

# Adaptive Biomedical Innovation: Evolving Our Global System to Sustainably and Safely Bring New Medicines to Patients in Need

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The current system of biomedical innovation is unable to keep pace with scientific advancements. We propose to address this gap by reengineering innovation processes to accelerate reliable delivery of products that address unmet medical needs. Adaptive biomedical innovation (ABI) provides an integrative, strategic approach for process innovation. Although the term “ABI” is new, it encompasses fragmented “tools” that have been developed across the global pharmaceutical industry, and could accelerate the evolution of the system through more coordinated application. ABI involves bringing stakeholders together to set shared objectives, foster trust, structure decision-making, and manage expectations through rapid-cycle feedback loops that maximize product knowledge and reduce uncertainty in a continuous, adaptive, and sustainable learning healthcare system. Adaptive decision-making, a core element of ABI, provides a framework for structuring decision-making designed to manage two types of uncertainty – the maturity of scientific and clinical knowledge, and the behaviors of other critical stakeholders.

The current system of biomedical innovation is unable to keep pace with scientific advancements. We need to reengineer the innovation system—the policies, processes, and structures that govern the translation of scientific innovation into patient and public health impacts—to accelerate reliable delivery of products that address unmet medical needs. We propose an innovation system that brings stakeholders together to set shared objectives, foster trust, structure decision-making, and manage expectations through rapid-cycle feedback loops that maximize product knowledge and reduce decision-making uncertainty in a continuous, adaptive, and sustainable learning healthcare system.

There are many reasons to be optimistic about the future of biomedical innovation. Potentially curative therapies are beginning to reach the market, with many more in the clinical development pipeline.<sup>1</sup> However, because the science is advancing faster than the system’s ability to translate medical advances into standard clinical care pathways, even the most brilliant scientific breakthrough, such as a gene therapy for a fatal disease, might well fail to deliver real value to patients and society.

The lagging evolution of the innovation system is an urgent problem. Patients and providers are understandably impatient for

affordable access to effective treatments,<sup>2</sup> and for accelerating the translation of emerging science into new treatments. Regulators are charged with often conflicting roles: both to ensure public and patient safety and to enable and facilitate access to new, needed medicines.<sup>3</sup> The challenge of finding the right balance between these two mandates was described by one senior regulatory official as: “. . .there are only two speeds of product approval: too fast and too slow.”<sup>4</sup> In addition, financial stresses are threatening the viability and sustainability of the innovation enterprise. Healthcare cost growth is leading to (1) payers struggling to provide the best care possible to the most people while maintaining sustainable financing for the long term; (2) patients unable to access treatments or if they do, facing severe financial stress; and (3) manufacturers facing greater uncertainties in bringing new curative therapies to patients, as it becomes less clear that they will bring a return on the research and development investments made.<sup>5</sup>

In many ways, the current innovation system has outlived its utility. It needs an overhaul, but closing the evolutionary gap between the pace of scientific advancements and the system that shepherds innovation through to impactful medical treatments is

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a massive undertaking in terms of scope, scale, and complexity. Unfortunately, change in healthcare is notoriously slow, fragmented, and inefficient.

Although the challenge is daunting, it is heartening to see important advancements emerging across this innovation system. Stakeholders are demonstrating greater proficiency and willingness to engage in collaborative forms of innovation across a range of settings. For example, public-private partnerships, in which companies and other stakeholders work together under precompetitive arrangements, are growing in use as external innovation environments.<sup>6</sup> Multistakeholder partnerships empower participants to tackle complex challenges across the innovation value chain, such as biomarker discovery and validation,<sup>7</sup> new clinical trial strategies and infrastructures,<sup>8</sup> policy innovations that enable earlier patient access to emerging medicines,<sup>9</sup> and enhanced post-authorization monitoring processes, tools, and methods.<sup>10</sup> In addition, emerging markets are a focus for new partnerships that support the Sustainable Development Goals issued by the World Health Organization.<sup>11</sup>

These advancements are promising, but the volume and fragmentation of related activities can fuel confusion and inefficiency. One challenge is that policy and process innovations are designed, named, and implemented at local levels, whereas diseases and biopharmaceutical companies are global. For example, the Adaptive Pathways pilot program,<sup>12,13</sup> launched by the European Medicines Agency (EMA) in 2014, is seen by some as a Euro-centric approach, although many of its underlying principles could apply globally. As a result, biopharmaceutical companies must respond to multiple approaches and procedures for researching and presenting research on medical innovations.

The good news is that many of the tools that are needed to reengineer the system already exist. We must now learn how to use them in ways that are more integrated and impactful. This will require process innovation, shaped by a coherent strategic approach to help us make sense of, and leverage synergies across, this dynamic evolutionary landscape.

## WHAT IS ABI?

Adaptive biomedical innovation (ABI) is a multistakeholder-driven approach to process innovation aimed at accelerating the delivery of clinical value to patients and society while continuously improving the knowledge/uncertainty profile of medicines. The goal of these improvements is to improve the overall effectiveness and sustainability of the biomedical innovation system itself.

ABI strives to address challenges associated with the following assumptions:

- Biomedical innovation involves significant uncertainties that must be progressively reduced through knowledge generation over the lifespan of a product in order to optimize its value to patients and society.
- All key stakeholders must make strategic “go/no-go” decisions about new treatment development and delivery in the face of incomplete and often evolving information.

- Development of shared goals
- Multi-stakeholder interactions
- Structured process for decision-making
- Uncertainty identification and management
- Proactive, rapid cycle learning, feedback and continuous improvement
- Building trust

**Figure 1.** Key elements of adaptive biomedical innovation (ABI).

- Each decision impacts other stakeholders’ benefit/risk calculations and behaviors—and especially those of patients.

The key elements of ABI are described herein, and summarized in **Figure 1**.

### Development of shared goals

ABI focuses on the establishment of a set of goals shared by all stakeholders at both a product and a system level, as follows:

1. **Product level: Timely, appropriate, knowledge-driven patient access to new treatments that improve health outcomes.** This focus is patient-centered, but conditions must also be acceptable to all other stakeholders, such as research scientists, healthcare providers, public health officials, policy-makers, regulators, payers, Health Technology Assessment (HTA) agencies, and sponsors. Every stakeholder is part of the process and the solution, and “wins.”
2. **System level: Continuous and sustainable flow of valuable biomedical innovations.** Patients benefit in timely and meaningful ways from emerging science. Technical, policy, and process elements of the system are designed to optimize patient benefit and to continuously improve, based on emerging knowledge, in order to maximize the system’s reliability, agility, and sustainability.

### Multi-stakeholder interactions

ABI aims to deliver better affordable treatments to the right patients faster, in ways that “work” for all stakeholders. Success requires early and iterative interactions among key stakeholders to enable prospective planning and coordination in decision-making across the lifespan of products. This involves significant process innovation given the linear, sequential, and siloed nature of decision-making in existing drug development and delivery systems.

### Structured process for decision-making

ABI relies on a structured process for decision-making based on the principles of iterative learning, confirming, and continuous improvement in the face of uncertainties that are inherent to the process of biomedical innovation. This approach is described in detail in subsequent sections of this paper.

### Uncertainty identification and management

Although there are many sources of uncertainty inherent in biomedical innovation, two are of particular importance to ABI,

Decision Maker	Sponsor	Regulator	HTA/Payer	Provider	Patient	
Decision	Development & delivery of product	Market access	Patient access	Patient use	Patient use	
Decision Factors	Demonstrated benefits greater than known risks	✓	✓	✓	✓	
	Comparative effectiveness		✓	✓	✓	
	Cost effectiveness		✓			
	Affordability		✓	✓	✓	
	Return on investment	✓				
	Public health impact		✓	✓*		
Uncertainty	Knowledge (stakeholder-specific)	<ul style="list-style-type: none"> <li>Optimal dose to achieve desired treatment effect</li> <li>Meet primary efficacy endpoint</li> </ul>	<ul style="list-style-type: none"> <li>Rare but serious safety issues not detected in RCTs</li> <li>Determining the importance of adverse events without the ability to calculate incidence</li> </ul>	<ul style="list-style-type: none"> <li>Durability of efficacy over time</li> <li>Changes in natural history of disease over time</li> </ul>	<ul style="list-style-type: none"> <li>Predictive value of RCT data to inform care of real world patients</li> <li>Treatment combinations</li> </ul>	<ul style="list-style-type: none"> <li>Interactions with my other medicines</li> <li>Right treatment for me</li> </ul>
	Behavior (of other stakeholders)	<ul style="list-style-type: none"> <li>Patient behavior: compliance/adherence</li> <li>Uncertainty for sponsor: implications for pay-for-performance agreements</li> </ul>	<ul style="list-style-type: none"> <li>Sponsor behavior: failure to deliver on post market learning</li> <li>Uncertainty for regulator: no reduction of knowledge uncertainty</li> </ul>	<ul style="list-style-type: none"> <li>Provider behavior: off label prescribing</li> <li>Uncertainty for HTA/payer: utilization costs</li> </ul>	<ul style="list-style-type: none"> <li>Payer behavior: pricing decisions</li> <li>Uncertainty for provider: affordability for patient</li> </ul>	<ul style="list-style-type: none"> <li>Sponsor/regulator behavior: compassionate use determination</li> <li>Uncertainty for patient: accessibility of product to address unmet need</li> </ul>

\* Public payers

**Figure 2** Adaptive biomedical innovation (ABI) stakeholder decision factors and uncertainties. ABI relies on the participation of diverse stakeholder groups, aiming to deliver better, affordable treatments to the right patients faster, in ways that work for all stakeholders. Shown are selected roles of six key stakeholders, with examples of factors that impact their decisions about a medical product, including examples of uncertainties that may enter into the decision processes. HTA, health technology assessment; RCT, randomized controlled trial.

described herein.<sup>14,15</sup> The first source of uncertainty refers to the robustness of relevant scientific and clinical knowledge, which must be addressed through the continuous development and application of knowledge. There are two significant sources of meaningful uncertainties inherent in biomedical innovation, which we will describe at greater length below. The primary source of uncertainty relates to the robustness of relevant scientific and clinical knowledge, which must be addressed through the continuous development and application of knowledge. This type of uncertainty is widely acknowledged as critical to identify, quantify, manage, and ultimately minimize over time. A secondary source of uncertainty, less overtly recognized, relates to behaviors of various critical stakeholders that might impact decision-making by others (see **Figure 2**). Behavioral uncertainties are addressed explicitly in ABI through the evaluation of and implementation of incentives, disincentives, and risk-sharing mechanisms defined through multistakeholder interactions early and iteratively throughout a product’s lifespan.

**Proactive, rapid cycle learning, feedback, and continuous improvement**

ABI systems enable reliable and timely generation and communication of knowledge to continually improve the use of existing products, inform new product innovation, and refine system elements, such as policies, infrastructures, and processes. ABI aims

to create a far more seamless knowledge continuum that spans traditional data and information siloes across the full innovation value chain.

**Building trust**

Success with ABI is far more dependent upon trust among stakeholders than is the case with traditional pharmaceutical innovation. All of the above elements become more possible within a culture of trust among ABI participants. Similarly, successful collaborative experiences will enhance trust, as stakeholders learn through repeated interactions that they can count on each other to uphold collaborative expectations. For example, the current trend for manufacturers to publicly share clinical trial data, regardless of whether it reflects positively or negatively on the company’s medicines, enhances trust by other stakeholders in the credibility of the data, the integrity of the firm’s practices, and their commitment to advancing medical science and patient care. Companies who demonstrate such openness consistently over time will benefit from the enhanced trust of key stakeholders, and advance the industry culture in ways that foster the evolution of ABI.

Importantly, ABI calls for progress toward a continuous learning system that generates a seamless continuum of knowledge and use spanning preinitial and postinitial authorization elements of biomedical innovation.

## Roots of ABI

The ABI approach draws from concepts associated with the field of adaptive management,<sup>16–18</sup> which centers on an approach to decision-making in the face of uncertainty. Adaptive management involves near-term decision-making linked to planned adaptation through an explicitly prospectively defined process for gathering information aimed at reducing specific uncertainties, and a protocol designed for reviewing and revising decisions based on new information. Adaptive management should be used not only to change a system or a process, but to learn about and continuously improve it.<sup>19,20</sup> The challenge in using the adaptive management approach lies in finding the optimal balance between gaining knowledge to improve management in the future while achieving the best near-term outcome based on current knowledge.

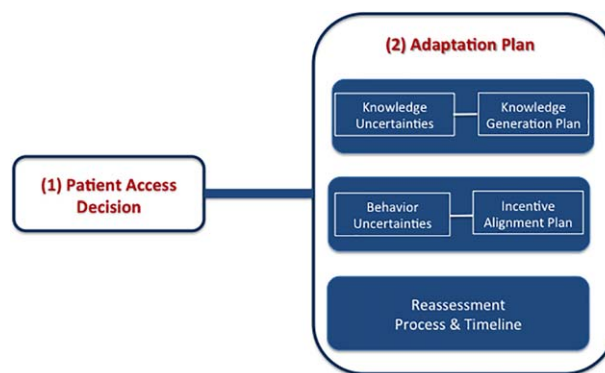
Adaptive management principles have been applied to decision-making in the face of uncertainty in settings involving complex and dynamic social, political, and technical systems, such as natural resource management in ecology and leadership of organizations. In this paper, we propose to apply these principles to biomedical innovation.

To be clear, although the term “ABI” is new, its underlying principles are not. It is a term that encompasses related application models originally explored under a number of names within biomedical innovation, such as “progressive licensing” in Canada,<sup>21</sup> “adaptive licensing” in the United States,<sup>22</sup> “staggered approval” and “medicines adaptive pathways to patients” in the European Union,<sup>23</sup> and “managed entry” in the European Union and Australia.<sup>24</sup> At the center of all these concepts are the core principles of ABI: progressively reducing stakeholder-defined uncertainties over a product’s lifespan, while optimizing the near-term clinical value delivered to patients and society.

ABI is a particularly timely concept in the era of “personalized medicine,” which centers on a recognition that the benefit/risk ratio for any given product may vary across the spectrum of potential patients and population. ABI offers an approach to product development and delivery that can be staged based on different benefit/risk profiles of subpopulations of patients with a given disease. This opens an important door in the world of personalized medicine, in which understanding, predicting, and harnessing the heterogeneity of treatment effects will drive timely and targeted clinical value for individual patients.

The scope of ABI is quite large, crossing a range of traditional functional, stakeholder, expert, organizational, and geographic siloes. Although the scope is, at times, unwieldy, it is important to use such a broad lens to identify and exploit opportunities for impactful synergies and efficiencies.

This paper focuses primarily on the application of ABI at the product level, rather than processes by which system level ABI innovation are developed. However, ABI at the product level involves the use of technical, operational, and policy advancements that result from system-level innovation. As such, ABI is enabled at the product level by these emerging system innovations. At the same time, continuous learning from their use at the product level can help to refine the innovations over time. Thus, enhancing the connections between product- and system-



**Figure 3** Adaptive decision-making in adaptive biomedical innovation (ABI). ABI seeks to empower appropriate and timely patient access to new therapies by using iterative decision-making that is governed by stakeholder agreed adaptation plans that flexibly manage dynamic uncertainties in knowledge about clinical and scientific aspects of the therapies and the behavior of key stakeholders. The two key outcomes, patient access and an adaptation plan, are shown in red. Multistakeholder interactions across all elements are important for the effective design and implementation of adaptive decision-making.

level elements is vital for improving translational science efficiencies, driving timely public health value, and ensuring the sustainability of innovation.

## THE ABI “TOOLKIT”

ABI focuses on adaptive decision-making that provides an explicit mechanism for addressing one of the critical challenges in pharmaceutical innovation: the need for different stakeholders to embrace their respective tradeoffs related to “level of evidence vs. level of access.”<sup>25</sup>

This adaptive decision-making process requires the integrated application by all stakeholders of a number of rapidly evolving types of technical, policy, and process elements, to which we loosely refer here as “tools”. One set of tools, for example, includes policies that enable appropriate accelerated access to new medicines for prospectively defined appropriate patients. Multi-stakeholder interaction processes offer another example.

These tools are used to drive two key, and tightly linked, decision outcomes:

- 1. Patient access decision.** This determines the timing of access to new medicines for specific, proscribed patient populations and the terms of this access. It usually includes decisions regarding product development, market access, payment access, and product availability (see **Figure 3**).
- 2. Adaptation plan.** This explicitly specifies how uncertainties that are meaningful to each stakeholder will be addressed, and how and when patient access decisions will be reassessed for reconfirmation or potential refinement (e.g., either broadening or curtailing current patient access, use with other concurrent medications, or appropriate dosing levels). Stakeholder-specific uncertainties, as noted earlier, are of two types. Knowledge uncertainties are addressed through collection and analysis of data and other information. Cross-stakeholder behavioral

uncertainties are handled via negotiation of incentives, disincentives, and risk-sharing mechanisms. The plan's reassessment process incorporates the timing, as well as the process, for both planned and ad hoc decision-making, informed by emerging information.

In contrast to ABI decision-making, the traditional biomedical innovation approach is a linear and sequential one, whereby stakeholder decisions and behaviors are driven by silo-specific incentives, and misalignment can produce unintended consequences.

Although many of the tools in the ABI toolkit focus on technical and policy advancements, others relate to this crucial difference between traditional vs. adaptive decision-making: the latter cannot be designed or implemented by a single stakeholder. Rather, adaptive decision-making requires a range of types of interactions among key stakeholders. The models and mechanisms by which these interactions occur over the product lifespan are among the most dynamic elements of the evolving ABI toolkit.

Work done by the Massachusetts Institute of Technology New Drug Development Paradigms Initiative (NEWDIGS) on Adaptive Licensing—a product-focused application of ABI—highlights the importance of precompetitive collaboration in the design and evaluation of new cross-cutting processes. The “safe haven” culture of NEWDIGS operates with a set of ground rules shaped by the group, with the Massachusetts Institute of Technology Center for Biomedical Innovation serving as neutral intermediary when issues of potential conflicts of interest and competition arise. It offers a platform for candid dialogue, brainstorming, and concept prototyping that can add value beyond more formal “safe harbor” initiatives involving legal provisions, such as that associated with the EMA's Adaptive Pathways pilot project.

The NEWDIGS Adaptive Licensing project also provides an illustration of the potential to drive greater value from existing ABI tools by leveraging the power of multistakeholder collaborative decision-making through the application of the tools. The NEWDIGS work helped inspire the EMA's Adaptive Pathways pilot program, launched in March 2014.

NEWDIGS demonstrated that, in some multistakeholder-designed scenarios, staging product access (beginning with patients with the highest tolerance for uncertainties regarding product performance and linking it to ongoing knowledge generation and feedback) could drive greater clinical value earlier for these patients, with acceptable tradeoffs for other stakeholders. Through interactive modeling and simulation of a range of “what if” scenarios involving stakeholder interactions earlier and iteratively across the lifespan of the products, new approaches to optimizing benefit, sharing risk, and managing knowledge and behavioral uncertainty were defined. For example, the risk of receiving regulatory marketing authorization for a product with no mechanism for reimbursement represents an unacceptable inefficiency in the innovation system and should be addressed early in the innovation lifespan.

Most importantly, much of the additional value created for these patients can be delivered without the need for new laws,<sup>25</sup>

or programmatic tools. Rather, often the major value driver was the collaborative process innovation that focused on how to strategically use existing elements of the ABI toolkit. These and other case-based findings from NEWDIGS helped to inspire the Adaptive Pathways pilot program.<sup>26</sup>

Another example that highlights the power of integrative, collaborative, and prospective processes for defining adaptive decision requirements is that of the Bill and Melinda Gates Foundation, which requires that all product development partners have both a “target product profile” (TPP) developed with input from all key stakeholders in the development and delivery continuum and an “integrated development plan” that details the roadmap for achieving the goals of the TPP.

TPPs and integrated development plans are standard concepts in traditional biopharmaceutical development. What is new here is their use—and the application of ABI principles—to accelerate impact from the efforts of globally distributed teams from disparate organizations that are focused on curing and preventing diseases in the developing world.

The Bill and Melinda Gates Foundation's TPPs and integrated development plans are developed with input from grantees, program experts from the foundation, experts in the global health community, regulators, and experts in product procurement and delivery in low-income countries. The Bill and Melinda Gates Foundation tries to take a lifespan approach to defining—and iteratively refining as knowledge emerges—a TPP tailored to specific requirements for clinical manufacturing, price-point considerations, delivery mechanisms, populations, dosage forms, ease of administration, and other parameters. This approach does bring particular planning challenges in identifying trade secret and commercial confidentiality issues across multiple competitors. It requires active management to effectively balance between the need for confidentiality and the need for transparency and coordinated decision-making required to drive success in both product innovation and public health impact.

All the elements of such adaptive decision-making are highly interdependent, but we look at two key outcomes, patient access decision (**Figure 4**) and an adaptation plan (**Figure 5**), separately below.

#### Patient access decision

Formal laws and policies play a major role in the parts of patient access decisions that are the responsibility of regulators and payers, although there is significant discretion in how these laws and policies are applied. In addition, they often differ across different geographic regions. There is, however, a growing trend, both on the part of regulators and payers, toward more flexible decision-making to expedite patient access to address serious unmet medical needs when patient and community tolerance of uncertainties about product performance is highest. These accelerated access pathways are, in most cases, linked to specific requirements defined by regulators, payers, and/or HTA agencies for ongoing knowledge generation. Thus, they connect with the ABI Adaptation Plan's Knowledge Uncertainties schema, covered in the following section. These pathways also face the challenge of how and when regulators, payers, and HTA agencies enforce

## Patient Access Decision Toolkit

**Scope:** Content of data required and timing, use guidance (e.g., product label) and conditions (e.g., price) associated with patient access to new medicine. Anticipates that elements of this decision will evolve over time as iterative knowledge emerges from the Adaptation Plan.

**Objective:** Provide timely and appropriate access for prospectively defined appropriate patients to new medicines, with acceptable tradeoffs for all stakeholders.

**Sample ABI Tools**

- Policies for regulators, HTA agencies, and payers that enable appropriate, accelerated access for prospectively defined appropriate patients to new medicines, tied to conditions associated with the Adaptation Plan.
- Structured, explicit, and transparent decision-making processes and product information and labeling.
- Multi-stakeholder interaction processes for earlier and more coordinated dialogue and guidance among stakeholders related to patient access decisions and post-access continued iterative knowledge generation, sharing, and decision-refinement.

**Figure 4** Patient access decision toolkit.

the manufacturer's delivery of this required knowledge, which connects them with the Adaptation Plan's Behavioral Uncertainties schema, also covered below.

For the US Food and Drug Administration (FDA), for instance, Accelerated Approval marketing authorization is linked to requirements for the sponsor to conduct confirmatory trials to verify and describe the product's clinical benefit (i.e., it must validate the unvalidated surrogate marker for clinical benefit that was used as the basis for the accelerated approval). Drug approval may be withdrawn, or the label may be changed, if trials fail to verify or demonstrate sufficient clinical benefit to justify drug-related risks. Similar authorities have been granted to regulators in the European Union under the Conditional Marketing Authorization pathway, in Canada under Vanessa's Law, and in Japan under the Regenerative Medicine Law, although these are implemented differently across regions.

Increasingly, policies that impact patient access are applied in ways that involve interactions among key stakeholders. These interactions benefit greatly from clarity and transparency in decision-making criteria, thresholds, and processes for each stakeholder, because the decisions of one stakeholder often have implications for another. A crucial element of this structured decision-making process is to define meaningful uncertainties for each stakeholder.

Additionally, it is key to use prospective planning with coordination among stakeholders, rather than taking the traditional linear, sequential, and siloed approach to decision-making. Where possible, the scope should include the entire lifespan of a product rather than a single, initial indication. Additionally, where possible, sponsors should be encouraged to develop and share specific potential "what if" scenarios, and associated thresholds and triggers for adaptation in future decisions. Such planning can increase comfort and reduce uncertainties among stakeholders and decision-makers, particularly regulators, HTA agencies, and

payers. Incorporating benefit, risk, uncertainty, and value preferences<sup>27–30</sup> for each of these players into these scenarios enables their translation into viable action plans and prospective "decision trees."

Moreover, it is especially important to incorporate emerging models and mechanisms for empowering meaningful patient participation in decision-making. At the product level, this allows patients to gain the earliest appropriate access to value consistent with their personal value assessment preferences (weighing potential benefits, risks, and uncertainties for their situation). Patients willing to tolerate more uncertainty are accommodated and embraced as full partners in the development of biomedical treatments, not denied participation in the intent to protect the more risk-averse. However, we are not advocating "hope" as a threshold for patient access. Rather, while respectful of patient uncertainty tolerances, the process must remain anchored in the scientific and clinical data, incorporating a minimal threshold for "potential benefits outweighing potential harms" and for value of the treatment informed by legal mandates as well as input from all stakeholders.

Models and mechanisms are emerging globally to enable cross-stakeholder collaboration in formal decision-making processes. Among examples:

- Breakthrough Designation (FDA), PRIME (EMA), and Saki-gake (Japan) are recently established regulatory pathways to accelerate the development and review of products that address serious unmet medical needs in which preliminary clinical evidence is promising. They incorporate process innovation that offers the opportunity for regulators and manufacturers (and other stakeholders, at the discretion of manufacturers) to interact earlier and iteratively over the product lifespan in order to enhance the efficiency of clinical development.

## Uncertainties Addressed in the Adaptation Plan

## a. Knowledge Uncertainties

**Scope:** Meaningful uncertainties related to safety, efficacy, effectiveness, and value, as defined by key stakeholders across the lifespan of the product.

**Objectives:** Identify key evidentiary needs and critical uncertainties for progressive reduction of uncertainty through the continuous, iterative, rapid-cycle generation and feedback of knowledge designed to improve subsequent decision-making by all stakeholders.

**Sample ABI Tools:**

- Interactive multi-stakeholder modeling and simulation processes/tools to support rigorous exploration of “what if” scenarios
- Policies that authorize decision-makers to require other stakeholders to generate additional knowledge; natural history registries
- Tools and platforms for data generation, access, and timely analysis;
- Common data models and standards that enable distributed access and/or sharing of data sources
- Methodological standards for the generation and use of real world evidence

## b. Behavioral Uncertainties

**Scope:** Behaviors of one stakeholder that—whether intended or unintended—may impact the benefit, risk, or value determination of another stakeholder, thus introducing uncertainties associated with appropriate patient access to new medicines.

**Objective:** Understand and reduce uncertainty about the behavior of other stakeholders that, if not proactively addressed, could create unintended impediments to planned decision-making.

**Sample ABI Tools:**

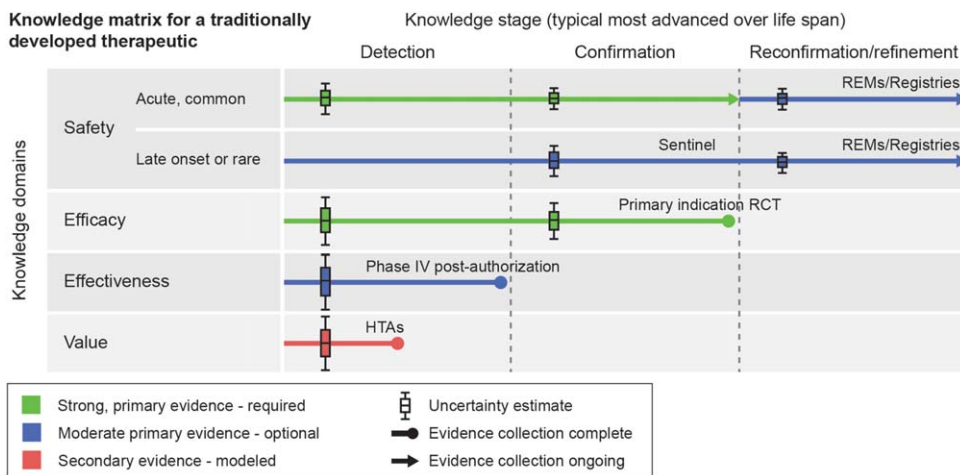
- Interactive multi-stakeholder modeling and simulation processes/tools to support rigorous exploration of “what if” scenarios (coordinated with application of same for knowledge uncertainties)
- Prior authorization procedures by payers to minimize off label prescribing of products by providers, where appropriate
- Mechanisms for both managed market entry and exit of products
- Explicitly defined incentives/disincentives to ensure that required learning from real world use of product is generated and reported in a timely way

**Figure 5** Uncertainties addressed in the adaptation plan.

- The European Network for Health Technology Assessment—a “facilitator” of collaboration across multiple HTA agencies among European Union member states—provides coordination and harmonization of decision processes that could enhance efficiency and predictability in decision-making at the payment access product level.
- The European Network for Health Technology Assessment and the EMA provide joint scientific advice through early dialogue with sponsors.
- The FDA and the EMA Parallel Scientific Advice provides a mechanism for receiving input on product development programs from both.
- The European Union Adaptive Pathways pilot program involves all key stakeholders, earlier and iteratively throughout the lifespan of a product. As noted earlier, the EMA instituted a “safe harbor” to encourage informal discussions among a range of stakeholders invited by the sponsor. These discussions foster coordination among regulators and payers, and participation in decision-making by patients and providers, thus providing more meaningful outcome measures and incorporation of patient preferences that may impact the benefit, risk, value, and uncertainty calculations of regulators and payers.
- The FDA’s Center for Devices and Radiological Health can conduct meetings with sponsors that also involve the Centers for Medicare and Medicaid Services when a significant gap is anticipated between an FDA authorization and a Centers for Medicare and Medicaid Services decision regarding coverage and reimbursement.
- The EMA and the FDA have set up a global working group to share experiences and best practices on engaging patients in development, evaluation, and postauthorization activities, including patient preferences in benefit-risk decision-making.<sup>31</sup>

**Adaptation plan**

Although much of the focus in discussions about ABI tends to focus narrowly on decisions about the timing of patient access, these decisions are inextricably tied to an adaptation plan designed to ensure the ongoing generation of iterative knowledge that will reduce remaining meaningful uncertainties about the product. The adaptation plan also must include explicit ways that this knowledge will be communicated and used to reassess and either reconfirm or, if necessary, refine the previous patient access decision. The ABI approach distinguishes between uncertainty arising from incomplete scientific and technical knowledge and



**Figure 6** Knowledge matrix for a traditionally developed therapeutic. Each domain has uncertainties including parameters to track, measurement precision, and required effect size. HTA, health technology assessment; RCT, randomized clinical trial; REMs, risk evaluation and mitigation strategies.

uncertainty due to unpredictability in stakeholder behaviors that have system-wide impact.

**Knowledge uncertainties**

As noted earlier, ABI calls for progress toward a learning system that generates a seamless continuum of knowledge and use spanning preinitial and postinitial authorization elements of biomedical innovation. Such a fully evolved learning system will materialize only if suitably compelling incentives are established. Attributes of such a learning system could include:

- Early, explicit, and proactive definitions of meaningful uncertainties by all key stakeholders. At an operational level, this would require that downstream decision-makers (regulators, payers, HTA agencies, providers, and patients) are engaged in upstream planning of research and data and other aspects of product development.
- Prospective determination of which data collection and analysis methods are acceptable to each decision-maker in terms of validity, transparency, and timing.
- Coordination in the generation and feedback of this full scope of emerging knowledge. Although different stakeholders may have different needs for knowledge—for example, regulators and payers may require different comparators—there may be opportunities to align around the timing and sequencing of some elements of evidence generation if coordination is fostered earlier and iteratively across the product lifespan.
- Continuous and iterative knowledge generation, rapid-cycle learning, feedback, and adaptation across a product’s lifespan, rather than by each single study. This is consistent with a Bayesian approach by which, rather than looking at each individual study, we look at the totality of the data at given points in time, elucidating uncertainties and then conducting focused studies designed to reduce them.
- A product lifespan plan that is stewarded by a sponsor, but which is as transparent as possible to all. Today, the sponsor may have a plan, but stakeholders see it revealed as one trial,

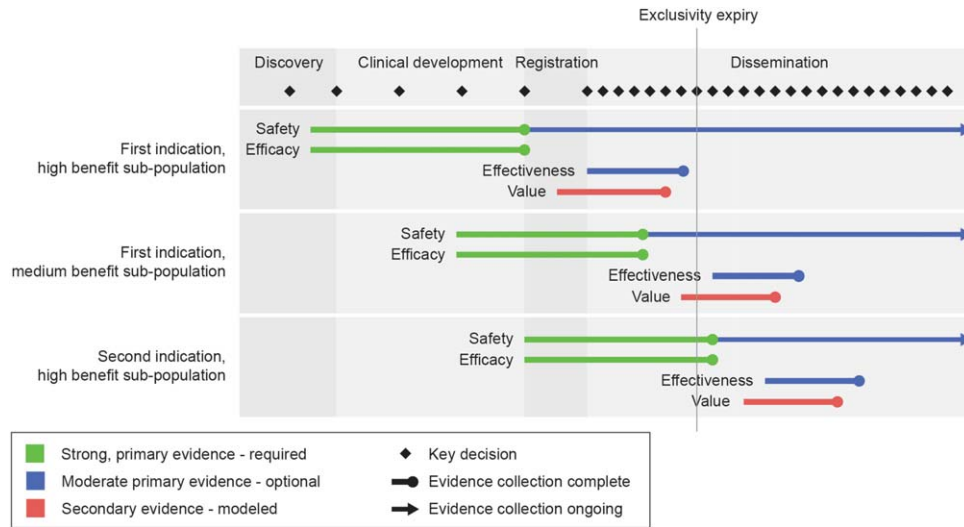
one indication, and one target population at a time. ABI envisions a prospective process that includes all intended indications as soon as they are identified and continue through initial product availability, generic entry, and on to product obsolescence.

- Clinical care and research that are more tightly integrated in order to bridge the efficacy-to-effectiveness gap.<sup>32</sup> Where possible, targeted populations, rather than just unconfounded efficacy-hypothesis testing of populations, would be leveraged for learning and delivering most relevant benefit/risk profiles as rapidly as possible.<sup>33,34</sup>

Reaching these goals requires a steady generation of knowledge in the domains of safety, efficacy, effectiveness, and value. (Manufacturing quality is also a critical fundamental knowledge domain that has important implications for benefit/harm metrics, but will not be considered here.) Definitions for these domains vary. Safety may be defined as a judgment of the acceptability of the known harm and potential unknown harm associated with a medical technology. Efficacy may be defined as the extent to which an intervention actually does what it claims to do and the probability to which it does within a certain population under ideal (i.e., unconfounded) circumstances. Effectiveness may be defined as the extent to which an intervention does more good than harm when used under the usual circumstances of health care practice (i.e., confounded by polypharmacy, uncontrolled variables, such as underlying diseases, overall health status, impacts of different nutritional status, or use of traditional therapies). The value of the medicine may be seen as the net of the clinical and economic and public health effects of its use at individual and societal levels in comparison with other available therapies and in comparison with the effects of the underlying disease.

The chain of decisions made across the lifespan of medicines requires information in all of these domains. Each domain has associated uncertainties and the parameters targeted to reduce these uncertainties are generally tailored to the specific context. For example, the uncertainty parameters addressed in oncology





**Figure 7** The biomedical innovation lifespan for a single product and multiple indications, with traditionally developed knowledge. On the top, a single-product indication across lifespan. Lower, the complexity of multiple indications over time with generic entries and additional studies or reports of safety, effectiveness and value. This complexity may be boosted by a lack of interaction among stakeholders.

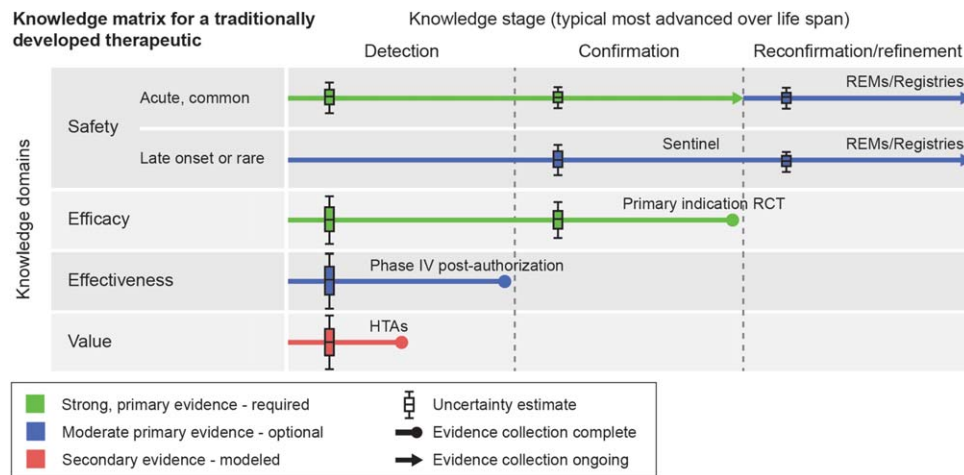
might include response rate, progression-free survival, and overall survival; measurement accuracy, precision, bias, and expressions of statistical uncertainty; and required effect size for actions to be taken, such as marketing approval, coverage decision, positive reimbursement recommendation from an HTA organization, and a physician treatment recommendation to a patient.

For each domain, biomedical knowledge generation proceeds along an empirical, scientific discovery path at three levels: (1) detection of a potential effect; (2) confirmation of the finding with sufficient rigor for decision-making; and then finally (3) monitoring (reconfirmation or, if required, refinement of the critical measures) for ongoing decision-making by specific stakeholders.

At each of these three levels of knowledge generation (detection, confirmation, and reconfirmation and refinement), its robustness for decision-making improves. The knowledge

becomes “fit for purpose” for a particular decision (such as product development, regulatory review, or payer coverage) when it has achieved the level of precision/rigor needed for that decision according to the decision-maker’s acceptance threshold criteria in conjunction with key stakeholders. As knowledge is iterative, any decision must be seen to be temporary and subject to modification as further knowledge is acquired, confirmed, and developed and previous decisions are reconfirmed or, if necessary, refined (see **Figure 6** for a traditionally developed product).

The limitations of this innovation lifecycle are highlighted by development of a single product with potential for multiple indications that demonstrate differing effects across subpopulations of patients based on molecular comorbidity and healthcare practice variation (see **Figure 7**). The complexity is substantial and occurs today with little stakeholder coordination among the



**Figure 8** Knowledge matrix for adaptive biomedical innovation (ABI). This approach improves knowledge quality and quantity over all four domains and connects across the knowledge stages to create a learning biomedical innovation system.

separate indication streams. Each is developed opportunistically by the sponsor, with other stakeholders participating reactively.

In contrast to such disconnected current approaches, ABI applies adaptive management mechanisms to better assemble an innovation chain's lifecycle activities and institutional stakeholders in order to generate the needed knowledge and to act upon it appropriately. Such actions should include using the knowledge to inform future biomedical innovation requirements to further the learning cycle. ABI catalyzes the formation of a continuously learning healthcare system (see **Figure 8**).<sup>35</sup>

### Behavioral uncertainties

Variability in human behavior at the micro decision-making and at the macro societal levels is a major driver of uncertainty in complex systems.<sup>36</sup> The behaviors of one set of actors in a system influence the performance metrics of a product (benefits, harms) as well as the benefit, risk, effectiveness, value, and uncertainty trade-off determinations that drive decisions of other stakeholders. In traditional medical innovation, stakeholder decisions and behaviors are driven by incentive structures within their institutional siloes. Incentives are not aligned, and often are in conflict, which can result in unintended negative consequences.

The ABI approach directs decision-makers to explicitly define and manage these uncertainties as early as possible, prospectively, and iteratively over the lifespan of the product. Mechanisms for addressing behavioral uncertainties generally must be negotiated between stakeholders, and often take the form of explicitly defined incentives, disincentives, and risk-sharing mechanisms.

One illustrative example pertains to two products authorized for use in weight loss in the United States, lorcaserin (Belviq; Arena Pharmaceuticals, San Diego, CA) and phentermine/topiramate (Qsymia; Vivus, Mountain View, CA). Both products had poor uptake in the market associated with highly variable insurance coverage and low prescribing rates by physicians. ABI, in theory, might have helped by coordinating the needs of payers to see the economic benefits by targeting patients with diabetes or prediabetes. The FDA and sponsor could have worked with payers to define an appropriate label. Payers then could have worked with the sponsor to drive more—and more targeted—utilization by promoting the drug for this very high-risk population. Economic benefits would be fueled from reduced use of antidiabetic medications and clinical benefits would come to patients by reduction in hemoglobin A1c and other risk factors for poor outcomes.

Examples of cross-stakeholder behavioral uncertainties that emerged in NEWDIGS scenario design sessions include:

- Likelihood that sponsors would—or would not—follow-through on the timely delivery of postmarket knowledge generation mandated by regulators, payers, and HTA agencies.
- Patient willingness to enroll in postauthorization studies.
- Patient adherence/compliance with conditions of use.
- Patient willingness to accept the withdrawal of a product from the market (“managed exit”) if postmarket knowledge failed to confirm positive benefit-risk profile for patients (for regulators), or relative clinical- or cost-effectiveness of the product (for payers).

- Patient willingness to provide timely patient-reported outcomes.
- Payer willingness to adapt prices going up, as well as down, based on emerging knowledge about a product's value.
- Provider compliance with prescribing only to prospectively defined, treatment-eligible patients.
- Provider compliance with reporting adverse events (including lack of efficacy/effectiveness).

As noted earlier in this paper, there is growing interest in developing more adaptive approaches to coverage and reimbursement, paying for value rather than costs, but also balancing this with affordability at both the patient and societal levels. The affordability issue is paramount in discussion about the emerging pipeline of “curative” therapies. This category includes many types of treatments and target populations, from gene therapies targeting small populations to disease-modifying treatments for higher prevalence conditions, such as hepatitis C. What is common to this diverse portfolio of products is an expectation for high prices that reflect their value on clinical outcomes for patients, raising questions of affordability when applied across the industry pipeline.<sup>5,37</sup>

Addressing affordability issues for products that fundamentally cure or prevent illnesses will require creative approaches not only for coverage and reimbursement decisions, but also for the financing and business models of pharmaceutical innovation so incentives remain for sustainable innovation. Affordability is not a new challenge, but it has never been as great.

Interest in performance-based risk-sharing agreements (PBRsAs) is growing rapidly as a mechanism for addressing uncertainties relevant to coverage and reimbursement of new medicines. These arrangements take many forms, but a key characteristic is that price, reimbursement, and/or revenue for the product are linked to the outcome of a data collection program—either explicitly by a preagreed rule or implicitly through an option to renegotiate coverage, price, and revenue at a later date.<sup>38,39</sup> A PBRSA should have a process in place to underpin a “decision with further evidence.”

However, experience so far with these PBRSA arrangements has shown that effective design and implementation are challenging. For example, in the United States, a policy established in 1994 by the Centers for Medicare and Medicaid Services that provides a mechanism for PBRsAs has been used with only four drugs to date. Barriers to use include unclear statutory authority to enforce the required ongoing generation of knowledge and the lack of a dedicated funding source.<sup>39,40</sup>

In The Netherlands, a review by the National Healthcare Institute (Zorginstituut Nederland, or ZIN)<sup>34</sup> highlighted a number of challenges with this approach, and emphasized the need for incorporating “managed exits” into decision-making about access and prospectively defined adaptation plans. The review also highlighted the importance of multistakeholder coordination in these planning processes—including government policymakers whose agreement may be required to organize and implement managed exit arrangements.

Low-income countries<sup>41</sup> offer the example of guaranteed purchases under several procurement programs for products for certain diseases (for example, vaccines). “Advanced market commitment” is an innovative financing program that guarantees manufacturers a long-term market that addresses a high-priority unmet medical need. Under this arrangement, international procurers pay a premium for initial doses sold to low-income countries. In exchange, companies agree to continue supplying the product over the longer term at more sustainable prices.

ABI seeks to align incentives so that patient-centricity is coupled with recognition of the need for acceptable conditions for all stakeholders—at the product level in the near term, and at the system level over time, in order to ensure both public health and the sustainability of innovation.

### The reassessment process

This explicitly defined process provides opportunities for iterative, knowledge-driven refinements in decisions by all stakeholders related to the access to and use of new medicines. In the process, emerging knowledge associated with the ongoing development and use of a new medicine is considered to reconfirm or, when necessary, refine existing product use. Modifications might include broadening or narrowing the scope of the treatment population within the existing indication, and/or expanding to new indications.

Reassessment mechanisms serve as important tools in the ABI toolkit, and currently exist in a variety of forms tailored to needs of specific stakeholders. As noted before, regulators across Canada, the European Union, Japan, and the United States all have policies in place that authorize them, as part of the initial marketing authorization decision, to provide reports from knowledge generated in order to further inform on-going decision reassessments.

At the level of the World Health Organization, initial provisional tender eligibility listing decisions made under the Emergency Use Assessment and Listing process focus on access for patients affected by public health emergencies of international concern. However, in addition, the product is required to continue progressing through ongoing data generation and reassessments informed by emerging knowledge to allow further assessment for full World Health Organization prequalification for procurement tendering and full national authorization.<sup>42</sup>

The conditions specified for reassessment of coverage and pricing is negotiated on a case-by-case basis between sponsors, HTA agencies (in the European Union), and payers.

### COMMON ABI MISCONCEPTIONS

ABI is a multifaceted concept subject to many interpretations and misinterpretations. Here are three misconceptions that have arisen about the EMA’s Adaptive Pathways pilot program—an example of an ABI application (tailored for the European Union)—and clarifications for each.

#### Lowered knowledge standards

ABI strives to increase knowledge over time through a structured, preplanned evidence development program that extends past the initial clinical development plan for the first indication to include postinitial authorization evidence collection for that indication.

It also includes plans for acquiring information on supplemental indications, additional populations, and additional safety analyses. Payers may receive estimates of efficacy and safety with broader confidence intervals for an initial high-benefit population. However, concerns may be amplified if payers do not actively participate in the ABI clinical development processes to define their knowledge requirements and decision criteria and thresholds. In addition, the process could be improved if payers have input into the label, allowing for indications that open the door for value-based contracts and for use achieving economic as well as clinical outcomes. Knowledge generation throughout the lifespan of a therapeutic would maximize opportunities to optimize product benefits and minimize harms and uncertainties. In addition, it could provide new approaches and hope for repurposing generics, and could find more and earlier supplemental indications for branded products.

We believe ABI will generate higher standards of knowledge to inform each decision point in the lifecycle of the product and will, in addition, have a prospectively defined and agreed plan in place to further reconfirm or refine previous decisions in a transparent, stakeholder-inclusive manner. Rather than lowering knowledge standards, standards are maintained or strengthened, whereas increasing patient access for predefined patient populations with the highest possibility of benefit.

#### Increased sponsor profitability

Although some argue that ABI is driven by an effort by industry to drive more profits faster, there are many factors that may come into play in ABI with potential implications for sponsor profitability.<sup>43</sup> For example, in some cases, profitability may be significantly impacted by smaller markets for initial authorizations for more targeted subpopulations of patients, particularly given the current laws and policies related to intellectual property and market exclusivities. It may be the case, for instance, that sponsors in Europe will see a loss of peak year sales if they begin a 10-year exclusivity period earlier for a smaller indication. In addition, requirements for more ongoing knowledge generation requirements, and reimbursement more closely tied to emerging knowledge, may have significant implications for profitability.

#### Unfettered patient access to therapeutics

ABI envisions more controlled, transparent, and stakeholder- and patient-informed access to therapeutics. The principle of appropriate access implies commercialization only when merited by the knowledge/uncertainty profile. There is a commitment to ongoing, real-world population learning, especially for first indications in first populations, including long-term postapproval monitoring. The ABI approach strongly encourages—and in some cases requires—patients who receive a new product to enroll in postauthorization studies with careful management of access, and transparent communication of potential benefits, potential harms, and remaining meaningful uncertainties.

#### ABI MOVING FORWARD

From our perspective, changes consistent with ABI already are unfolding across jurisdictions and the global industry, although

slowly, inconsistently, and in fragmented ways. Without a shared integrating approach, it can be difficult to make sense of incremental advances and to identify high-leverage opportunities. In some cases, these opportunities can build on current tools for which their potential value has not yet been fully exploited. In other cases, new tools are needed.

Across this entire landscape, multistakeholder interactions will be critical for progress. Globally, we are seeing the rapid evolution of models and mechanisms of such interactions. As described throughout this paper, many formal processes are emerging to enable more coordinated, collaborative, and more widely informed decision-making among stakeholders related to individual products. We also are seeing a major increase in activities involving multistakeholder public-private partnerships and pre-competitive collaborations, many of which are driving the development of system level policies, processes, and infrastructures that are important components of the evolving ABI toolkit.

The scope, scale, and complexity of the ABI evolution highlight the need for innovating how we innovate, at both the level of products and the system. The Massachusetts Institute of Technology NEWDIGS initiative, as one illustration, focuses on advancing our ability to work together effectively in multistakeholder innovation. NEWDIGS is developing, and continuously improving, generalizable collaboration methods and open access tools<sup>44</sup> in its targeted project areas. This approach to “crossing the bridge while remodeling it” aims to deliver timely, scalable ABI solutions in such critical areas as adaptive financing of curative therapies and lifespan approaches to real-world evidence use, while enhancing the multistakeholder “science of collaboration.”<sup>45</sup>

Currently, ABI principles are applied primarily to products that target serious life-threatening unmet medical needs. However, as the system evolves, ABI may be considered for a broader range of products in the near future.

Additionally, the evolution of ABI brings other macroscale implications:

1. **Innovation incentives and sustainability.** Discussions about coverage and reimbursement of new medicines, particularly those representing curative therapies, focus on a convergent set of inter-related challenges. A viable path will require value-based pricing that adequately incentivizes the sustainability of biomedical innovation, while ensuring affordability by patients, payers, and society. This challenge is now playing out on a case-by-case basis for individual products, but probably will require system-level solutions in the form of payer policies and innovative industry financing models. ABI will have implications for this challenge, both at the product and system levels. The growing interest in more adaptive approaches to coverage and reimbursement in the evolving area of PBRsAs was covered earlier. In addition, the traditional incentives of intellectual property and market exclusivity are being actively evaluated in the European Union within the ADAPT-SMART consortium of the Innovative Medicines Initiative as the EU Adaptive Pathways pilot program unfolds. These topics are important in this context because Adaptive Pathways often involves the approval of a product for a small sub-population of a disease earlier than in traditional pharmaceutical

innovation, which may have significant implications for intellectual property and market exclusivity for sponsors.

2. **Workforce development.** There is need to train stakeholders about ABI concepts and interactions so that they can learn how to work together in fundamentally different collaborative ways. Traditional education fosters the development of technical expertise that is narrow and deep. ABI will be fueled through training that augments these technical proficiencies with a broader awareness of the context within which they will be applied and how they relate to the roles and decisions of other stakeholders. For example, students from Massachusetts Institute of Technology’s schools of science, engineering, business, and humanities are gaining insights into ABI principles by participating in multistakeholder modeling and simulation exercises in NEWDIGS.
3. **Educating the public and policymakers.** We also must carefully consider how we can best educate policymakers and the public about the need for responsibly managed collaboration among stakeholders throughout product life, particularly those involving novel science. This education will enhance informed decision-making by all stakeholders and mitigate against concerns about conflicts of interest and inappropriate corporate collusion.
4. **Funding.** We need resources to support and coordinate the advancement of the system as efficiently as possible.<sup>46</sup> The more global the initiative, the harder it is to determine who will provide needed financial and human resources. Today, funding mechanisms tend to come from a single player (government or industry). They drive important but fragmented advancements. ABI creates shared value for all stakeholders, not for the single stakeholder.

## CONCLUSION

Today, laboratories around the world are making powerful discoveries that hold the promise of transformative progress against many forms of disease. Delivering timely and meaningful value to patients from these breakthroughs will require a new wave of advancements targeting the processes, policies, and structures that comprise our global innovation system for emerging medicines. Success and sustainability will require that we work together in new ways across myriad traditional siloes to optimize benefit and share risk; identify, reduce, and manage knowledge and behavioral uncertainties; and develop the knowledge required for earlier, appropriate access to new medicines for patients.

ABI addresses these complex challenges with a flexible, continuous-learning approach that can help to align stakeholders to accelerate and amplify the collective impact of their efforts to improve patient outcomes while enhancing the sustainability of innovation. As we work together to broaden and deepen ABI, we hope to take steady steps that result in a more effective global biomedical innovation system for all stakeholders.

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