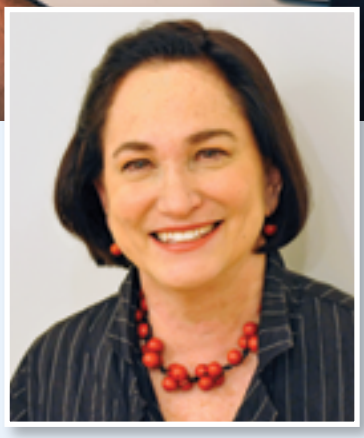

Advancing Healthcare through Innovation and Collaboration

An Interview with Gigi Hirsch, MD

Executive Director, Center for Biomedical Innovation,
Massachusetts Institute of Technology and Director NEWDIGS

NEWDIGS is an exciting and innovative approach to developing solutions for systemwide impediments to biomedical innovation and patient care. The non-competitive, collaborative environment encourages novel and fresh ideas and interactions to truly move the industry forward in positive ways. Evidera is currently participating along with other experts from across the healthcare spectrum in the new Learning Ecosystems Accelerator for Patient-Centered, Sustainable Innovation (LEAPS) project, which is designing and piloting an ecosystem for purpose-driven evidence generation and integration focused on a critical disease area (including both real-world evidence and data from randomized controlled trials).

Dr. Debra Schaumberg, Vice President, Scientific Affairs, Real-World Evidence at Evidera recently sat down with Dr. Hirsch to discuss the NEWDIGS initiative, the LEAPS project, and the hope for transformation of the healthcare ecosystem.

Debra Schaumberg

Please tell our readers a bit about the MIT NEWDIGS consortium.

MIT NEW Drug Development ParadIGmS (NEWDIGS) is an international "think and do tank" dedicated to delivering more value from biomedical innovation faster to patients, in ways that work for all stakeholders. NEWDIGS designs and pilots system-level innovations that are too complex and cross-cutting to be addressed by a single organization or market sector. Its members include global leaders from patient advocacy, payer organizations, biopharmaceutical companies, regulatory agencies, clinical care, academic research, and investment firms.

The LEAPS Project focuses specifically on aspects of a learning healthcare system that improves our ability to get the right treatment to the right patient at the right time – that is, optimization of therapeutic regimens. Within this context, there are a number of relevant challenges to attaining a true learning healthcare system. In laying the groundwork for the LEAPS Project, we think of these challenges falling broadly into three, inter-related categories associated with real-world evidence and learning.

1. **Planning.** Traditionally in biomedical innovation, evidence-based learning stops at the point of regulatory approval. Consequently, most of the evidence needed for real-world decision making by patients, providers, and payers is missing. A true learning health system requires that evidence essential for real-world decision making is prospectively planned with input from all key stakeholders in order to be fit-for-purpose to improve decisions and patient outcomes.

2. **Production.** The current approach to producing real-world evidence is fragmented, inefficient, and extremely costly. Applying traditional approaches to fill current real-world knowledge gaps that undermine our ability to optimize therapeutic regimens – i.e., one study/drug/stakeholder at a time - will simply not get us where we need to go.

3. **Use.** A true learning healthcare system would fully leverage evidence produced by making it available in timely ways to those making clinical decisions, updating policy and practice standards, and informing next generation biomedical innovation priorities and strategies.

Designing and implementing a scalable, sustainable learning system must address all three of these domains through the coordinated evolution of policies, processes, and technologies – and, most importantly, the associated alignment of incentives around patient-centered learning.

Evidera is collaborating with NEWDIGS on the LEAPS project. Could you explain to our readers more about this initiative and its goals and methods?

The LEAPS Project of the MIT NEWDIGS consortium focuses on transforming how key stakeholders in a disease ecosystem (i.e., patients, providers, payers, regulators, and developers) work together in the planning, production, and use of real-world evidence in order to more reliably optimize regimens of therapeutics.

Success in the LEAPS pilot will require that stakeholders collaborate to create new infrastructures - evidence generation platforms - designed for patient-level impact, scale, and sustainability. Collaborators will create a "Learning Engine" for a target disease that has significant implications for value creation and capture by all parties in two key domains: 1) the translation of data into knowledge that improves decision making related to therapeutic development, access, and use; and, 2) the impact of therapeutics on clinical outcomes.

Success metrics include both improved patient outcomes, as well as reduced waste and inefficiency across the system. LEAPS collaborators are designing a model system for rheumatoid arthritis (RA) for a pilot in Massachusetts (MA), the "RA MA pilot," and will extract generalizable design principles to inform related efforts in other diseases and geographies. The RA MA pilot is expected to launch in 2020.

Dr. Hirsch is the Executive Director of the MIT Center for Biomedical Innovation (CBI), which focuses on improving global health by overcoming challenges to the development, diffusion, and adoption of biomedical innovations.

Her current efforts at CBI center on leading the New Drug Development Paradigms initiative (NEWDIGS), a program that is re-engineering pharmaceutical innovation to deliver new, better, affordable therapeutics to the right patients, faster. Within the broad strategic framework of "Adaptive Biomedical Innovation (ABI)," NEWDIGS' flagship project focused on aligning stakeholders around more adaptive, patient-centered approaches to the management of risk and uncertainty across the life span of new medicines. This project helped inspire the Adaptive Pathways pilot program launched by the European Medicines Agency (EMA) in March 2014.

Under Dr. Hirsch's leadership, NEWDIGS continues to channel multi-stakeholder thought leadership to advance other critical enablers of ABI such as structured evidence planning and production across the product lifecycle; efficacy-to-effectiveness (E2E) strategies, tools and systems; precision financing models for curative therapies; and, simulation methods/tools for collaborative innovation.

Dr. Hirsch has held a number of leadership roles that leverage her broad clinical background (internal medicine, emergency medicine, and psychiatry) along with her passion for innovation, entrepreneurship, and improving patient outcomes. Prior to joining CBI, she served as Director of Academic and Professional Relations at Millennium Pharmaceuticals and was founder and CEO of a boutique entrepreneurial venture (MD IntelliNet), funded by Boston's Beth Israel Hospital. She has held faculty appointments at the medical schools of Harvard, Brown, and Tufts after receiving her medical degree at the University of Cincinnati.

Why is it important to engage multiple stakeholders in this effort?

LEAPS builds on NEWDIGS' guiding principles for collaborative system design where success requires a multi-stakeholder view of the following dimensions:

- **Identifying the problem/need** - what is working and not working in the current target area of the system, from each stakeholder's perspective
- **Defining the design "space"** - given the highly regulated nature of this industry, identify which aspects of the system that may be contributing to the problem(s) are fixed versus flexible, and consequently, which ones are approachable for innovative solutions

- **Understanding success drivers** - including value and risk drivers for each stakeholder, and critical inter-dependencies across stakeholder silos in the target area of system improvement

Effective and sustainable success in system level transformation requires that all stakeholders be actively engaged from the outset of any design initiative within NEWDIGS.

How hard is it to get stakeholders to start to "think differently"?

One of the greatest challenges, and most warmly embraced aspect of collaboration in LEAPS, is the opportunity to work together with other stakeholders in ways that are simply not possible in one's day job. Collaborators often comment that they are smarter after a LEAPS Design Lab than when they came in.

Examples of guiding principles in NEWDIGS, and in LEAPS, designed to foster innovative thinking include:

- ***Patient-centered innovation cannot be achieved one silo at a time.*** Rather, it requires stakeholders to work together in fundamentally different ways to optimize tradeoffs and "collective impact" for patients.
- ***Decisions made in one silo have implications for other silos.*** Patient-centered decision-making requires the explicit exploration of tradeoffs, and collaborative approaches to reducing risk or uncertainty can change decisions, actions, and outcomes.
- ***Science evolves from left to right (i.e., from discovery to development to delivery). Evidence, on the other hand, should be planned from right to left (i.e., informed by downstream decision-makers).*** Value (as defined by patients, clinicians, and payers) must be considered earlier in drug development.

2019 is the 10th anniversary of the MIT NEWDIGS initiative, and much of our success is driven by the collaborative design tools and methods, and our safe haven, the pre-competitive Design Lab environment that we have developed to support "thinking differently" in ways that drive timely, real-world impact. We have a track record of advancing from concept to real-world pilot within three years, which helps collaborators trust in the process we use to think outside of one's silo.

What is your (LEAPS) perspective on closing the gap between how medical products are developed (e.g., the randomized controlled trial infrastructure that has evolved to address regulatory requirements) and the evidence needed to guide real-world use of the products (e.g., RWE)?

Closing the knowledge gaps between the *development* and the *real-world use* of biomedical innovations is critical to the future of biomedical innovation and is at the heart of the NEWDIGS LEAPS project.

As value-based healthcare gains traction, the future of biomedical innovation is at risk, as illustrated by the current state of RA in which massive, complex knowledge gaps exist that undermine our ability to optimize treatment regimens. The future depends on answering the questions underlying these knowledge gaps, yet the current approach to biomedical evidence generation is expensive, lengthy, laborious, and narrowly focused, i.e., "one question, one drug, one stakeholder." Biomedical innovation cannot succeed without transforming evidence generation such that we are able to answer more questions, better, at scale, and at lower cost.

The LEAPS vision builds on the recognition that we simply cannot get where we need to go using traditional approaches to evidence generation. As detailed in the earlier question about the challenges in building this new ecosystem, we need to fundamentally transform how we plan, produce, and use real-world evidence to ensure that biomedical innovation, and value-based healthcare, are both successful and sustainable.

What role do you envision for the evolution of a real-world evidence infrastructure to enable the development of a learning ecosystem?

As noted earlier, our ability to optimize therapeutic regimens is undermined by current gaps in real-world knowledge that are massive and complex, and current approaches to evidence production are too fragmented, inefficient, and costly to successfully meet the challenge.

Central to the LEAPS approach to addressing this challenge is the use of *platform strategies* to develop better real-world evidence, faster, and at lower cost. Platform strategies have driven the advancement of the high-tech industry but have only recently been explored for evidence production in healthcare, beginning with adaptive platform trials of investigational drugs to advance precision medicine in oncology.[1] Recent real-world evidence generation platforms have leveraged learnings from these innovative clinical trial designs and integrated them with a novel approach to point-of-care studies, embedded into clinical practice.[2] This concept is illustrated in Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which is evaluating multiple domains for treatment of community-acquired pneumonia across multiple intensive care units (ICUs) in Australia, New Zealand, and Europe. The REMAP-CAP platform is embedded within the electronic health record (EHR) of participating institutions and is designed to simultaneously address multiple questions regarding treatment of community-acquired pneumonia, such as the best way to manage the ventilator, the best antibiotics and fluids, and whether steroids should be administered, etc. Ongoing evaluation of patient outcomes informs changes in platform design elements as data accumulates allowing clinicians to respond more quickly to both successful and unsuccessful therapies. Thus, as the platform generates

evidence, treatment improves, and so does the chance of patients receiving the most effective treatment for their situation.[3]

Using RA as a model, LEAPS is harnessing lessons learned from these pioneering endeavors to target the next frontier in biomedical evidence generation platforms: applying platform strategies to the real-world treatment of chronic diseases in ambulatory settings. The LEAPS Learning Engine will consist of multiple coordinated platforms, each tailored to address a specific type of knowledge gap in terms of data collection, analysis methods, and data sources. For example, the LEAPS RA MA pilot will initially include two separate, but coordinated, platforms. The *Real World Discovery Platform* (RWDP) will apply artificial intelligence and machine learning to a diverse, distributed set of data sources to identify and replicate predictive markers. In contrast, the *Adaptive Point of Care Platform* will be embedded in decision making at the point of care and will employ adaptive methods to continuously learn and improve treatment selection for a given patient.

How are patients informing this transformation?

Designing and implementing an effective learning ecosystem requires the active participation of patients and patient advocacy groups. Patient engagement in LEAPS goes far beyond simply inviting patients to participate in our Design Lab events and extends to their involvement in the work of our multi-stakeholder design teams. Patients provide valuable input on understanding unmet needs, designing and vetting emerging solution concepts, and planning specific aspects of the blueprint for our RA MA pilot. We are particularly excited to have the opportunity to work with the Arthritis Foundation at both the national and state (Massachusetts) level in LEAPS.

Are we missing any critical elements? What skill sets are needed or need to be further developed within the healthcare industry writ large?

In many ways, LEAPS is about shifting our focus in biopharma and healthcare from bigger data to smarter evidence. As this transition unfolds, it will be critically important for organizations that have historically collected data from their daily work to enhance their understanding of how to more fully exploit the value of the data for their organizations and for others in the ecosystem. This will require a deep understanding of the context of this data, and how to leverage it to improve decision making within the organization as well as more broadly within the ecosystem. Advanced analytics and research methods will certainly be an important part of this evolution, but so too will strategic systems thinking, science-driven policy making, and adaptive organizational leadership – both within individual firms as well as within pre-competitive, public-private collaboration environments.

What's the "downstream" vision for LEAPS? In other words, in the land of LEAPS, how do we generate and use evidence?

Learning in the "Land of LEAPS" will be fueled by harnessing the data that is generated as a byproduct of the daily lives of stakeholders across the value chain, from bench to bedside to home to bench. Platform strategies will leverage targeted access to associated distributed data sources, and appropriate analytic methods, to produce better evidence faster and at lower cost. Wherever possible, data access and analytics will be embedded in work flow processes to enhance scalability and sustainability. Dissemination of evidence will be optimized for timely delivery to decision makers at the point of care, and in meaningful ways for incorporation into processes by which policy and practice standards are updated for key stakeholder groups.

For example, the LEAPS RWDP is now being designed to enable hypothesis generation related to identifying subpopulations that are "super-responders" or "non-responders" to specific classes of RA therapeutics. Once validated, evidence emerging from the RWDP will ideally impact clinical practice, payer step therapy policies, and potentially future clinical guidelines. The ability to identify non-responders to a TNF inhibitor therapy, for example, would more rapidly allow patients to move from a non-effective therapy to one that could potentially be more effective for them, thus providing earlier symptom relief and preventing further disease progression. Evidence generated from the RWDP would also likely impact decisions within biopharma companies, with the potential to influence product development strategy and clinical trial designs. ■

For more information on NEWDIGS and LEAPS, visit https://newdigs.mit.edu/.

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