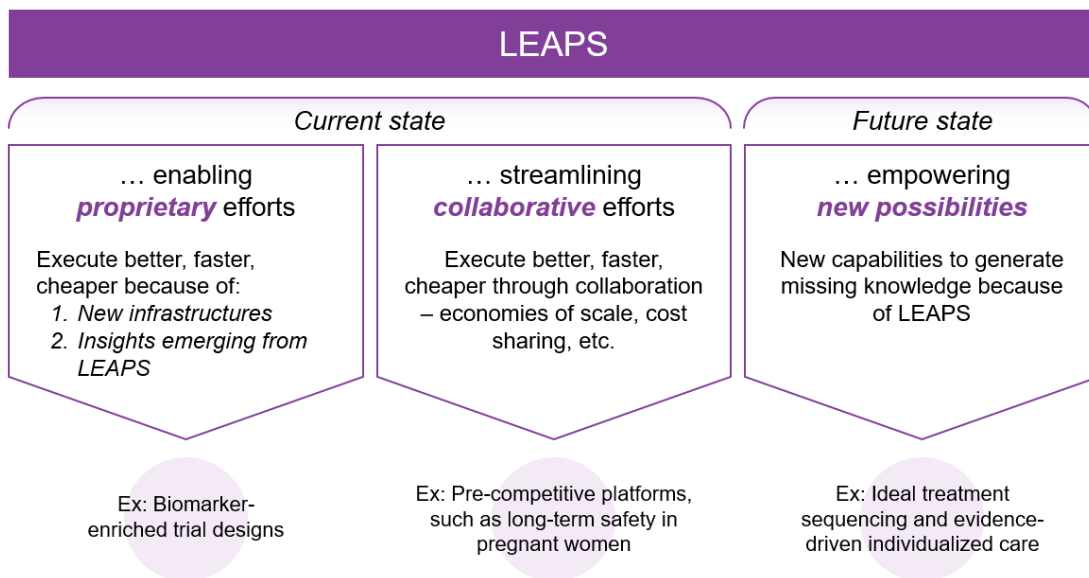
Defining the collaborative space for disease-focused RWE production will drive value for both proprietary and collaborative efforts, and for both the current and future state (Figure 5). Collaborative RWE production will meet some current state RWE requirements more efficiently and effectively than currently done. Biopharmaceutical companies can capitalize on new infrastructures created and insights gained from collaborative work to increase the efficiency and value generated through their own proprietary efforts. New infrastructures created and insights gained will also yield new capabilities that drive new possibilities and fuel future state value.

**CONCLUSION**

Mapping the concept of downstream innovation has created a buzz of excitement not only from LEAPS, but also other collaborators critical to the development. While post-marketing activities are still disparate in nature, the team is optimistic that this first step in bringing the players and evidence generation activities into a framework and assigning common terms will be fundamental to identifying and leveraging powerful synergies among downstream stakeholders, as well as enabling alignment with those upstream.

The downstream challenges discussed in this research brief have been well known for many years, but the solutions presented are novel and must be put to the test. The Downstream Innovation System’s platforms, governance, and incentives will be tested and further refined in tight coordination with Upstream Innovation in Part II of this module: The RA MA pilot.

**Figure 5: Value Streams of LEAPS**



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## 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 will be piloted in Massachusetts (2020 launch), 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.

### *Research funding*

This research was wholly funded by the NEWDIGS Initiative Consortium Members run through the MIT Center for Biomedical Innovation. It received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### *Acknowledgements*

MIT NEWDIGS would like to extend special thanks to representatives from Evidera for their support and contribution towards this publication.

### *Please cite using*

MIT NEWDIGS Research Brief 2019L311v045-Downstream Innovation Part I