NEWDIGS

LEAPS

Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation

Design Lab

July 17, 2018 – Day 1 Afternoon

Massachusetts Institute of Technology

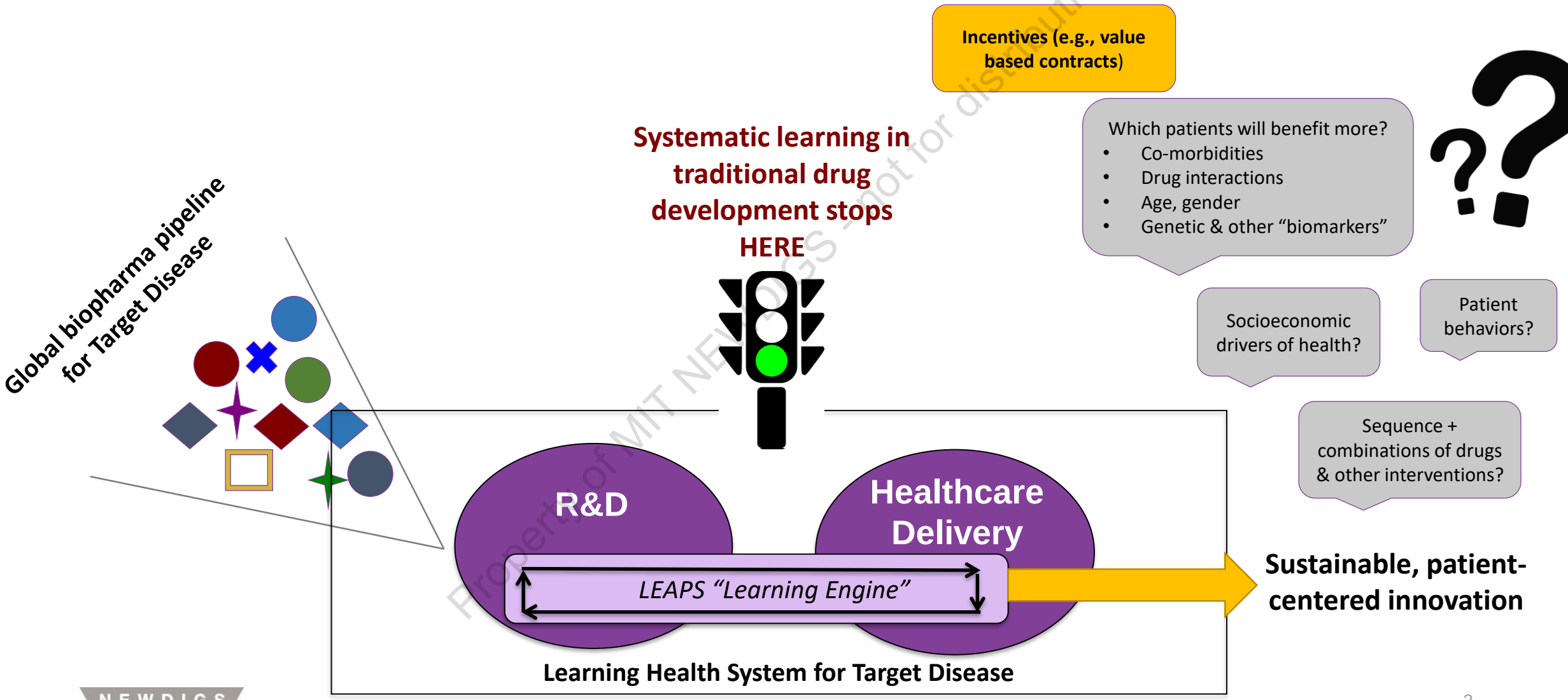
MIT CENTER FOR BIOMEDICAL INNOVATION

Why do we need a new approach to evidence planning & production?

"High-quality evidence is what we use to guide medical practice. **The standard approach to generating this evidence** — a series of clinical trials, each investigating one or two interventions in a single disease — **has become ever more expensive and challenging to execute**….. The common denominator is a **need to answer more questions more efficiently and in less time."**

(Woodcock & LaVange, Aug 2017)

Emerging science brings more hope… and more questions – now with incentives to find answers - better, faster, at lower cost

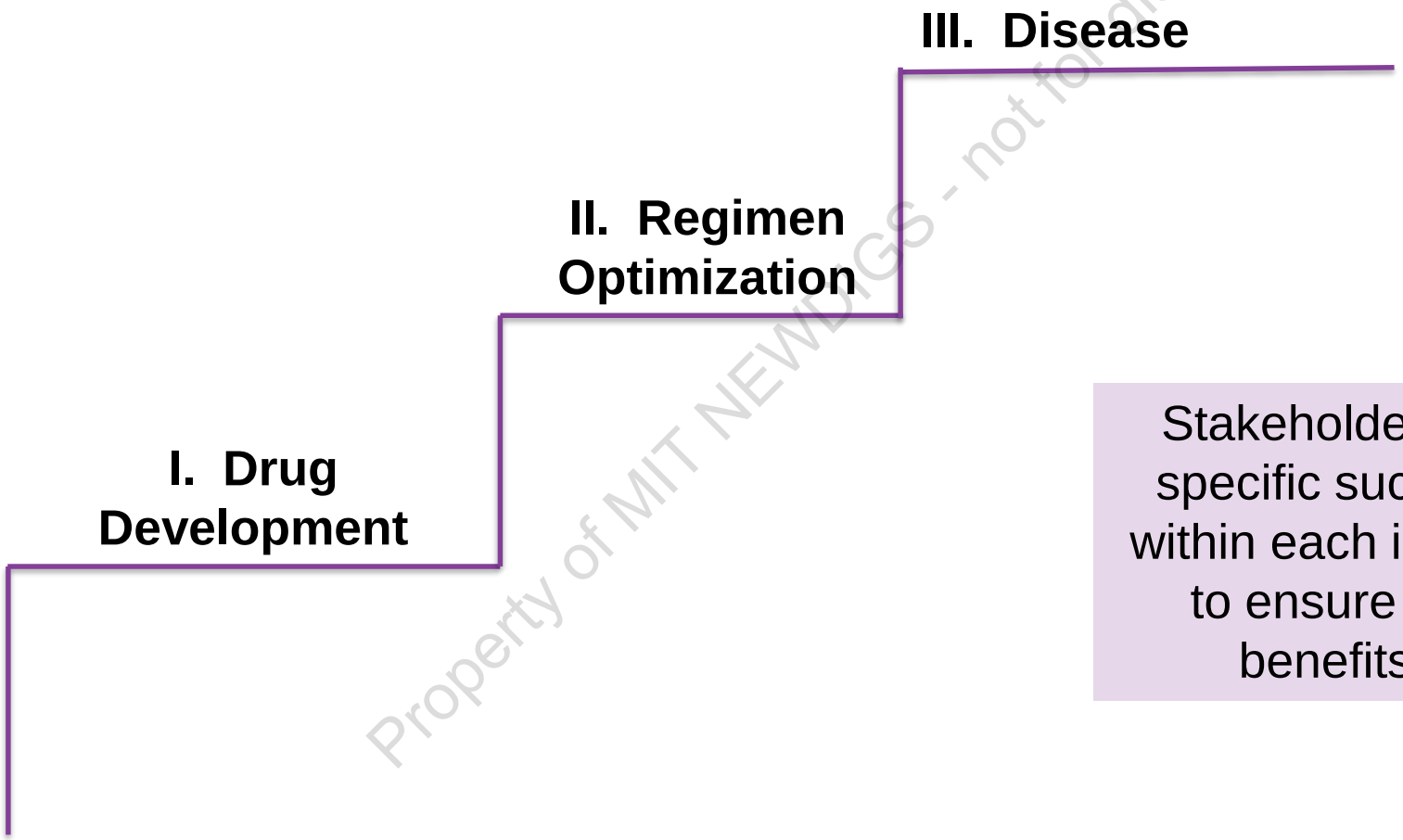


Key Question for LEAPS

- How do we “answer more questions more efficiently and in less time?”

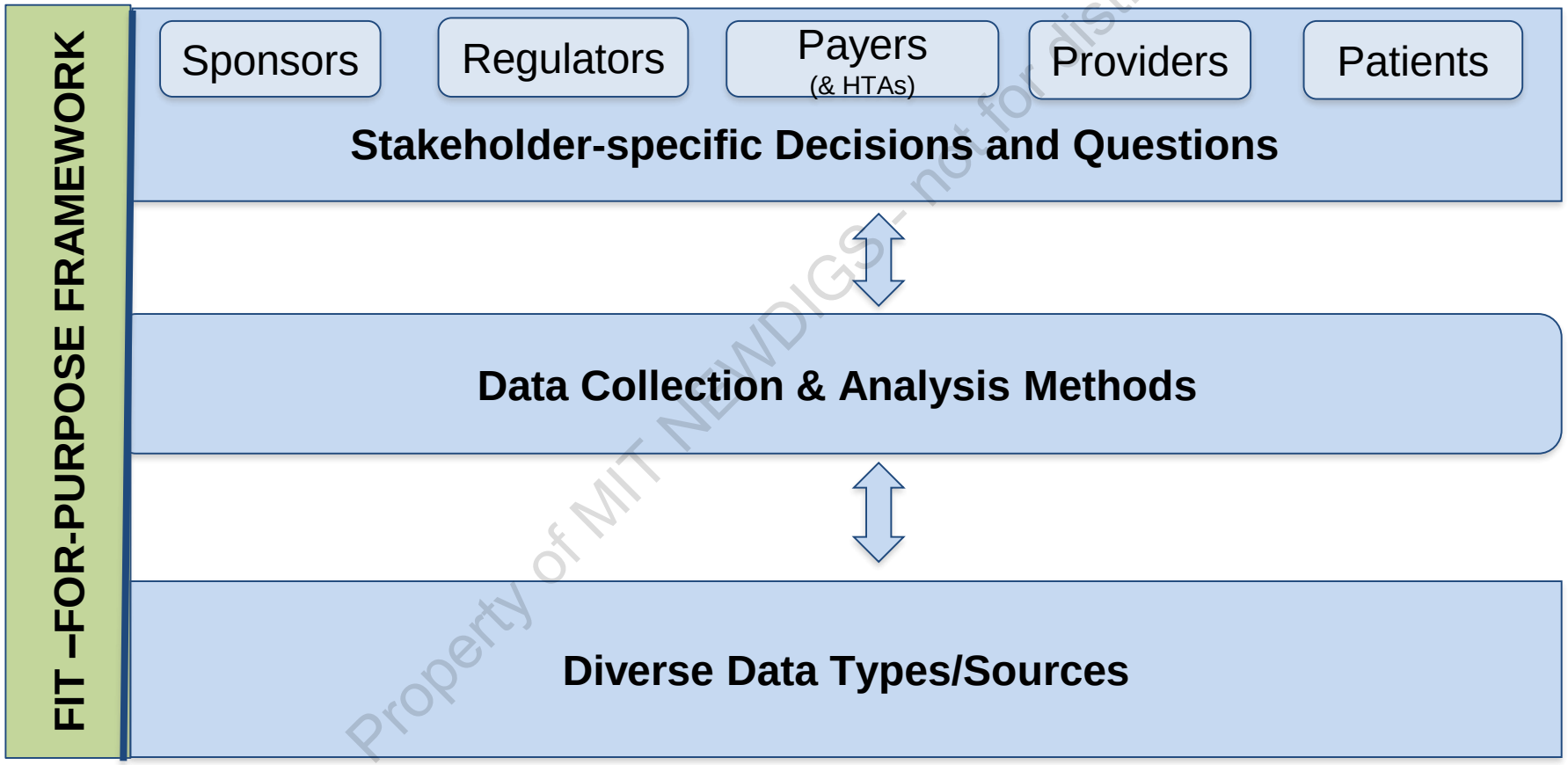
- How will we know if we are succeeding?
  - Near term
  - Longer term

The LEAPS Evaluation Design Team will develop a comprehensive impact assessment framework for further discussion at December Design Lab

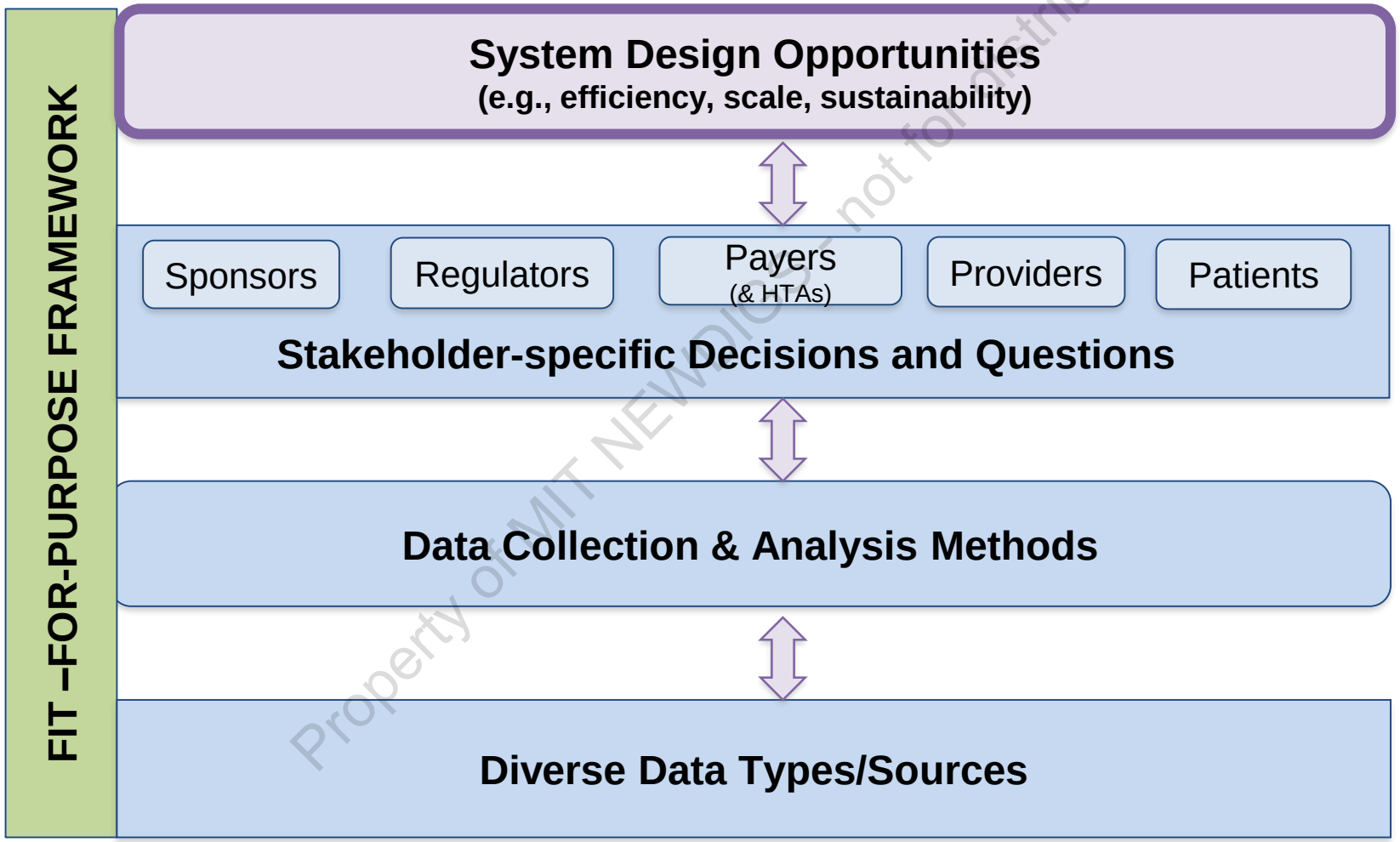


Stakeholders will define specific success metrics within each impact domain to ensure meaningful benefits to them.

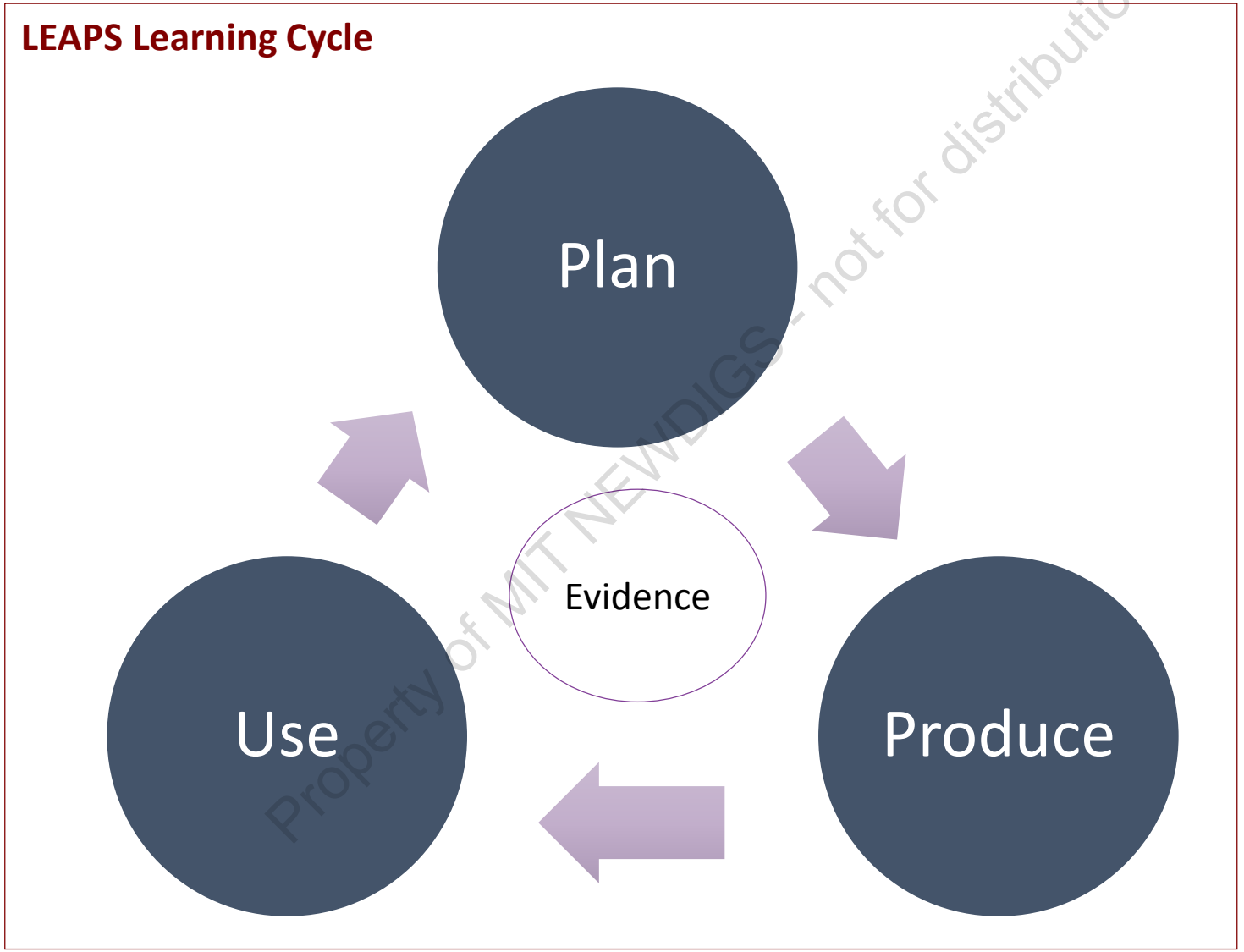
Impact Driver in LEAPS:
Evidence that is Fit-for-Purpose for each product…..



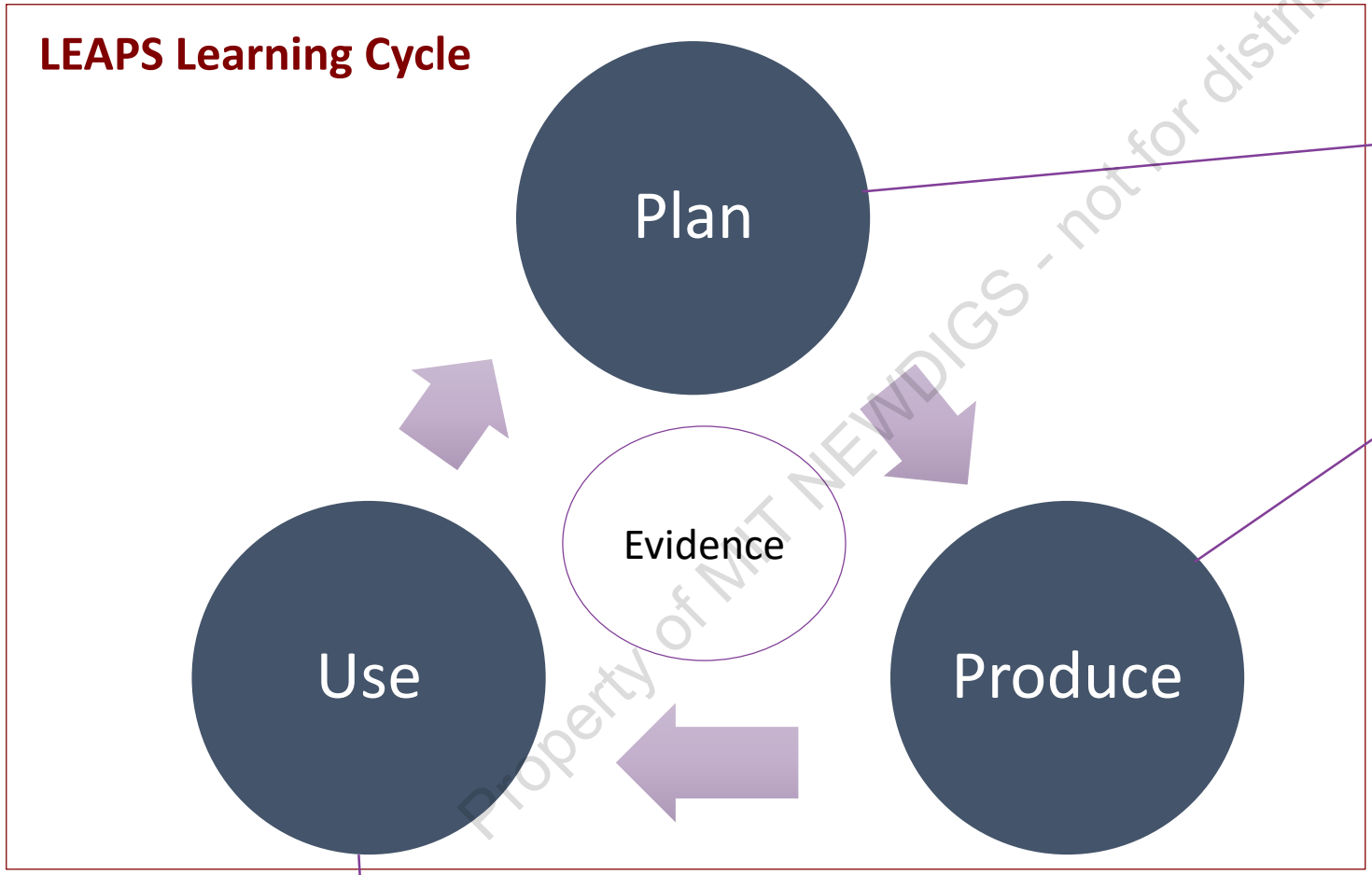
… scaled to a Fit-for-Purpose Learning System for a target disease (and industry portfolio of products)



Key LEAPS Design Concept: A LEAPS Learning Cycle



The value of evidence can be enhanced in different ways within each component of Learning Cycle



Sample Value Factors

Plan
- Fit-for-purpose
- Minimal but sufficient

Produce
- Efficiency (time, cost)
- Scalability (expand, connect)

Use
- Available when needed?
- Reuse potential

Key LEAPS Design Concept: Value of Evidence

Value of Evidence (VoE) =

Impact from Evidence Use

vs.

Cost* to Develop the Evidence

*Cost: includes financial and non-financial

VoE Example: PCSK9 Inhibitors

Safe Haven/Context Setting

- **NOT**: Monday morning quarterbacking / “gotcha”
- **IS**: A quick, high level “what if” thought exercise…..

Two PCSK9 inhibitors approved in 2015

- Initial indication: Lowers “bad” cholesterol (LDL)
  - Impact on cardiovascular mortality and morbidity not determined at time of initial approval

PCSK9 Inhibitors – What kinds of questions could not be answered from data that informed regulatory approval?

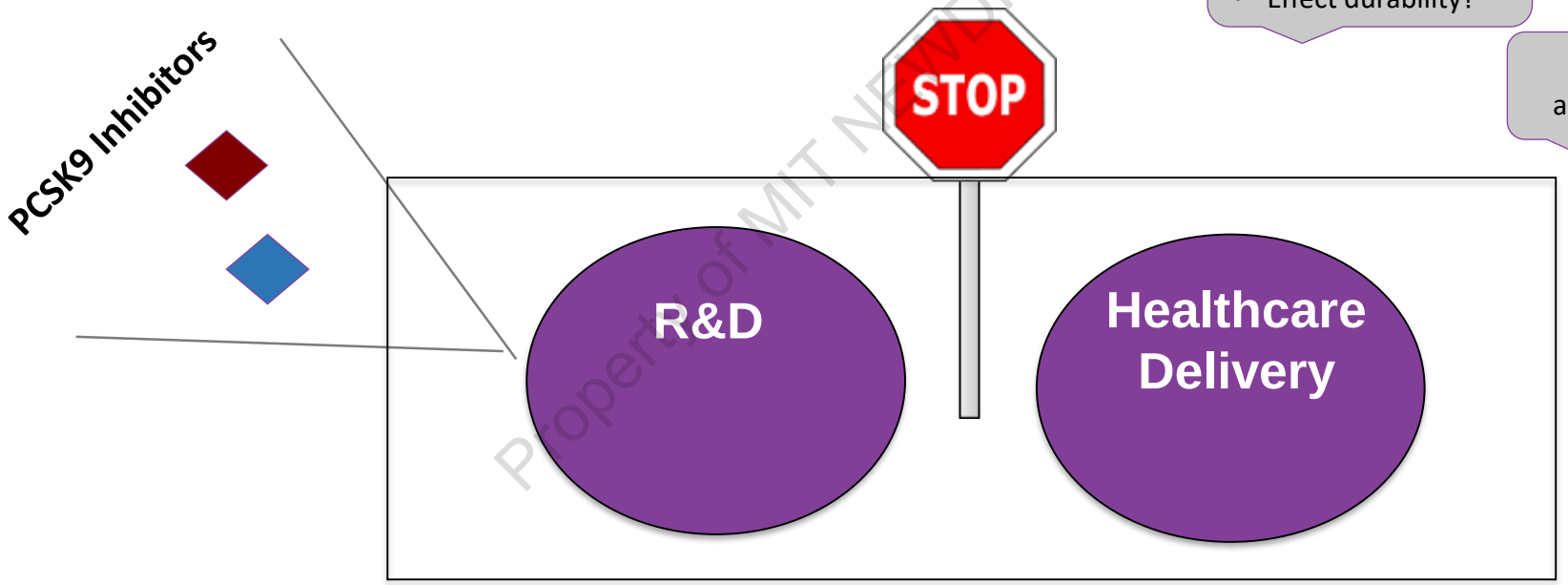
Systematic learning in traditional drug development stops HERE

Impact on cardiovascular morbidity & mortality?

Timing:
- Effect onset?
- Effect durability?

Which patients will benefit more?
- Refractory to statins
- With/without genetic mutation
- Prior MI
- Future MI – who?

Patient adherence?



PCSK9 Inhibitors: (Standard) Phase 3 Outcomes Studies - to evaluate impact on cardiovascular morbidity & mortality

Sponsor	Amgen	Sanofi/Regeneron
Drug Name	Repatha (evolocumab)	Praluent (alirocumab)
Outcome trial	Fourier N=27,000 Median f/u 2.2 years 1° endpoint – time to first occurrence of major cardiovascular event: a) Cardiovascular death, b) Myocardial infarction c) Stroke d) Hospitalization for unstable angina, or coronary revascularization. Randomized (1:1) Placebo Controlled Optimized on Statin therapy	Odyssey N=18,000 Median f/u 3 years 1° endpoint – time to first occurrence of: a) Coronary heart disease death b) Acute nonfatal myocardial infarction c) Ischemic stroke d) Hospitalization for unstable angina Randomized (1:1) Placebo Controlled Optimized on Statin Therapy

PCSK9 Inhibitors/Phase 3 Outcomes Studies: Answered some but not all questions….

VoE = Impact from Evidence Use vs Cost to Develop

I. **What do we know now that we didn't before the studies – and why does it matter?**
   - Lowering of LDL from PCSK9 inhibitors leads to decreased cardiovascular morbidity
   - "In my experience, it has changed very little."
     – *Cardiologist at leading academic lipid center (regarding payer coverage)*

II. **What remains uncertain –and why does it matter?**
   - Impact…on cardiovascular mortality?
     - Important for assessing clinical value of product
   - Which patients will have a cardiovascular event?
     - Important for targeting product use

PCSK9 Inhibitors/Phase 3 Outcomes Studies: answered some but not all questions…. despite substantial costs

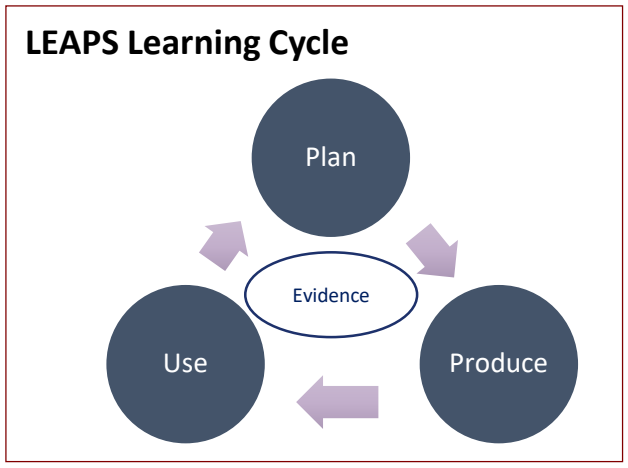
VoE = Impact from Evidence Use vs Cost to Develop the Evidence

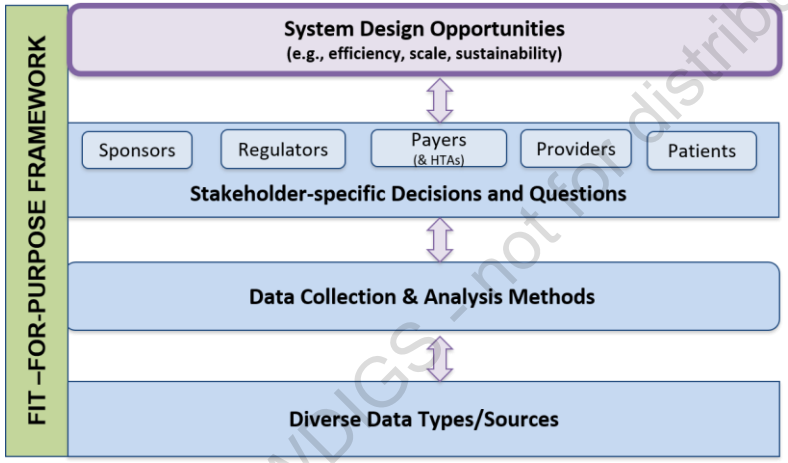
Costs:

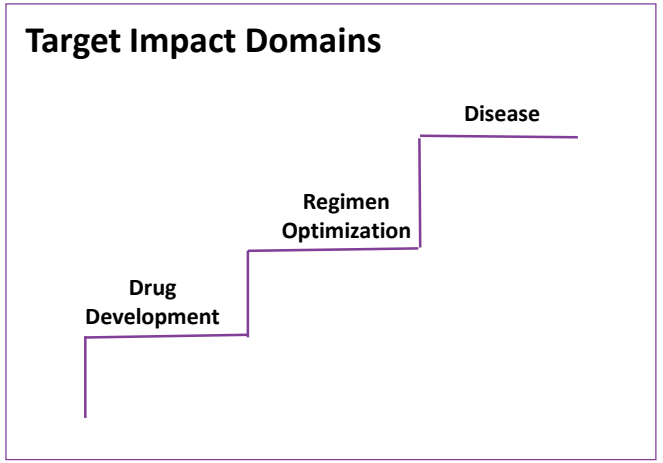
- **Patients:** Time, possible opportunity costs – placebo injection 1-2 times/month for 2-3 years for over 22,000 patients.
- **Industry:** $2B total cost of both studies
- **Ecosystem:** Opportunity cost related to a disease for which total economic burden in US is $440B annually.

PCSK9 Inhibitors – Thought Exercise: Potential Ways to Enhance the VoE

Tools







	Question	Opportunity to Enhance VoE
Plan	Which patients will benefit most?	Longitudinal disease registry: longer term outcomes; predictive biomarkers
Produce	How can we reduce time/cost of evidence generation?	Potential for multi-sponsor platform trial rather than one-offs
Use	Can we foster patient adherence to prescribed drug, despite silent symptoms?	Effective communication of evidence-based insights from registry

Our Goal Today

- Apply VoE framework to elucidate important issues related to:
  - Today: top ranked diseases for MA pilot
  - Tomorrow: 2 case studies (enhancing existing evidence generation platforms)

- Refine concept of VoE through above
  - (Input to VoE Design Team*)

**New team members welcome! (Sign-up sheet by charging station)*

LEAPS Roadmap

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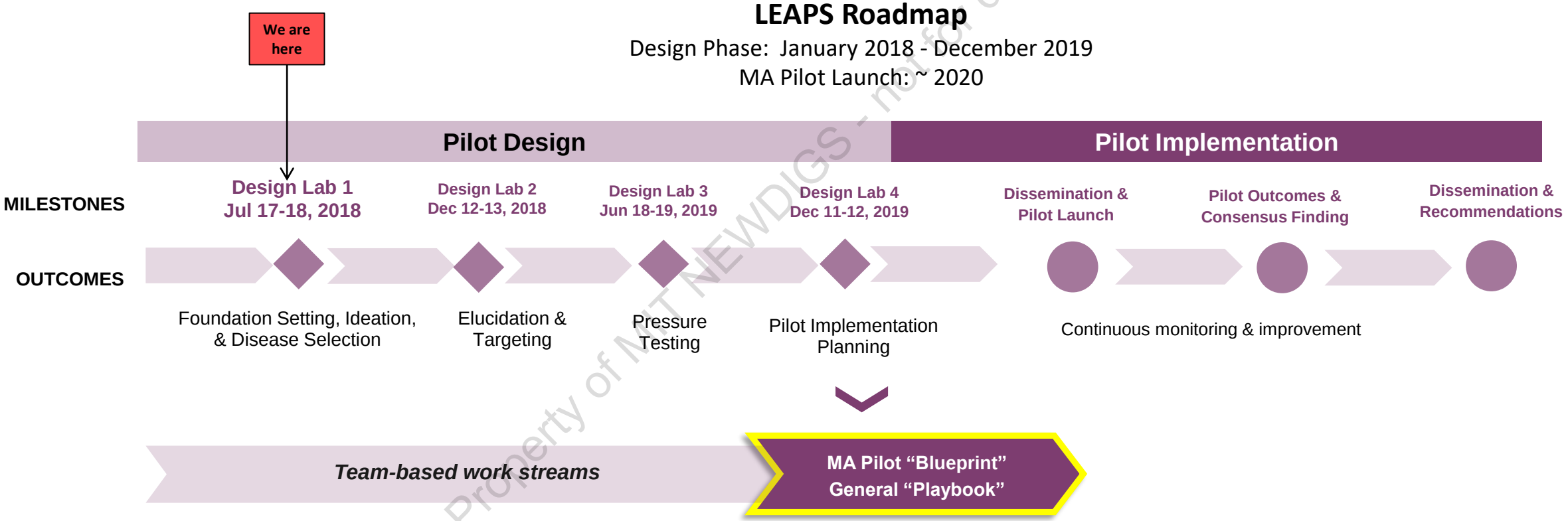
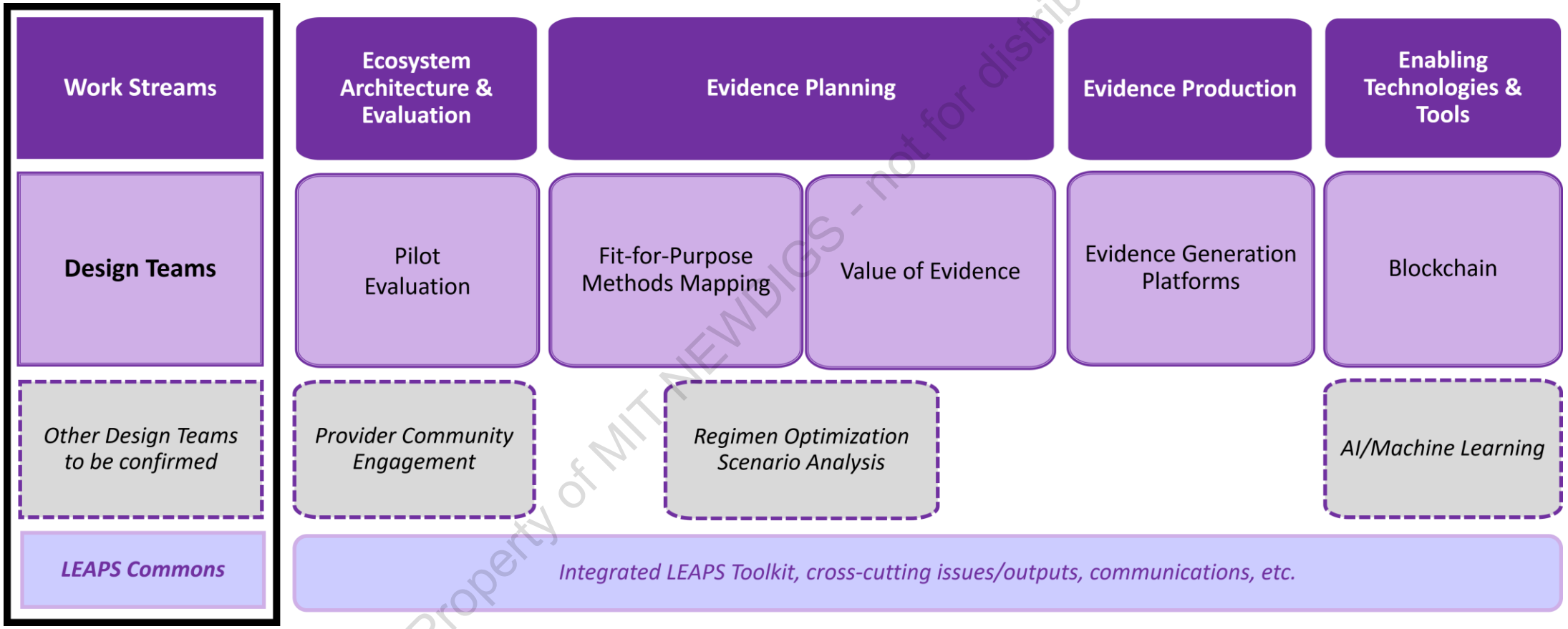
Years 1-2 focus on **design of MA Pilot** and **generalizing insights** for application in other diseases



LEAPS: Evolving Team Structure, July 2018



Priorities Following the July Design Lab

Next Steps

Multi-Stakeholder Teams	2018: Q3-4 Deliverables for December Design Lab	2019: Q1-2 Inputs to 3rd Design Lab	2019: Q3-4 Inputs to final Design Lab of Design Phase	Integrated Outputs
Pilot Evaluation	Develop & present Evaluation Framework for MA Pilot	Identify relevant data to define baseline benchmarks for Pilot	Develop plan for continuous monitoring & feedback during Pilot	• MA Pilot "Blueprint" • "Playbook" of generalizable principles
Methods Mapping (MM)	Develop & present MM Design Principles for MA Pilot	Coordinated modeling & simulation of platform prototypes for MA Pilot	• Refining / pilot planning for initial Learning Engine components for MA Pilot • Synthesis of generalizable design principles for application beyond MA Pilot	
Value of Evidence (VoE)	Develop & present VoE framework			
Evidence Generation Platforms	Prepare/lead case-based platform design exercises at Design Lab			
Blockchain	Identify & propose potential use case(s)	Prototyping for at least one use case	Pilot planning for at least one use case	

Priorities Following the Design Lab

Design Teams	Responsibilities & Initial Deliverables *(Time Commitment: 1.5-2 hours per month, including team calls)*
Pilot Evaluation	Develop preliminary LEAPS Evaluation Framework for MA Pilot, including success metrics defined by key stakeholders
Fit-for-Purpose Methods Mapping (MM)	Develop LEAPS MM Design Principles to improve decision-making for all stakeholders participating in the MA Pilot
Value of Evidence (VoE)	Develop VoE Framework & Tools that will be applied in December Design Lab to enhance the design of Evidence Generation Platforms for the MA Pilot
Evidence Generation Platforms	Apply the generalizable platform design principles from Day 2 of July Design Lab to set-up the interactive case-based Evidence Generation Platform design exercises in December Design Lab
Blockchain	Identify and propose potential high-impact use cases for demonstrating the value of blockchain as an enabling technology in the LEAPS Learning Engine

Key Dates

- ~**July 25**: Announce target disease & distribute survey for your feedback
- ~**August 8**: Design Team (DT) descriptions disseminated
- ~**August 30**: Finalize initial members of DT
  - Schedule initial DT calls ASAP
- **September 28:** DT Project Plans V1.0 completed & targeted distribution of Design Lab Summary
- **October 3:** Integrated LEAPS Project Plan reviewed by Steering Committee
- **December 12-13:** Initial DT deliverables presented/discussed at Design Lab