Massachusetts Institute of Technology

The Next Wave in Adaptive Biomedical Innovation:

Advancing Platform Trials into End-to-End Rapid Learning Systems

A summary from the December 12th and 13th, 2017 event

MIT NEW Drug Development ParadIGmS (NEWDIGS)
Cambridge, Massachusetts

NEWDIGS

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Summary

Context: Innovating How We Innovate

In many ways, biomedical science is advancing faster than the drug development/delivery "system," delaying the delivery of value to patients, and threatening the sustainability of innovation. The complexity of the problem is apparent in three seismic shifts that are concurrently underway in pharmaceutical innovation, driving the need for change:

1. Commercial Success: "Regulatory Approval + Strong Marketing" →"Regulatory Approval + Demonstrated Value"
2. Disease Targets: Phenotypically defined → Mechanism-based
3. Innovation: Silo-driven → Patient-centered

To achieve change, we need to bridge the chasm between drug development and care delivery. There is no first mover advantage to this change and no single point of control; therefore change needs to be a coordinated effort across traditional siloes. One-off, fragmented innovation is not enough to solve the problem. Without systemic innovative change, the system will fail waiting patients in need of new therapies. Stakeholders need to work together in very different ways than previously, essentially innovating how we innovate.

Adaptive Biomedical Innovation: A Vision for Sustainable, Patient-Centered Drug Development, Access, and Value

Adaptive Biomedical Innovation (ABI) is a powerful strategic vision that connects the topics addressed in the Forum. The most important aspect of ABI is that it is anchored in a shared goal of all stakeholders: to drive more value faster to patients *in ways that work for all stakeholders*. In this manner, ABI seeks to promote sustainable, patient-centered innovation. A shared goal forces stakeholders to interact differently, across siloes. ABI is a principle driven approach to redesign the biomedical innovation system to make it easier for stakeholders to do the right thing, utilizing input from all stakeholders across the lifecycle of a product using shared metrics.

Much of the paradigm shift of ABI centers on dismantling outdated dichotomies entrenched in the current biomedical innovation system. The dichotomy of pre-licensing versus post-licensing creates an arbitrary learning versus usage phase in drug development that deemphasizes real-world evidence. Learning is a continuum and does not stop upon

marketing approval. The dichotomy of research versus clinical practice similarly hinders learning. Every patient encounter should be a learning encounter for the system.

A key feature of ABI is early, ongoing input from *all* stakeholders in the development and delivery of new drugs. Bringing different stakeholders together is important work and there is much insight to gain from it. In the pharmaceutical industry we are very good at optimizing our own silos. It is much more difficult to optimize horizontally, yet this must be done to meet the challenges facing biomedical innovation.

Historically, patients have not been meaningfully engaged, thereby omitting a critical information source. Patients that share a particular disease status are not a monolithic group; patient preferences and tolerance for risk can vary widely. Additionally, the existence of powerful therapies does not equate to patient access due to the potential burden, both financial and lifestyle. Understanding how these forces affect real-world use of drugs is key to successful drug innovation and starts with engaging patients.

The goal of ABI is to improve the system for patients, but its implementation benefits all stakeholders. Successful uptake of ABI will depend partly on stakeholders realizing how ABI can benefit them. Sponsors will need to see practical benefit, i.e., clear value, high probability of success, to "buy into" this paradigm shift. Fostering trust among stakeholders, along with a shift in thinking toward greater understanding of other stakeholders and the constraints in which stakeholders are/are not able to operate will be key to adopting the principles of ABI.

Roadmap to the Future: From Platform Trials to Disease Ecosystems

The Healthcare Crisis and Biomedical Innovation

There is a critical need to address the looming healthcare and economic crisis we face. The cost of healthcare is staggering and economically destabilizing. About 80% of healthcare expenditures are in Alzheimer's disease, cancer, and diabetes, cases of which are all expected to increase substantially in the next decade. Cancer in particular is increasing at an alarming rate. The WHO declared cancer the pandemic of this century as cases worldwide are projected to increase by 70% over the next 20 years. The current state of healthcare and biomedical innovation is unsustainable, driven by the lack of an evidence base for healthcare practice and the high cost of medical product development.

Lack of Evidence Base

The discussion surrounding healthcare cost typically focuses on the high cost of new therapies, but that is only a fraction of the cost of healthcare, most of which is spent on non-evidence based practice. Currently, evidence generation is costly and fragmented. Digital health records are not systematically used to improve clinical practice, and when they are used, their utility is limited by deficiencies in the medical records. There is a need for a learning healthcare system in which evidence generation is "baked-in." Integrating evidence generation into healthcare will make evidence generation less expensive and more accessible, with the ultimate goal of implementing a system that continuously

evaluates how medical interventions work in real-world practice. Through this process we can systematically improve health outcomes, thereby lowering cost systemically.

Costly Clinical Evaluation and Slow Knowledge Turns
Much of the high cost of medicinal product development is driven by the high cost and high failure rate of clinical evaluation. On average, from 5,000-10,000 compounds in pre-discovery, only 1 compound makes it through to FDA approval. Clinical development is long and very expensive. The process of moving that 1 compound from pre-discovery to FDA approval takes 12-15 years and costs roughly $2 billion. This long duration creates a "knowledge turn," or time to move from hypothesis to results to a new hypothesis, of 12-15 years. These long knowledge turns cannot keep pace with science and disease. Recent explosion in scientific knowledge has yielded greater understanding of the complexity of disease, which in turn has enabled identification of many more disease targets while also bringing about the realization that single interventions will not be sufficient in many disease settings. The current paradigm is not conducive to adequately evaluate a substantially greater number of disease targets or identify successful combination therapies. There is great need for a new drug development paradigm that can identify the winners, losers, and best combinations much more quickly, and where learnings are shared broadly and incorporated into the development plan.

Driving a Learning Healthcare System
Creating a learning healthcare system will require shifts in the current paradigm, including reintegrating clinical research and clinical care, integrating community practice into the scientific inquiry process, and viewing pre- and post-marketing as part of a continuum rather than two different systems. Platform trials can be leveraged to drive this transition, thereby addressing the two major problems threatening the sustainability of biomedical innovation: lack of an evidence base for clinical practice and the slow, costly process of drug development.

Platform trials are adaptive, multi-arm designs that continuously evaluate multiple treatments in the context of a single disease, both in parallel and sequentially over time. The focus on a disease rather than a single-agent fosters a more comprehensive approach to evaluating disease management and development of the best methods to evaluate the effects of this disease. This design moves away from answering the question of which therapy is best for the (imaginary) average patient, to finding the right treatment for the right patient at the right time. Additionally, with design efficiencies, platform trials have the potential to reduce the drug development knowledge turn, weed out unsuccessful drugs earlier, and efficiently identify the right drugs for the right patients.

While the initial use of the platform trial design is as a tool for drug development, it has the potential to evolve into a standing integrated research platform designed for truly patient-centered inquiry into a particular disease. As a platform trial progresses, there is the opportunity to use existing infrastructure to expand evidence generation into natural history, biomarker qualification, patient registries, long term outcomes, development of

new disease-relevant outcome measures, etc. In this manner, platform trials could facilitate a transition to a learning healthcare system.

Platform Trials

Platform Trial Elements

The shift in focus of platform trials to a particular disease rather than a single agent makes planning, designing, and implementing platform trials different from traditional clinical trials. Generally, platform trials utilize a master protocol, which requires substantial up front planning but offers efficiencies to enroll multiple drugs and answer multiple questions more quickly. Platform trials often employ adaptive design elements enabling an innovative learning system, whereby patient outcomes are evaluated on an ongoing basis to inform changes in design elements as the data accumulates. As such, unsuccessful therapies can be discontinued while successful therapies can be moved on more quickly, and the patient population in which a drug will be most successful is efficiently identified.

Examples - Oncology

I-SPY

I-SPY, a trail-blazing family of platform trials, is built upon a reengineered, disciplined approach to clinical trials. Through focused research and adaptive randomization, I-SPY's goal is to create a learning system that efficiently identifies treatments that have a big impact on breast cancer patient outcomes.

I-SPY 2 is an adaptive, multi-arm phase 2 platform trial that screens drugs for locally advanced breast cancer in combination with standard chemotherapy in a neoadjuvant setting. Its success stems from standardization of key science, business, and legal processes, as well as a culture of collaboration and innovation. Some key features of I-SPY include:

- Required data is limited, but certain key things (imaging, pathology) must be collected in a standard way for consistency across the platform. Every patient must also have an expression profile to further knowledge of targeted therapy.
- Drugs tested are from multiple industry partners. All partners learn what treatments are going to have the most impact on patient outcomes.
- Engagement from many different stakeholders, especially patient advocates, at every step of the way.
- FDA engagement for regulatory guidance on and recognition of pathological Complete Response (pCR) as an early endpoint.
- Closed loop following all patients, allowing feedback on performance.
- Able to add new treatment arms efficiently.

I-SPY's infrastructure and use of pCR enables rapid evaluation of new drugs. In December 2017, the platform started its 14th and 15th compounds; six compounds have "graduated" to phase 3. I-SPY has also demonstrated that pCR is meaningful: in 10 agents tested in I-SPY, pCR predicted event-free and distant disease-free survival across all tumor subtypes relative to the control arm.

Glioblastoma Multiforme (GBM) and GBM AGILE

The motivation for GBM AGILE arose from the fact that, while a lot is known about GBM, treatments for this aggressive disease remain bleak and have not advanced in the last decade. This lack of progress stems from absence of a clear clinical development plan for GBM therapies exacerbated by the paucity of GBM drugs being developed, such that when an agent is identified with an indication for GBM, it is a scramble to plan a trial.

To meet this need, GBM AGILE assembled clinicians and researchers to determine the best phase 2/3 development plan for GBM to use as the foundation for a platform trial. GBM AGILE is an emerging adaptive platform trial with integrated phase 2 and phase 3 components. This platform will test multiple agents and combinations for GBM, moving agents from phase 2 to phase 3 via an algorithm for clinical success. If a drug progresses to phase 3, sponsors do not need to run a separate study. If it is unclear whether or not a signal exists, sponsor can use the rich biomarker dataset GBM AGILE is building for further learning.

The sound development plan of GBM AGILE coupled with increased efficiencies and systematic learning make it easier and more attractive for companies to develop in GBM, something that will help improve the treatment landscape and patient outcomes for this devastating disease.

Pancreatic Cancer and Precision Promise

The current state of pancreatic clinical research is limited by three major factors: 1) the most compelling science not being incorporated into clinical trials, 2) lengthy lag from concept to trial initiation such that science evolves before trial starts, and 3) lack of learning from patients as biopsies are not routine due to the difficulty in accessing pancreas. Precision Promise is a new, emerging pancreatic cancer platform trial set to launch in July 2018 to address these challenges. It is a novel model for clinical development based on several key principles: a novel model of cooperation among companies typically thought of as competitors, deep learning from patients through required tumor annotation before and during treatment for all patients, pharmaceutical commitment with a high level champion from every partner, and remaining strongly patient-driven.

Examples – Beyond Oncology

Platform trials in oncology simultaneously test multiple therapies, gaining operational efficiencies as well as rapid learning about compounds, biomarkers, and subpopulations that inform next steps. Efforts are underway to learn from and build on oncology platforms to bring platform trials to other disease areas where traditional approach to drug development is not working. Different disease areas have their own specific challenges to identify and solve.

Tuberculosis and endTB Platform Trial

endTB is an ongoing adaptive platform trial testing new all-oral regimens for multi-drug resistant tuberculosis (MDR TB). Treatment of MDR TB remains difficult due to the

challenge of implementing the complex treatment regimen (24 month multidrug regimen comprised of very toxic agents and daily injections for up to 8-12 months) in third world countries impacted by TB. Recently, 2 new oral drugs were conditionally approved for MDR TB. endTB set out to transform the treatment landscape of MDR TB in two ways. First, to increase access to the new drugs, the drugs were initially added to the standard 24-month regimen as part of an observational study. Second, endTB initiated a Bayesian adaptive clinical trial within a subset of the observational study sites to test 5 all-oral 9-month experimental regimens.

Alzheimer's and Innovative Medicine Initiative's (IMI's) European Prevention of Alzheimer's Dementia (IMI-EPAD) Consortium

Progress for Alzheimer's disease will require treatments that intervene earlier on the disease pathway than recent clinical candidates. However, understanding of the early stages of disease is limited, and it is difficult to identify pre-symptomatic patients. These challenges will be best met by public/private partnerships and multi-stakeholder involvement. IMI's EPAD partnered with existing registries of patients at risk of developing Alzheimer's to identify those patients at highest risk to initiate an ongoing longitudinal cohort study. Cohort patients are followed and characterized by risk and amyloid status. EPAD will draw from this cohort of high-risk patients to launch a platform trial of drugs designed to prevent Alzheimer's in the coming year. This approach is hoped to reduce the screen failure rate, which is currently 9 out of 10 in Alzheimer's trials.

Drug Resistant Infections and Biomedical Advances Research and Development Authority (BARDA)

BARDA is scoping a platform trial to address the challenges of drug development for drug resistant infections. One challenge of this area is that the issue of rare patients is compounded by the fast pace of infection, which necessitates quick action. A platform trial may alleviate this challenge by extending into community sites where such infections are being seen. Another challenge is that most large companies have left the antibiotic space, and the small and medium sized companies that remain have limited resources. A platform trial would offer shared infrastructure and the potential to increase efficiencies.

Crohn's Disease and Janssen Pharmaceuticals

Janssen has had a lot of success with traditional drug development for Crohn's disease, and is in the process of finalizing a platform trial to test multiple internal candidates for Crohn's disease. The platform trial design is desirable at this stage for a number of reasons. One, the traditional development model takes too long, with phase 2 often being the bottleneck taking up to 8-9 years. Two, it is becoming more and more apparent that new drugs will need to demonstrate superior efficacy to be successful. No pre-clinical models of Crohn's disease can predict superior efficacy, therefore more candidates need to be evaluated clinically. Finally, the clinical trial design for Crohn's disease has crystallized in recent years and it does not make sense to spend time and resources creating the same trial over and over again.

Common Benefits of Platform Trials
The descriptions and rationales for current and emerging platform trials reveal common themes:

- Sponsors benefit from a built in randomized group, allowing sponsors to enter drug candidates as a single arm with a knowable plan, timeline, and expense.
- Platform trials reduce inefficiency in planning and start up each time to essentially ask the same question over and over: is a new therapy going to improve survival (or another measure) over standard of care?
- Platforms can learn from every patient enrolled allowing continual feedback and improvement of the system.
- There is a large up front cost of establishing a platform trial, but once established it has the potential to run indefinitely.

Enablers of Platform Trials
Already, new and emerging platform trials benefit from the trailblazing by iSPY. Industry buy-in to a platform trial over a "hand-crafted trial" has been uncertain, but platform trials are advancing to the point where they may have enough scale and credibility to start seeing network effects and the possibility of large uptake. Some emerging enablers include:

- Infrastructure: Growing platform infrastructure brings the potential to link networks for greater efficiency.
- Accelerated, differentiated learning: It is increasingly important to differentiate new drugs, and it is a sponsor's best interest to know early on in development if their drug works or is likely to be outpaced by a competitor. Platform trials enable such evaluation. Cross trial comparisons are made anyway; it would be better done within a platform when data can be appropriately compared.
- Outreach: Publications, press, presentations all serve to get the word out for platform trials and lay the groundwork for expanding the platform design to other indications.
- Collaboration: Collaboration with other companies not only increases learning, but also enables robust discussions with regulators that could not be done as one entity.
- Sample Size Efficiencies: Bayesian adaptive randomization is much more efficient than standard randomization, allowing smaller sample sizes. Once the trial has enough controls, the pool of all platform controls may be used instead of concurrent controls in some scenarios.

Challenges and Barriers
Finance
While a platform trial may be more cost-effective in the long run, there is the challenge of meeting sizable up-front costs. The upfront cost of platform trials is substantial, but if a new treatment comes out of it, the potential benefit likely surpasses that initial cost. However, this requires a shift in thinking about how to fund clinical research.

Innovation happens on all levels of platform trials, funding space included. Some funding options discussed included:

- Establishing stand-alone 503c organizations as the platform trial sponsor.

- Joint fundraising between the platform organization and drug sponsor.
- Licensing agreements
- Tiered "Pay to Play"
    - Sponsors pay for "a seat at the table" to help drive platform development.
    - As platform progresses, sponsors have access to rich data source (biomarkers, etc.) it generates.
    - Potential for future platform add-ons such as supportive care research (pain management, nutrition) that bring value to stakeholders.

Pipeline

For a platform trial to be efficient, a robust pipeline that continually feeds the platform new candidates is required. It is estimated that it takes 3-4 compounds to cycle through before the efficiency benefit of the platform design is realized. Cost becomes a problem if a platform trial is open, but there are no drugs to feed into it or when there are long spaces between compounds.

Lessons Learned

Groups designing and operationalizing different platform trials struggle with many of the same issues (e.g., how do you set up a master protocol that is open while fulfilling regulatory requirements) and leverage design innovations and operational enablers to overcome these issues. Platform trials and adaptive design elements are complex, and thus require thorough knowledge gathering, planning, and discussion at each stage. All stakeholders should be involved in planning and design and must agree on the overall trial goals and endpoints. Doctors and patients must review the protocol to ensure that it can be implemented "on the ground." Appropriate time and resources are necessary to implement complex designs such as Bayesian adaption must be considered. It is helpful to engage the FDA early and often. The operating system for a platform trial needs to be very stable and comprehensively managed long-term because the trial could, in theory, continue forever.

One key learning from iSPY that relates to platform trials facilitating a transition to a learning healthcare system is the importance of disciplined data collection and integration of clinical research with clinical care. The data physicians need to take care of patients is the same data needed for clinical research. Therefore, integrating clinical research into clinical care to enable a learning health system does not need to be overcomplicated.

Stakeholder Perspectives on Platform Trials

Platform trials may be conceptually sound, but this approach must make sense to all stakeholders and the larger system as a whole. If we all agree that platform trials are the best way to develop new drugs for optimal patient outcomes, we should be able to set ourselves in any stakeholder position and feel that it is the best approach to deliver the goal of sustainable, patient-centered drug development. Innovation requires risk-taking. An effective strategy to engaging stakeholders in innovation is to focus on the value proposition, what is to be gained by taking the risk.

Stakeholders shared the key benefits and concerns for platform trials. As the goal of ABI is to promote sustainable, patient-centered innovation, the impact of platform trials for patients is significant. The platform design is overall more patient-centric in that it is designed to optimize patient outcomes in a particular disease area, rather than optimizing for a particular drug. Platform trials have also become rich areas for patient advocacy, with the potential to meaningfully engage patients in trial design and outcomes that matter for them. It was noted that regardless of the research design, patient-centric programs are important and patients should be meaningfully engaged early in the process. Though rare diseases may not look like a traditional fit for platform trials because of small patient numbers and limited drug candidates, clustering of orphan disease designations and patient advocacy organizations may facilitate a rare disease platform trial.

Promising elements of platform trials from a payer point of view include efficiency, potential for a sustainable learning system, and increased affordability of drugs through decreased clinical development costs and reduced drug development failures. Early engagement with payers will inform appropriate endpoints that meet payer requirements for assessing new drugs. These elements where echoed by the sponsor, with the addition of platform trials making it easier to identify the patient population in which a sponsor's drug is likely to be most successful. This is a challenge in the traditional approach to clinical trials, especially if the biomarker is not well understood or not highly prevalent. Through adaptive designs, Bayesian randomization, multiple drug candidates, and continuous learning, platform trials identify the best patient/drug match as the trial goes forward. Participation in a platform trial also requires a shift in mindset for sponsors to take a risk of upfront time and resources as well as to relinquish some control by allowing decisions on study design and other elements of drug development to be made externally. The investor noted that as science has advanced, drug development has become less about making one carefully crafted individual drug and more about strategizing portfolios within a particular disease area to maximize market success. Platform trials can help evaluate portfolios with the potential to foster expansion into other areas in the disease pathway such as diagnostics or supportive care. Platform trials also offer the possibility of assembling assets from different companies to evaluate novel combinations to drive progress in areas without a lot of activity.

Outside-In Learning: Insights from the Evolution of Industry Platforms in Other Vertical Markets

While platform trials are early in their evolution, the phenomena of "internal" and "external" platforms in other vertical markets offer valuable perspectives to consider. There are many different types of platforms, generally defined as a foundation that connects different people or groups either for a common purpose or to share a common resource. While a *product platform* works within an organization or supply chain, an *industry platform* works both in and outside an organization, i.e., within "the ecosystem." The critical difference between these two platform types is that while the product platform generates value from sales of related products and services, an industry platform generates value from "network effects" which in turn increase the utility of those products and services. Network effects are positive self-reinforcing feedback loops whereby every

additional user or innovation increases the value for users, dramatically increasing the growth potential.

Success in industry platform markets is typically associated with the best platform rather than the best product. Characteristics of successful platforms include: open access to allow network effects, modular architecture allowing flexibility and innovation, and compelling "complements" with other players. Medicine and biotech, however, present challenges in platform development as the industry is tightly regulated, less modular, and driven by strong intellectual property protection with a zero-sum game rather than "grow-the-pie" or "win-win" mentality. Platform innovation in medicine and biotech will require development of positive feedback loops and learning within the system, adoption of efficiency and best practices (data standards, shared technologies and infrastructure, etc.), and creation of win-win scenarios where the potential benefit surpasses what one company could achieve alone. Successful adoption of these innovations will require a shift of mindset from strict competition among companies to "coopetition" (cooperation + competition), as well as willingness for some stakeholders to take on some risk to initiate a change within the system.

Future Direction
Platform trials have the potential to be transformative to drug development. They can be innovative, collaborative, evidence-generating engines used to advance biomarkers and quickly identify the right therapy for the right patient. They have the potential to evolve into disease ecosystems that effect change on the disease level by encouraging Research and Development within a particular disease space, optimizing treatment regimens, enabling earlier diagnosis and treatment, and expanding into supportive care. Thus far, platform trials have been driven by non-profits. However, industry uptake is critical to advance platform trials and ensure sustainability.

Connecting Data and Evidence Across the Product Lifecycle
A learning healthcare system requires cohesive evidence generation and use across the product lifecycle. Currently, evidence generation and use is currently not well connected. Furthermore, how to accomplish greater connection of data and evidence across the product lifecycle is not very well defined.

As we move into the era of "precision medicine", the shared goal of all stakeholders is to identify the best therapy for the right patient at the right time, and at the right dose. In order to meet that goal it is important to produce the needed evidence earlier than is currently done. This is a key theme in the 2016 JAMA article by Califf, Sherman and Slavitt, entitled "Knowing When and How to Use Medicinal Products: A Shared Responsibility for the FDA and CMA," which identified three chasms in biomedical innovation:

1) Regulator / Payer: The different information needs of these stakeholders create tension: Regulator (Can the drug work?)/Payer (Will it work in my patient population?)

2) Pre- / Post-Licensing: Learning once ended upon regulatory authorization, but the market and science has changed such that learning must continue post-licensing.
3) Randomized Controlled Trial (RCT) / Real-World Evidence (RWE): RCTs were once the only methodology for drug development, but real-world evidence is important to inform the post-licensing side of the chasm. Can we bridge these two methodologies?

These chasms affect individual stakeholder groups and hinder biomedical innovation overall. Sponsors are at the receiving end of the demands for information on either side of these chasms, which has substantial opportunity cost, and makes some areas of drug development inaccessible, particularly to smaller companies. Increasingly, sponsors need to develop a target value proposition that produces evidence for payers and formularies in parallel with the target product profile of their regulatory program. The regulator is at the front end of the post-licensing chasm and faces the challenge of making inferences for post-marketing surveillance based on limited evidence. The more we move toward precision medicine, the more important precise individual data, e.g., tumor, histology type, biomarker, treatment history, etc., will become. Payers are at the far end of the post-licensing chasm, and are therefore positioned to play an important role in post-marketing surveillance and learning by building the ability to conduct longitudinal studies in populations that are large both in breadth and volume.

The impact of this disconnection on stakeholders identifies three main issues with evidence generation in the current biomedical innovation system. One, the data needed for regulatory and post-marketing programs do not overlap. Two, post-marketing surveillance is focused on safety, but could this system be harnessed for effectiveness learning to improve positioning of medications? Finally, three, the post-marketing evidence currently available is not fit for purpose (FfP), i.e., it does not adequately address the question being asked by stakeholders post-marketing.

Solutions to these three issues centered on stakeholder agreement, FfP evidence generation, and patient involvement. Stakeholder agreement begins with transparency in all stakeholders' evidence requirements and decision-making thresholds. Agreement comes with common ground on endpoints, design, and data standards. Stakeholder transparency and agreement help define FfP evidence by stakeholder. Generation of FfP evidence requires incentivizing evidence generation, building infrastructure, and leveraging existing data sources to better meet the needs of decision-makers. Finally, the patient is the ultimate arbiter of what is relevant to the patient. As such, patient involvement in determining relevant outcomes is key.

Evidence Planning in Adaptive Biomedical Innovation: Field Observations

ABI facilitates FfP evidence generation, as a key feature of ABI is the development of an evidence generation plan early in the product lifecycle that incorporates input from downstream decision-makers (payers, patients, clinicians), and is iteratively refined based on emerging evidence. Panelists shared experiences from pioneering ABI programs.

bluebird bio
bluebird bio was one of the first companies to participate in the EMA adaptive pathways pilot with a gene therapy drug for β-thalassemia, providing a concrete example of ABI in the field. The most helpful part of the pilot for bluebird bio was the safe harbor multi-stakeholder discussions, during which the EMA recommended they add RWE to their development plan. This was lengthy process that involved finding a data source (e.g., a patient registry), determining whether or not it contains the required data elements, and navigating a number privacy, ownership, and operational issues to gain permission and access. Improving the quality, access, and harmonization of real-world data sources would catalyze evidence generation, enabling to drug development in general and ABI in particular. A patient advocacy group could be a strong force to drive this change.

NICE and the Cancer Drug Fund (CDF)
The Cancer Drug Fund (CDF), which operates under NICE, illustrates a specific example of an adaptive approach in which evidence generation is an essential component. NICE's appraisal of cancer compounds occurs upstream, with draft guidance issued shortly after and in advance of marketing authorization. The CDF offers managed access arrangements for drugs that have insufficient evidence to fit the NICE advisory committee's routine appraisal decisions (recommend versus not recommend for routine commission), but have a plausible clause from available evidence that NICE criteria, including cost effectiveness, could be met. Following the data collection period (typically around 2 years), the drug is re-appraised by NICE. In the reappraisal phase, the company may adjust pricing based on learning from data collection period. This is a key part of the process and an important component of the trust needed for adaptive pathways. If adaptive approaches are employed, adaptation in both directions (i.e., price up or price down) must be allowed. If it is possible for a drug to exceed expectations, it is important to have the option for the price to increase.

Quality of Evidence – Regulator Perspective
Regulators need to manage uncertainty and evaluate how evidence reduces uncertainty both before and after market authorization. Uncertainty can often be categorized as avoidable and unavoidable. *Avoidable* uncertainty is the most frustrating to face at different decision points, no matter what stakeholder or what stage of development or use. Whether from real world or clinical trial data, contrived evidence is not meaningful. The best thing would be to move seamlessly across the product lifecycle with less contrived evidence all around. We need to engage across stakeholder groups and consciously think about consistently employing the right methods to reduce avoidable uncertainty at every time point.

Stakeholder Agreement and the Path Forward
The evidence base all stakeholders need is actually quite similar. Identifying where points of difference are and making trade-offs will help realized the goal of better serving patients. It is also important to recognize that it might not be possible to get agreement on all design elements or to get all the evidentiary elements required into one trial, as stakeholders ask different questions. However, transparency and input is key. It is okay if stakeholders want

some different things, but sponsors want to know what they want early in the process. Sponsors develop evidence plans for payers, but due to anti-kickback legislation, it is hard to get payer input in the US. It needs to be easier to get clarity on what payers and regulators want. Once a sponsor is informed, it is up to them to do the best job and decide if/when to include certain data elements in a RCT, RWE efforts, or specific stand-alone study. A final push to embed RWE into routine practice will also drive FfP evidence generation.

Driving Value for Patients from Real World Evidence: Snapshots of Evolving Ecosystems

RWE generation at the ecosystem level is key to optimizing innovation value and sustainability. Panelists shared experiences of evolving ecosystems in RWE generation.

University of Pittsburgh Randomized, Embedded, Multifactorial Adaptive Platform (ReMAP)

Randomized, Embedded, Multifactorial Adaptive Platform (ReMAP) is a Phase 4 adaptive platform trial has two initiatives that evaluate real world practice in critical care settings. One initiative evaluates multiple domains for treatment of community-acquired pneumonia across 100s of ICUs. The second initiative embeds a multi-domain intervention around optimizing perioperative care across multiple hospitals within hospitals in the University of Pittsburgh Medical Center (UPMC) healthcare system.

HealthCore

HealthCore, the research subsidiary of Anthem health plans, has developed a claims data environment that increases research capabilities of administrative claims enabling implementation of more elegant claims-based designs. HealthCore also leverages their data environment to conduct pragmatic clinical trials (PCTs).

GlaxoSmithKline and the Salford Lung Study

GlaxoSmithKline recently conducted the Salford Lung Study, a Phase 3b PCT using mostly EHR data from COPD and Asthma patients in the Salford, a suburb of Manchester, UK. The PCT design was not necessarily faster than a traditional RCT, but the evidence it produced provided meaningful real-world insight. The health system in the UK provided an integrated, closed system in which patients' general practice (GP) was fully integrated with the local hospitals. Patients were randomized at their point of care with their regular doctor. Thus, treatment was not interrupted and they did not have to travel to a special research site.

Platform Development and RWE

The requirements for further development of platforms to enable RWE can categorized by data, analytics, and convergence. The volume of real-world data and increasing number of specialized purpose data sources is promising, but data quality and completeness remain a problem. It is necessary to incentivize data generators without increasing burden. Statistical methods have also improved greatly such that we can get closer to causal conclusions with non-randomized data. However, there needs to be more transparency for

decision makers to evaluate the quality of studies. Convergence of RCT and RWE is emerging as evidenced by the PCT design. The next step is to calibrate RWE with RCT data, that is, the difference expected when evaluating the same patient in RCT data versus EHR data. This would bring much more value to RWE and the EHR, enabling generalization to a target population and expanded application of RWE.

Progress in RWE generation will require incentives and tools to produce high quality data generation as well as effective communication strategies. Potential incentive methods include feedback loops that reinforce the data generator, quality metrics, patient feedback, and engagement of patient advocacy groups. Tools needed to support RWE generation include standardized EHR entry and interoperability, embedded evidence generation both in terms of data capture and culture of care, removal of barriers for informed patients to share data in a transparent way, and support of patient organizations to meet data quality standards. Once RWE is generated, an ecosystem network with feedback loops will be necessary to appropriately inform stakeholders on multiple levels (i.e., population level for payers, individual level for patients and physicians). A key component will be appropriate evaluation of design and analysis methods such that disseminated evidence is well vetted.

Can Technology Enable Data Sharing, Integration, & Trust?

We live in a data-rich age, but accessing and using this data is challenging due to security, proprietary, and privacy concerns. MIT's OPAL (**OP**en **AL**gorithms implementation) addresses these concerns, making it possible to use data to obtain answers about the aggregate without owning the data or violating any privacy or locality requirements. MIT's OPAL is guided by 3 principals:

1. **Share answers not data.** A key component of OPAL is that all data is stored locally. It is easier, less expensive, and more secure to store data locally in a heterogeneous system. OPAL uses a federated data system, in which data is stored locally, queried by investigators, the query is executed locally, and the answer disseminated with data encryption at each step.
2. **Log everything on blockchain.** The system needs to be as transparent as possible to ensure there is no introduction of bias or sampling errors. Contrary to typical practice, algorithms applied to the data are open and logged so that the user can trust the answer, and the system can be audited. If a mistake is made, the data is still safe due to consensus pattern. Many users would need to make the identical mistake before data is compromised. Additionally, because the data is stored locally, the actual raw data cannot be altered.
3. **Never decrypt data.** Data is very difficult to access when encrypted, and almost all questions can be asked and answered on encrypted data. Legally, it is also very important and advantageous to keep data encrypted at all times. If encrypted, access and use does not violate privacy, ownership, or locality restrictions. This enables use of a much larger pool of data sources.

Applied to medical data, these principals open the door for substantial opportunities for a data-sharing ecosystem to support RWE generation. This system is implemented with

blockchain layered on top of existing databases. Blockchain serves as an operating system by checking permissions, applying algorithms, and producing results. A user queries the data, relevant code is executed locally behind the firewall, and the answer is posted. Data is encrypted at every stage through secure multi-party computation, where each party could calculate a statistic without knowing the other parties' individual inputs.

For medical data, OPAL can provide decentralized analytics with dynamic algorithms to yield useful attributes of aggregated medical data, e.g., the success rate of a particular medical procedure among multiple hospitals, without exposing any one hospital's success rate or any individual patient information. Additionally, with constant data encryption, intermediate results are already encrypted and consequently do not need to be protected. Therefore, intermediate results can be cached and shared on existing infrastructures, enabling faster results.

Advancing from silo-driven to ecosystem-driven innovation

It is clear that one-off, fragmented innovation within traditional siloes is not enough to address the challenges that face the biomedical innovation system. The goal of sustainable, patient-center innovation that works for all stakeholders requires affecting change on the ecosystem level. How can ecosystem-driven innovation be achieved in the complex, fragmented biomedical innovation system?

Ecosystem-Enabled Innovation: Insights From the International Neonatal Consortium

A movement within the neonatal and pediatric healthcare communities provides insight toward ecosystem innovation. There is a lack of significant research and drug development to inform neonatal and pediatric healthcare. At least half (and likely up to 75%) of drugs prescribed in pediatrics and 90% of drugs prescribed in neonates have not been tested in this population and medical setting. Historical barriers to drug development and research in these populations include the population's vulnerability and logistical challenges (small patient populations, lack of universal standards or definitions for basic measurements).

Driven by regulators and government, there has been a recent shift in attitude and priority regarding clinical research and drug development in neonatology and pediatrics, resulting in the passage of a number of new regulations including the Best Pharmaceuticals for Children Act (BPCA), the Pediatric Research Equity Act, and the FDA Safety and Innovation Act. Supported by these regulations, physician investigator advocates are implementing strategic initiatives with diverse stakeholders to remove barriers to clinical research and drug innovation in infants and children.

As such, vision in the neonatal community is to enroll every neonate admitted to a hospital in a clinical research protocol designed to optimize outcomes in this population. The primary goals in implementing this vision address many of the current deficits and challenges in neonatal clinical research: standardize definitions and data collection; established normal laboratory values based on birth weight, gestational age, and post-natal

age; and sustainable infrastructure to support research studies to completion. The Critical Path Institute's International Neonatology Consortium is a global consortium of diverse stakeholders established to enable this vision.

In pediatrics, the Nationwide Children's Hospital "Learn From Every Patient" Pilot took a systems engineering approach to integrate research and clinical care by collecting research caliber level data on all child patients as part of routine, billable care within one clinical program at one clinical center. The pilot demonstrated that a learning healthcare system is within reach, and can improve care while reducing costs.

Key insight from development of these emerging ecosystems is the importance of cohesion among and alignment with providers. Innovation cannot occur within a cottage industry where common practices and standards vary provider to provider. A learning healthcare system has the best chance of success when it is implemented **for** doctors. It is essential that the system is aligned with doctor's interests and that they understand how it will improve their delivery of care and the care of their patients.

Advancing Adaptive Biomedical Innovation: Designing Disease Ecosystems

To truly advance ABI, individual advancements will need to connect in end-to-end learning systems to optimize efficiency, value, and sustainability. The Learning Ecosystem Accelerator for Patients and Sustainability (LEAPS) Project builds on the concept of platform trials and continuous learning, evolving to the next level of innovation by fully leveraging platforms throughout the biomedical innovation system, i.e., end-to-end from Research and Development through to healthcare delivery, thereby creating a continuous learning disease "ecosystem" that transforms the planning, generation, and use of knowledge within a disease. The goal of LEAPS is to drive significant impact in biomedical innovation in three dimensions: Product Innovation, Regimen Development, and Disease Management.

Implementation of the LEAPS project will follow the Design Lab methodology. The first step will identify and bring together the ecosystem stakeholders. Taking a broad view of the disease, tools that can be leveraged for the greatest patient benefit while keeping enough benefit for all other stakeholders will be explored. Stakeholders will determine the specific aims of the pilot. This reflects the key element of understanding the individual value to each of the stakeholders; if stakeholders do not see value, they will not come to the table. All stakeholders need to benefit or the system will not work.

Evidence planning begins with the critical decisions to address, not with the data. What evidence do stakeholders need, and what are the requirements that will make the evidence FfP for their decisions? Every player in the biomedical innovation system generates evidence in the course of his or her daily activities and work. Every player also makes decisions that affect other stakeholders and cannot be answered with his or her own evidence alone. The idea behind LEAPS is to leverage FfP evidence to inform individual stakeholder decisions, but also provide all stakeholders within the ecosystem the benefit of the collective data to enable improved decision-making overall.

Innovation in Fragmented Health Ecosystems
Understanding healthcare delivery as a complex adaptive system can help us design a system that is more efficient, effective, and equitable. Managing innovation in complex, fragmented systems is challenging. In discussing innovation, it is important to make the distinction between *invention*, i.e., a new process or device, and *innovation*, i.e., change in the marketplace. Innovation may rely on invention(s), but invention is not required for innovation.

To manage innovation in complex ecosystems, a multi-level view of the system from work practices (people) at the bottom level, to delivery operations (processes that support work practices), to system structure (organizations), and finally the domain ecosystem (society) at the top is important. Innovation needs to occur a multiple levels of the ecosystem, not just the lower levels. The higher levels of the system (i.e., system structure and domain ecosystem) can both enable and constrain lower levels, with fragmentation at higher levels restricting innovation at lower levels. Systems that are more fragmented often produce more inventions because the different pieces of the system do not know what the other is doing. However, conversion to innovation in fragmented systems is much slower.

There are different types of innovation (e.g., service, process, information, etc.) and ways to implement change, the easiest to implement being modular or "plug and play" changes which minimize disruption to other pieces of the ecosystem. Some innovations that may move the health system towards operating like an integrated system include personalized medicine (using technology to customize practice to individual patients), telehealth (video-conferencing between clinicians and patients), mHealth (mobile-based or mobile-enhanced health delivery), population health (integration of healthcare, education, and social services), and enabling technologies such as advanced data analytics, artificial intelligence, remote sensing, and portable digital devices.

Fragmentation reduces the efficiency and effectiveness of the health system. It also increases uncertainty, which compromises decision-making. We have the tools to begin to act like an integrated system, but need cross-silo, multi-level cooperation and coordination to foster innovation. The biggest pitfall of the current domain ecosystem is that health is not assigned a value. In a healthy population more people work, something that has tremendous economic upside, but is not counted. We need to invest in health, but without assigning a value to it, the investment will not be sufficient. This requires approach the problem from a different angle by starting with the goal of population health: a healthy, productive, educated population that is competitive in the global marketplace.

Evolving the Global Ecosystem: The Adaptive Biomedical Innovation Game and Biomedical Innovation Models
Games can help people view a scenario from the perspective of another person. To this end, MIT developed Rx, a pharmaceutical simulation game to put different stakeholders in the shoes of another stakeholder. Rx has 5 players, each representing a stakeholder in drug

development: Patient, Prescriber, Sponsor, Regulator, and Payer. Each stakeholder has his or her own individual goals and abilities. The players are tasked with moving a drug from discovery through approval and use with the system level goal of successfully treating patients with the new drug. As in drug development, the personal and system goals are in conflict, and the actions of each stakeholder affect the other stakeholders and the system as a whole. Two scenarios were simulated: 1) current approach to drug development and 2) an ABI scenario: increased transparency among stakeholders and the option for conditional approval. In the ABI scenario, patients with advanced disease received the drug sooner and the sponsor had a more successful drug launch.

While simplified, the Rx simulation game can be used as an educational tool to help people understand the conflicting motivations within the industry and open discussion for problem solving. The game works through scenarios without specific facts to help players discover the key aspects of success and failure within biomedical innovation.

A range of individual drug development and care models exist, but biomedical innovation lacks robust, multi-perspective system simulation such as in military war-gaming, urban planning, climate change, and systems biology. As a result, healthcare innovations are all considered in isolation. To adequately evaluate potential innovations, a model that enables evaluation of the integrated effect of innovations within the system, as well as the effect of connecting multiple innovations is needed. NEWDIGS has developed tools towards an integrated healthcare model, including: Rx simulation game, viewpoint and risk comparators, evidence-planning frameworks, ABI development model SureReal, Portfolio and Financing System (FoCUS), and patient registry simulators.

The Political Context for Biomedical & Healthcare Innovation

The genetic revolution in healthcare will enable effective, personalized treatment of disease. However, the introduction of personalized medicine does not come without added cost. Broadly speaking, the benefits of highly targeted, personalized drugs are unlikely to outweigh the costs of developing these agents. Understanding its impact on the insurance market is critical.

Insurance coverage for the population

The insurance market is dependent on the sharing of risk. However, in the genetic age, how do you ensure the population is properly insured? Genetic profiles of risk make identification of the people likely to become sick easier and easier, enabling insurers to discriminate based on risk. Without finding another way to share their risk, the healthcare and insurance systems will fail these patients. Addressing this problem ultimately rests in how much we are willing to socialize insurance through risk-pooling mandates that do not allow insurance companies to discriminate between healthy and sick people.

Specialty drugs insurance coverage and reimbursement

Determining insurance coverage of a particular drug is a trade-off between risk sharing and overuse. A key component in determining insurance coverage is availability of alternatives,

but in specialty drugs there are no alternatives. Therefore, price cannot be addressed through strategies to shift consumers toward cost-effective alternatives. There is no choice but to set the specialty drug price by determining how much we are willing to pay for the drug. Economically, this is a matter of putting a value on the number of years of life saved (or improved), but from a political standpoint it is very challenging to attach a dollar value to life.

Funding specialty drug research
Specialty drugs serve narrow populations, but drug development is incentivized for large target populations to tap into the biggest market. The private market will not overcome this challenge on its own. Society needs to consider to what extent we can socialize drug development with the public sector financing more of the cost of research, thereby reducing these incentives. E.g., government pre-commits a certain amount of money to development of a drug in exchange for price control.

Driving Continuous Improvement Across the System
The concept of a learning healthcare system can be extended to bridge the gap between pharmaceutical R&D and care delivery. If done properly, all of healthcare, including medication use, is co-developed. Stakeholders need to tear down boundaries, work together, and learn from each other. Focusing on the shared goal of driving more value to patients enables this. When the patient is at the center of the conversation, barriers come down. Learning about any particular drug never ends; every patient is an opportunity to learn something new. In drug development, big data opens the possibility to learn at a level of granularity previously not possible. In routine clinical practice, every time a drug is used on a patient, it is a test, an opportunity to learn.

To move the vision of an end-to-end learning system forward, continuous learning needs the dignity it deserves in terms of attention and investment. A key part of this is fostering cross stakeholder relationships. There is a lot to learn from these relationships; investing time into building them is important.

Leaders can enable advancement of a learning healthcare system by modeling the change. A key quality of leaders is curiosity. If the leader of an organization is authentically curious, they will not stay within the confortable confines of a known culture and will be receptive to innovation. Another important component of leadership is to communicate clearly defined aims, as improvement does not happen by accident. All stakeholders should strive for the goal of better care and better health at lower cost.

Action Plan
The LEAPS project will put principles discussed during the forum into action to create a continuous learning disease ecosystem that drives significant impact in biomedical innovation in three dimensions: Product Innovation, Regimen Development, and Disease Management. LEAPS will begin with a feasibility assessment and design phase during which critical stakeholders will be identified, goals defined, governance established, and

designs iteratively modeled/evaluated through successive NEWDIGS Design Labs. The pilot implementation will follow the feasibility and design stage.

The pilot will be Massachusetts based on a disease suitable for a geographically defined ecosystem that represents an unmet need and an indication in which there exists substantial innovation activity. LEAPS will leverage and tailor Design Lab methods and other NEWDIGS tools for concept prototyping, analysis and refinement, and real-world pilot design. Planned innovative system components include design of distributed ecosystem architectures, financing and incentive models, process innovations and behavior change, integrated application of emerging technologies, and evidence-driven policy recommendations.

The LEAPS project envisions the creation of a learning engine within a disease ecosystem, in which a cross-stakeholder infrastructure of evidence-generation supports decision-making of all stakeholders throughout the drug lifespan.

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