Leaping Together Toward Sustainable, Patient-Centered Innovation: The Value of a Multistakeholder Safe Haven for Accelerating System Change

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Successfully delivering on the promise of emerging science in a world of value-driven healthcare requires that we fundamentally reengineer biomedical innovation processes to be both patient centered and sustainable. Massachusetts Institute of Technology’s New Drug Development Paradigms (NEWDIGS), a “think and do” tank launched in 2010, provides a safe haven, precompetitive environment for multistakeholder collaboration to innovate how we innovate. Its newest project, Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation (LEAPS), will pilot an innovation system designed to enhance decision making, outcomes, and trust among key stakeholders.

THE CASE FOR CHANGE

Although science brings with it the hope of life-changing treatments, it also brings risk and uncertainty that challenge the system to deliver, when operating in usual siloed ways.

Take, for example, the accelerated approval of eteplirsen (Exondys 51) for Duchenne’s muscular dystrophy in 2016, which offered hope as the first treatment available for this fatal childhood disease. Its path through development, market access, and clinical use highlights an extreme set of misalignments across the bench-to-bedside value chain that represent unworkable limitations of an innovation system in urgent need of reform.1–3 Specifically, this case illustrates how the lack of coordinated, prospective planning among stakeholders on evidence standards and context-specific decision factors fueled risk, uncertainty, mistrust, and polarization between, and within, stakeholder groups. And, most important, it threatened access to a potentially life-saving treatment for a desperate patient population.

Traditional biomedical innovation involves a linear series of decisions and actions (i.e., “behaviors”) implemented within stakeholder silos, each with their own set of incentives and risks, and without coordination across them. However, what happens in each silo affects perceptions of risk, uncertainty, and value for those in other silos, and ultimately, as was seen with eteplirsen, can undermine what works best for patients.

1. A common overarching goal: to drive more value faster to patients, in ways that work for all stakeholders, and for the system (i.e., minimize waste and inefficiency).

2. Decision making involves greater interactivity among stakeholders to enable more explicit exploration of tradeoffs, and to improve decisions, actions, and outcomes, in alignment with the shared goal.

3. Decisions about patient access to therapeutics are flexible (not binary) and are iteratively refined over the lifespan of products as critical uncertainties are reduced.

4. Uncertainties about a product that must be progressively reduced are explicitly identified and addressed among stakeholders, and fall into two types:

NEWDIGS ENABLING LEAPS THROUGH ADAPTIVE BIOMEDICAL INNOVATION

Adaptive biomedical innovation (ABI) is a principle-driven approach to the development, access, and use of biomedical products that enables sustainable, patient-centered innovation.4 ABI represents a broadening of lessons learned from the Massachusetts Institute of Technology (MIT) New Drug Development Paradigms (NEWDIGS) Adaptive Licensing Project (2011–2014)5 and the related European Medicines Agency (EMA)–led Adaptive Pathways pilot project (2014–2016).6 It offers a holistic framework for process innovation across traditional stakeholder silos in research and development and healthcare delivery. At the core of this approach is a belief that greater coordination across silos is essential to improve the effectiveness and efficiency with which we progressively reduce uncertainty, collaboratively manage risk—both patient-centered benefit/risk (i.e., the biology) and product development risk (i.e., the business)—and ultimately optimize the value of innovation for patients and for the system.

Defining and interrelated characteristics of ABI include the following:

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Figure 1 Complex behavioral dynamics in biomedical innovation, as seen in the case of eteplirsen (Exondys 51). This behavioral dynamics map builds on Table 1. It is not meant to be a comprehensive representation of all stakeholder behaviors that played out within the eteplirsen case. Rather, it is designed to show some representative examples, and the complex interplay among them, when biomedical innovation is performed through linear, sequential, siloed decision making. The story in this illustration begins with the sponsor’s decision (BEHAVIOR) to use an unvalidated surrogate as an end point and ultimately ends by highlighting that, although patients are at the center for the image, they are fully dependent on the collective behaviors of all other stakeholders. This depiction illuminates that the unintended negative consequences of stakeholder behaviors may play out in terms of the following: (i) the BEHAVIOR (i.e., decisions and actions) that is executed, (ii) the CONCERNS that are considered in choosing a behavior, and/or (iii) the IMPACT of one’s behavior on another stakeholder.

a. Knowledge uncertainties, which are addressed through the ongoing generation of evidence across the product life span, with evidence planned prospectively and refined iteratively. This requires that downstream decision makers (patients, payers, and clinicians) provide early and ongoing input into the evidence required for them to assess the value of the product for a specific population or individual patient, complementing the evidence regulators need to evaluate whether benefits outweigh risks for the average patient in a clinical trial (informally referenced within NEWDIGS as the “benefit/risk-value evidence gap”).

b. Behavioral uncertainties of one stakeholder that may negatively or positively affect other stakeholders are addressed by aligning incentives among the relevant parties.

Although most of the elements of ABI have been well described, behavioral uncertainties (4b) have, until recently, not been explicitly recognized or systematically considered as factors that may undermine patient-centered decisions, actions, and outcomes. And yet—even if the most
Table 1 Illustrative stakeholder behaviors in eteplirsen (Exondys 51) that affected other stakeholders in ways that may undermine patient-centered innovation

| Stakeholder behavior (actual and potential) | Impact on other stakeholders |
|--------------------------------------------|------------------------------|
| **Sponsor:** Selects unvalidated surrogate as end point | **Regulator:** Fuels polarization in preferences among regulators and experts—i.e., those more afraid of approving an ineffective drug (type I error) vs. those who fear failing to give access to a treatment that might work for an otherwise fatal disease (type II error) |
| **Regulator:** Grants expedited approval for marketing authorization for product for all patients with the disease on the basis of a subset of clinical data | **Patients:** May fuel false hope; potential exposure to safety issues yet to be identified; risk of inability to access product because of payer decision to deny coverage; risk of product being withdrawn from market if evidence of safety problems or lack of effectiveness emerges **Providers:** Must play important role in helping patients temper hope **Payer:** Must decide whether to cover with inadequate evidence of effectiveness for treatment-eligible population |
| **Sponsor:** Unwilling to share risk by using value-based contracting | **Payer:** May or may not provide coverage; coverage may be limited only to those included within the subset of clinical data that led to regulatory approval, rather than all treatment-eligible patients **Provider and patient:** Increases uncertainty about patient ability to access the drug; patients for whom end point was not meaningful (i.e., wheelchair bound) at higher risk of access denial |
| **Payer:** Denies coverage for patient access | **Patients:** Must decide if they are willing to take on the substantial financial burden to access treatment with uncertain effectiveness |
| **Sponsor:** End points defined without adequate input from patients | **Provider and patient:** Label may be too narrow and could limit access for other patients who might benefit **Payer:** May be missing opportunities to improve quality and reduce cost of care over lifetime of disease |
| **Sponsor:** (Potential) inadequate tracking of clinical outcomes associated with postmarket regulatory commitment | **Regulator:** Increases perceived risk associated with early access decisions **Payer:** Concerns that they may be paying for product that is not effective **Provider and patient:** Increases risk of suboptimal use of product or exposure to safety issues |
| **Patient:** (Potential) refusal to allow product to be withdrawn from market if postmarket evidence fails to confirm effectiveness or reveals safety problem | **Regulator and payer:** Increases perceived risk associated with early access decisions |

Stakeholders may behave in ways that are rational given the incentives within their silo, but that have unintended negative consequences in terms of the impact of these behaviors on other stakeholders, and ultimately for patients. Examples above from the case of eteplirsen include actual stakeholder behaviors executed, as well as potential behaviors that were likely considered, either implicitly or explicitly.

The perfect body of evidence for a product were available to all to inform decisions—stakeholders may interpret the evidence in ways that lead to behaviors that are rational given the incentives within their silo, but have unintended negative consequences for other stakeholders, especially patients (see Figure 1 and Table 1 for examples from the eteplirsen experience).

Stakeholder behaviors, including the subjective weighting of decision factors (i.e., “preferences”), which often differ between, and within, stakeholder groups, can contribute substantial waste and inefficiency across the system. For example, products may be approved by regulators through expedited pathways, but payer decisions may limit or deny their access for patients, as was the case with eteplirsen. This case also highlights that no stakeholder group is monolithic, as was seen with the deeply polarizing preferences that played out among regulators, and among payers. Understanding these potential misalignments earlier in the process through more explicit discussions among relevant stakeholders can play a powerful role in reducing risk, uncertainty, mistrust, and waste of valuable resources.

Adaptive platform clinical trials, conversely, demonstrate a robust example of stakeholder alignment that fuels innovation, with their design and implementation enabled by collaboration among the US Food and Drug Administration (FDA), multiple competitive industry sponsors, and academic researchers. This exciting new model aligns with ABI principles by creating greater efficiencies through prospectively planned master protocols and patient-centered clinical trial designs with prenegotiated, embedded rules for real-time, adaptive decision making.

Adaptive biomedical innovation offers a timely, unifying vision for the evolution of the global biomedical innovation system. Because the system typically evolves in fragmented ways that are tailored to context, change may look different across geographies and diseases. This is seen, for example, in the limited population pathway for antibiotics, granted through the US 21st Century Cures legislation in 2016. This pathway provides a mechanism for initial product approval for a subpopulation of patients within a broader indication—an authorization that is aligned with a key element of adaptive pathways. From a principle point of view, the intent of these two advancements is similar, despite their different forms that were required for successful local adoption. ABI provides a lens for seeing the common principles and potential synergies between disparate system advancements across the global industry.

There are, however, challenges in advancing ABI. In contrast to the business of pharmaceutical innovation, where getting to market first with a novel therapeutic often has competitive advantages for a company, being an early adopter of ABI approaches at this stage of system evolution can be difficult. For example, a company participating in the Adaptive Pathways pilot reported that, although valuable insights were gained from the experience, the lack of clear, convergent feedback from health technology assessment officials and additional resource requirements for the generation of real-world evidence led it to withdraw from the pilot. Such experiences underscore the
The importance of multistakeholder initiatives, like NEWDIGS, for accelerating the evolution of technologies, processes, and policies that will enable ABI.

Although many exciting and relevant system innovations are appearing, they must be connected to drive impact. For example, value-based contracts are critical components of ABI. However, their implementation in the United States requires interdependent changes in policy (e.g., Medicaid best price and antikickback policies), advancements in data and analytics (e.g., the ability to link laboratory test data with the tracking of product prescriptions and use by patients), and learning from experimentation in contract designs, to be successful.

LEAPS, THE NEXT WAVE OF ABI

In December 2017, MIT NEWDIGS launched its LEAPS Project. The vision for LEAPS is to demonstrate a scalable learning system that makes it easier for stakeholders to apply ABI principles. The first LEAPS pilot will target one disease (rheumatoid arthritis) and will be implemented in Massachusetts, a state known globally for its innovation leadership in life sciences, medical care, technology, and health policy. LEAPS offers an opportunity to drive greater collective health impact from biomedical innovation in Massachusetts by connecting these stakeholder silos, recognizing that the value of therapeutic products is largely assessed and managed at the state level in the United States.

LEAPS provides a multistakeholder, geographically defined testbed at a time when the healthcare system is shifting to one that rewards value over volume. This shift creates powerful new incentives for addressing the many knowledge gaps that exist about optimal product use at the time of market entry. Although several emerging policy, technology, and process innovations are pointing the way forward on addressing these gaps, each individually is insufficient. They must be connected into a system that improves decision making, actions, and outcomes for all stakeholders, and especially for patients.

The project builds on the recognition that all stakeholders generate data in their daily activities, but they need more than just their own data to make good decisions. Collaborators will work together to design a LEAPS “Learning Engine,” consisting of a distributed network of purpose-driven evidence generation platforms, that draws from an array of disparate data sources. It will deliver evidence that is fit for purpose to improve decision making across the value chain and produced in ways that are efficient, scalable, and sustainable.

NEWDIGS’ guiding principles and proven tools and methods for collaborative system innovation within a safe haven environment will be key in fostering rapid-cycle prototyping and greater trust among stakeholders throughout pilot design and implementation.

“The most dangerous thing in the world is to leap a chasm in two jumps,” as David Lloyd George, British Prime Minister, noted during the First World War. Our hope is that LEAPS will offer the opportunity, environment, and tools to bridge the chasm to patient-centered innovation together.

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CONFLICT OF INTEREST

The author declared no competing interests for this work.

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