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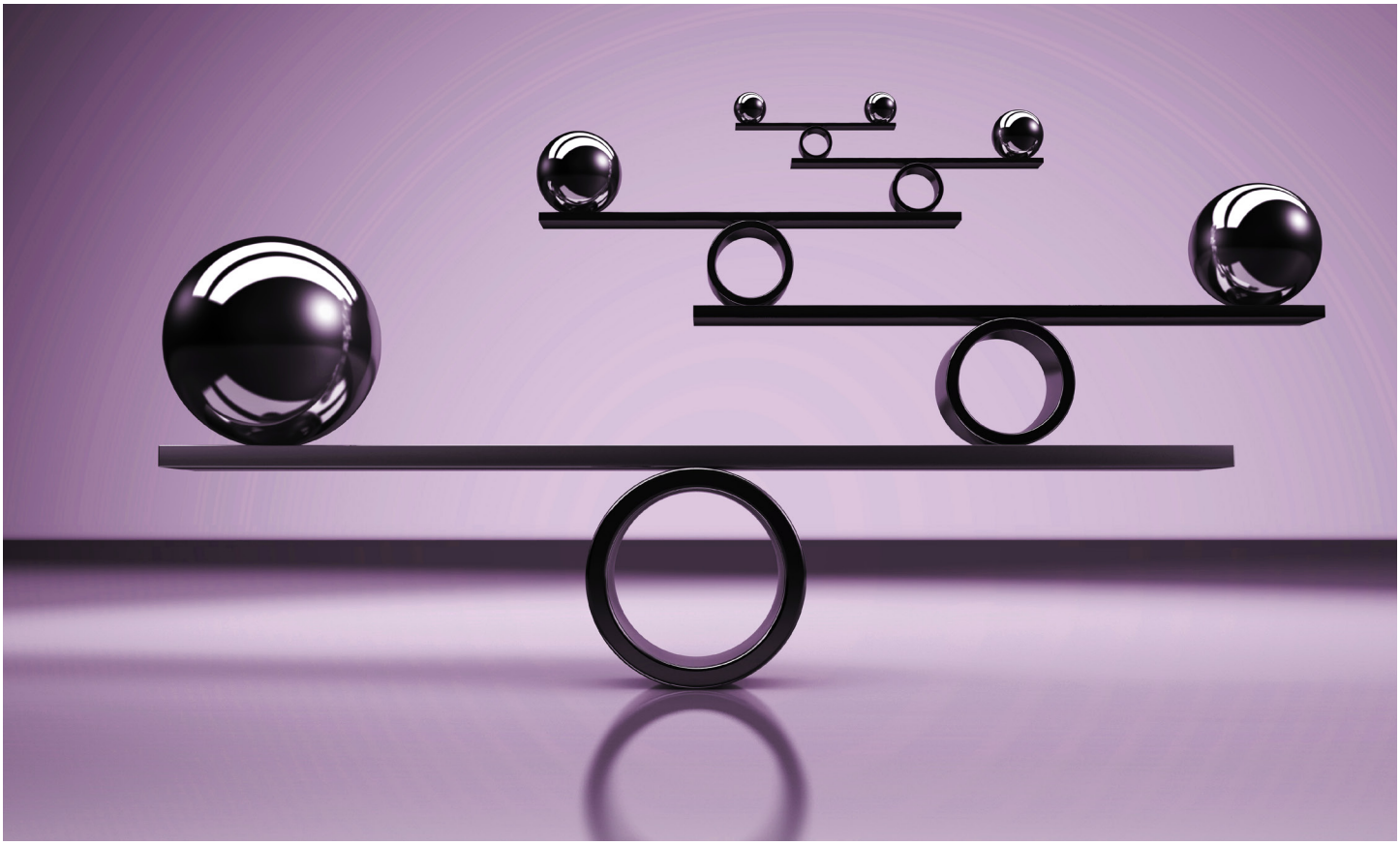
NEWDIGS

LEAPS

Learning Ecosystems Accelerator for
Patient-centered, Sustainable innovation



DESIGN LAB BRIEFING

November 2022

CONFIDENTIAL

Tufts Medical Center Institute for Clinical Research and Health Policy Studies
Center for Biomedical System Design

LEAPS Design Lab Briefing, November 2022
CONTENTS

November 2022 Design Lab
Agenda

November 15–16, 2022
Samberg Conference Center
50 Memorial Drive, Cambridge

Objectives

- Align awareness and understanding of current activities and priorities in LEAPS.
- Advance implementation planning for prototyping of federated learning via the Predictive Outcomes Platform for the NSCLC case study through team meetings and joint team design exercises.
- Explore future directions for LEAPS including a potential new program for scaling generalizable design principles to a range of disease areas.

DAY ONE	**11:00am – 6:30pm**	
11:00am – 12:00pm	Lunch and registration	
12:00 – 1:00pm	Introductions And Frame The Day	Gigi Hirsch & Mark Trusheim
1:00 – 1:45pm	Team Updates	
	Joint IO/Core Protocol	Gigi Hirsch & Elizabeth Apgar (NEWDIGS)
	Methods Innovation	Fotios Kokkotos (NEWDIGS)
	METRICS	Jane Barlow (NEWDIGS)
	Precision Reimbursement	Mark Trusheim
1:45 – 3:15pm	Team meetings	
3:15 – 3:30pm	Break	
3:30 – 4:30pm	Team Reports and Group Discussion	
4:30 – 4:45pm	Wrap-up and Day Two Preview	Mark Trusheim
4:45 – 6:30pm	Reception	

DAY TWO	**8:00am – 1:00pm**	
8:00 – 9:00am	Networking breakfast	
9:00 – 9:30am	Frame the Day & System Design Connections Overview	Mark Trusheim & Gigi Hirsch
9:30 – 11:00am	Whiteboard Sessions	
	Track A – Predictive Outcomes Platform (POP) Prototyping: Strategy & Implementation Planning	Facilitators: Gigi Hirsch & Asvin Srinivasan (Onc.AI)
	Track B – Defining Stakeholder-Specific Thresholds for Outcome Metrics	Facilitators: Jane Barlow & Mark Trusheim
11:00 – 11:15am	Break	
11:15 – 11:45am	Whiteboard Sessions Report Out	
11:45am – 12:15pm	Forward Planning	Gigi Hirsch
12:15 – 1:00pm	Networking Lunch (with To Go option)	

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Downstream System Design Module

The LEAPS Project of NEWDIGS focuses on enhancing our capacity to leverage real-world evidence (RWE) to predict individual treatment responses to drug therapy regimens and tie that to reimbursement.

The Downstream System Design Module of LEAPS provides a blueprint for action including:

1. Predictive Outcomes Platform (POP) for a scalable approach to predictive modeling
2. Precision Reimbursement (PR) models that align stakeholder incentives around patient-centered decisions
3. Operational connections between the two for efficiency and ongoing learning/improvement

The initial methodology to be explored for the POP is an emerging approach to machine learning called Federated Learning.

We take a case-based approach to developing generalizable principles for Downstream System Design. For each case we explore the Planning, Production, and Use of the RWE needed to improve patient outcomes while also enhancing the sustainability of the system.

Introduction

The LEAPS Project is focused on modernizing how we plan, produce, and use real-world evidence (RWE) to optimize drug therapy regimens. Specifically, we are focused on building new capabilities to **leverage real-world evidence (RWE) to predict individual treatment responses, and tie that to reimbursement.**

Challenges

The backbone of biomedical innovation lies in the progressive reduction of uncertainties about new products. In the United States, the Food and Drug Administration (FDA) is the key arbiter of market access, utilizing information available at the time of submission and provided primarily by the product's developer. At the point of regulatory approval, some of the critical uncertainties about the safety and efficacy of new drugs have been addressed, but many knowledge gaps persist that constrain the decisions made by clinicians, patients, and payers. For example, safety and efficacy are estimated for the average or typical patient in an approved indication; registration trials may have excluded certain subpopulations (e.g., older patients, patients with multiple comorbidities, racial and ethnic minorities, poorer and less educated patients) or may have insufficient data

for these subgroups due to under-representation or simply small sample sizes.

Unfortunately, in most cases, "systematic learning about new therapeutics stops at the point of regulatory approval." [1] Generating the RWE necessary to inform the targeted use of drug therapy regimens is critical but challenging for many reasons, including:

1. **Inefficiencies in RWE production processes:** The predominance of "one-and-done" studies means that the cost of creating an infrastructure for RWE production and analysis is borne in full by each study, with few efficiencies of scale. In addition, the static nature of this approach stands in contrast to what we know about the dynamic nature of knowledge creation, which should include continuous learning and improvement processes as new information becomes available over time. The importance of accelerating the evolution from individual studies to evidence generation platforms to enhance learning efficiency, scalability, and sustainability has been highlighted in recent literature, fueled by successful early demonstrations. [2-4]

2. **Misaligned incentives:** While developers generate the evidence required for regulatory approval, it is not realistic to expect them to produce all of the RWE that is needed to optimize the use of their product in treatment regimens across the patient journey for the approved indication. The knowledge gaps are massive and complex and their incentives are not currently aligned with the production of post-approval evidence that could reduce the market for their products to a responder sub-population. Payers, clinicians, and patients who would benefit significantly from RWE to inform the targeted use of treatments find that costs are prohibitive due to current inefficiencies in RWE production as noted above.

3. **Biases in data that fuel health disparities:** RWE generation in the U.S. often relies on the same, most readily identifiable data sources, such as insurance claims and electronic health records from academic medical centers. This reliance can exacerbate existing disparities in health care. For instance, patients without insurance coverage and those treated at rural and community hospitals may be left out of RWE analyses. Other sources may be unbalanced in race and gender composition or may not report race and ethnicity at all, marring one rationale for post-approval evidence development. Finally, advances in machine learning and artificial intelligence hold both promise and risk for precision medicine. Efficiencies may be gained with increased use of these analytic techniques on large-scale databases, but care must be taken that the algorithms generated do not reflect and amplify existing biases. [5]

The LEAPS Approach

The Downstream System Design Module of LEAPS (see Fig 1) offers a blueprint for action to address these challenges, including:

1. **Pillar I - Predictive models:** A new *"Predictive Outcomes Platform"* for the ongoing generation and refinement of predictive models from real-world data in efficient and scalable ways.
2. **Pillar II - Reimbursement models:** A new Precision Reimbursement framework for aligning incentives across stakeholders to incorporate the predictive models into patient-centered decisions and actions.
3. **Connecting the Pillars:** Technology, process, and policy enablers that link the generation and validation of the predictive models with decision-making for payers, providers, and patients.

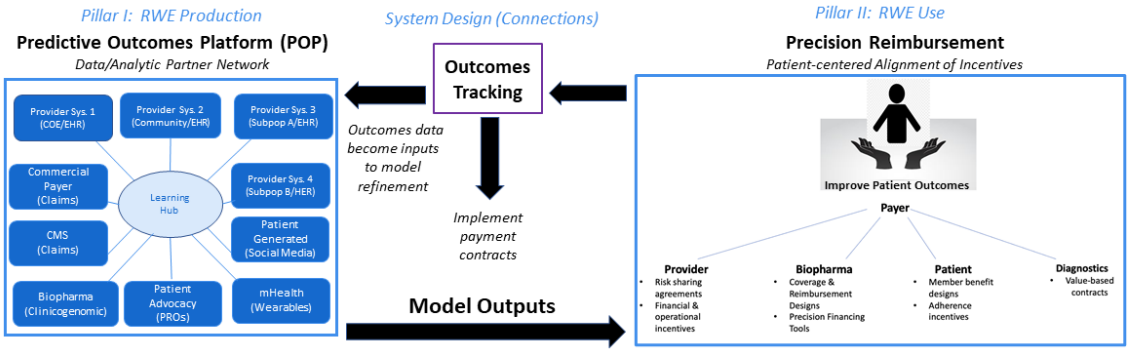

Fig 1: The evolving blueprint for Downstream System Design in LEAPS centered around a scalable approach to predictive modeling (the POP) linked to reimbursement models (Precision Reimbursement) that align incentives for all stakeholders around patient-centered decisions.

Our First Case Study

We are taking a case-based approach to developing generalizable principles for Downstream System Design. Our first in a series of case studies is focused on advanced Non-Small Cell Lung Cancer (NSCLC) and specifically:

1. Can we improve our ability to predict which patient sub-populations with advanced NSCLC will benefit from the use of immune checkpoint inhibitors (ICIs)?
2. Can we generate the predictive models in ways that minimize the risk of bias and associated health disparities?

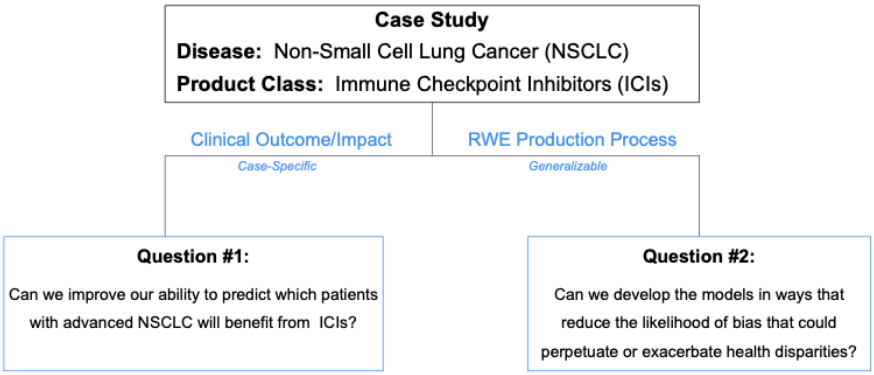

Fig 2: Key questions in the NSCLC/ICI case study for consideration at the November 2022 Design Lab. Question #1 focuses on what evidence is needed (predictive models) to improve outcomes for this case study, while Question #2 focuses on how we produce it for this and future case studies.

Exploring a New Approach to Predictive Modeling

The initial methodology to be explored for predictive modeling in the coming months in LEAPS is an emerging approach to machine learning called Federated Learning. [6-8]

Today, AI and Machine Learning still struggle with two main challenges: (1) isolated islands of data and (2) data privacy and security. Many methods have emerged to address these issues, such as data lakes or blockchain, but these, too, have their limitations. Federated Learning, first described in 2016, is a distributed machine learning approach that "trains" an analytic predictive

model through iterative cycles and refinement using a large portfolio of separate, decentralized data. A central premise of Federated Learning is that only the models and their encrypted learnings are shared between a central server and the data servers. In this way, the data remains private and secure within each separate device or server.

Federated Learning is now being explored in healthcare as an approach that leverages the value of large data sets without the privacy and security risks associated with the sharing of patient-level data. While Federated Learning offers the potential opportunity to include diverse types of data, demonstration projects now underway in healthcare tend to involve multiple data sets of the same type, such as electronic health record (EHR) data from multiple provider systems [9-10]

LEAPS will be exploring the feasibility of using diverse data types to enrich predictive modeling of treatment responses in two ways:

1. A wide array of diverse data types (e.g., EHRs, administrative claims, wearables, social media, patient reported outcomes, etc.) to enhance the richness of potential signals for hypothesis generation
2. Inclusion of data sets that include patient sub-populations that are often under-represented in data sources that are typically used for modeling in healthcare in order to reduce the risk of biases that could perpetuate or exacerbate health disparities.

If successful, the predictive models developed could be valuable across the biomedical innovation value chain in drug discovery, clinical trial design and recruitment, and development of diagnostics, as well as informing healthcare policy and practice standards. In addition, the POP infrastructure could be readily scaled to generate more predictive models beyond the case study to other areas of oncology, as well as other diseases and product classes.

While the concept of Federated Learning is exciting and potentially transformative, it is important to recognize that this approach is new and must be validated. Target proof points for associated LEAPS activities include:

1. **Demonstrate the application of Federated Learning** as a methodology for the modeling of predictive outcomes.
2. **Develop predictive models that:**
    a. Are "fit-for-purpose" for decision-making by payers, providers, and patients.
    b. Inform the targeted use of treatments to patient sub-populations.
    c. Minimize the risk of biases that could fuel health disparities.
3. **Enhance capacity to scale from individual studies** in predictive modeling through the design and development of a platform.

These issues will be at the core of our working sessions during the November Design Lab as we define our priorities for 2023.

References

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LEAPS Downstream System Design Module Case Study #1: Immuno-oncology

Addendum to Landscape Analysis: Health Disparities in Advanced NSCLC

The LEAPS Project of NEWDIGS focuses on enhancing our capacity to leverage real-world evidence (RWE) to predict individual treatment responses to drug therapy regimens, and tie that to reimbursement.

The Advanced NSCLC case will address two critical questions:

1. Improve our ability to predict which patients with advanced non-small-cell lung cancer (NSCLC) are likely to benefit from treatment with immune checkpoint inhibitors (ICIs) using Federated Learning approaches.
2. Can we generate predictive models in ways that minimize the risk of bias and associated health disparities through methods that combine evidence from diverse data sources (socioeconomic, biologic, clinical, insurance claims, patient-generated, wearables, etc.). Traditional bias mitigation approaches assessing the probability of risk of models may also be used.

We take a case-based approach to developing generalizable principles for Downstream System Design. For each case we explore the Planning, Production, and Use of the RWE needed to improve patient outcomes while also enhancing the sustainability of the system.

For further details click here: *Downstream System Design Module Overview*

Immuno-Oncology Case Study

The first case study for the Downstream System Design Module is Immuno-Oncology, specifically the use of immune checkpoint inhibitors (ICIs) for advanced non-small-cell lung cancer (NSCLC). The June 2022 Landscape Analysis focused primarily on medical or biologic factors associated with response to ICIs to inform the original case study objective (see Framing the Case Study below). Discussions and research following the Design Lab highlighted the need for additional factors to be considered in predictive modeling in order to minimize the risk of bias that could perpetuate or exacerbate health disparities.

To that end, this document supplements the June 2022 case study materials with background related health disparities in general, and NSCLC specifically, as well as methodologic considerations to mitigate bias.

Framing the Case Study

June 2022 *Objective:* Improve our ability to predict which patients with advanced non-small-cell lung cancer (NSCLC) are likely to benefit from treatment with immune checkpoint inhibitors (ICIs).

Specifically, can our model, comprising multiple features from diverse data types, predict benefit of ICIs in patients with advanced NSCLC better than the current practice of predicting response to ICIs via programmed cell death receptor-1 (PD-L1) immunohistochemistry alone?

November 2022
Following recommendations from the June 2022 Design Lab and subsequent team discussions, the Immuno-Oncology case study was further refined to include a second question:

Can we generate predictive models in ways that minimize the risk of bias and associated health disparities?

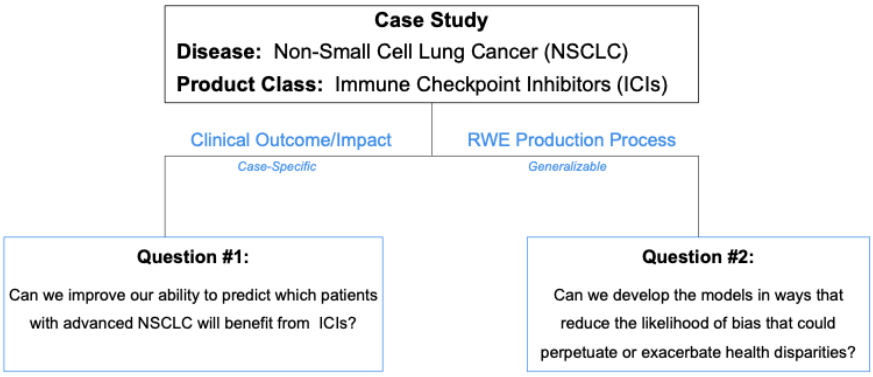

Fig 1: Key questions in the NSCLC/ICI case study for consideration at the November 2022 Design Lab. Question #1 focuses on what evidence is needed (predictive models) to improve outcomes, while Question #2 focuses on how we produce it.

Health disparity is defined by the National Cancer Institute as "A type of preventable health difference that is closely linked with social, political, economic, and environmental disadvantage. Health disparities may occur because of race, ethnicity, sex, gender identity, sexual orientation, age, religion, disability, education, income, where people live, or other characteristics." (1)

Social Determinants of Health (SDOH)

SDOH broadly refer to non-medical influences on health outcomes. The World Health Organization (WHO) defines SDOH as "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life" including "economic policies and systems, development agendas, social norms, social policies and political systems." (2) Research suggests 30-55% of health outcomes can be attributed to SDOH. As such, they play

a large role in health disparities and are fundamental to promoting health equity, defined as "the absence of unfair and avoidable or remediable differences in health among populations groups defined socially, economically, demographically, or geographically." (2)

The Healthy People 2030 initiative's framework groups SDOH into 5 domains (Figure 1). (3) Common measures (and proxies) of SDOH in literature include income, employment, health insurance, education, geography, healthcare utilization patterns, and race. SDOH contribute to inequities in clinical research and across the full continuum of health, e.g., for cancer, exposures to risk factors, prevention measures, early detection, comprehensive testing, appropriate treatment, and mortality. (4-6)

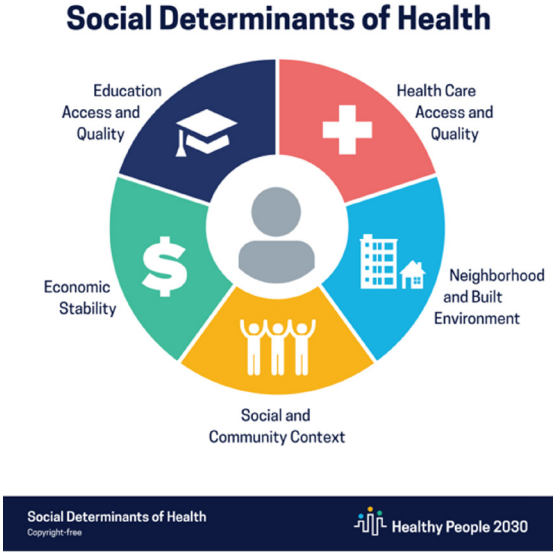

Figure 2. Social Determinants of Health can be grouped into 5 domains, as illustrated by the Health People 2030 Initiative's framework. (3)

Race and Social Determinants of Health

Race is fundamentally intertwined with SDOH due to the longstanding inequalities across all SDOH domains that stem from structural racism. (5) Racial disparities in cancer outcomes are well documented. In analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program from 2006-2012, 5-year cancer mortality risk among cancer patients (all sites) was significantly higher than white patients for all other racial groups, even after adjusting for sex, age, and stage at diagnosis. The largest increase in risk for was Black and American Indian/Alaska Native (AIAN), which had 33% and 51% higher mortality risk compared to whites, respectively. (7)

Racial disparities relevant to lung cancer exist across the disease continuum and are observed in relation to incidence, mortality, smoking prevalence and risk, screening rates, age and stage at diagnosis, imaging, genetic testing, treatment (surgical and pharmacological), and participation in research. (8) A biologic basis exists for some portion of racial differences in lung cancer incidence and outcomes, e.g., variations in tumor genetic profiles and apparent differential impact of smoking on risk by race. (8) Yet using race as the sole proxy for risk factors undermines evaluation of the fundamental causes, both medical and non-medical, of risk and health outcomes, thereby impeding both health equity and scientific progress. The American Medical Association's (AMA) 2020 policies recognizing race as a social rather than biological construct reflect this principle. (9)

The racial imbalance of cancer research and biomarker testing, dominated by populations of European origin, further compounds the consequences of using race as a proxy for other risk factors. (8, 10) A recent review of genomic research studies indicated underrepresentation of populations of non-European origin, hindering evaluation of gene-disease associations in these populations. (11)

Factors of Health Disparities in Lung Cancer and NSCLC

While health disparities are well documented, the fundamental cause(s) prove difficult to isolate and mitigate due to the interconnected, multi-faceted aspects of health equity. For lung cancer, disparities in outcomes are often broadly categorized as attributed to tumor and patient (biologic) characteristics (e.g., genetic markers, BMI, etc.) versus disease management and treatment. Evidence related to tumor and patient characteristics that may impact response to ICIs in patients with advanced NSCLC were summarized in the June 2022 materials. This addendum therefore focuses on non-medical factors that impact disease management and treatment of patients with NSCLC, and thus influence equitable development and use of predictive models of ICI response.

Disparities in disease management and treatment throughout the disease continuum based on race or socioeconomic factors have been established in NSCLC generally. (6, 8) For example, lower rates of guideline-recommended low-dose computed tomography screening and follow-up are associated with non-white race, public insurance, and rural residence. (12) In one study, eligible black individuals were 54% less likely to report screening in the prior year than eligible white individuals. (12) Additionally, while screening guidelines are established for high-risk adults over 50 years, late-stage diagnosis is significantly more likely in younger individuals, and black individuals are more likely to be diagnosed at a younger age with higher stage disease. (8, 12, 13) This leads to significant lung cancer health disparities for black individuals. (12) Furthermore, black and Hispanic/Latinx individuals are less likely to receive guideline-recommended imaging at diagnosis and standard of care treatment (8), and surgical intervention is less likely or delayed among black patients. (8, 14)

Researchers with the Accountability for Cancer Care through Undoing Racism and Equity (ACCURE) pragmatic trial demonstrated that a systems-based intervention can reduce racial disparities in cancer care. The ACCURE trial employed an antiracism intervention comprised of (1) real-time warning system to identify unmet care milestones, (2) race-specific feedback on lung cancer treatment rates to providers, and (3) nurse navigators for patients. In an analysis of time to surgery after diagnosis of stage I or II NSCLC, the ACCURE intervention improved surgery rates for all patients and reduced the racial differential. The percentage patients receiving surgery within 8 weeks was as follows: **intervention** 87.1% black patients, 85.4% white patients, **concurrent controls** 64.9% black patients, 73,2% white patients, and **retrospective controls** 58.7% black patients, 75.0% white patients. (14)

Research examining disparities with respect to newer therapies, including ICIs, is still emerging. The sections below summarize factors related to disparities in genetic testing and targeted therapy and disparities related to receipt of immunotherapy-type compounds.

Disparities in Genetic Testing and Targeted Therapy

While not specific to ICIs (and e.g., PD-L1 testing), a recent review of factors associated with genetic testing and receipt of targeted therapy in patients with NSCLC (15) provides an overview

of the disparities as they relate to precision medicine in this population. Table 1 summarizes the findings of Curtin et al., which show consistent disparities in genetic testing rates and receipt of targeted therapy among patients of lower socioeconomic status, who have public health insurance, are Black, and live in rural areas. (15)

Of note regarding Curtin et al.'s findings on race, many studies show increased prevalence of oncogenic drivers in Asian populations, particularly epidermal growth factor receptor (EGFR) mutations (16, 17), which likely contributes to higher testing and targeted treatment rates observed in this population. This also highlights the importance of increasing racial diversity in biomarker testing to identify factors that influence disease and treatment response.

Additionally, Table 1 includes other characteristics examined by Curtin et al. (age, sex, smoking status, comorbidity status) as they can relate to SDOH. However, the studies were not able to differentiate SDOH from a medical factor, e.g., patient unable to tolerate biopsy due to age or advanced disease, and therefore should be viewed more as potential factors to consider.

Table 1. Summary of Findings by Curtin et al. Factors associated with disparities in genomic testing and receipt of targeted therapy in NSCLC patients. (15)

Testing	Targeted Therapy
Income (and insurance & geography as proxies)	
Lower testing rates were associated with lower income as assessed by Medicaid, poverty quintile, or eligibility/receipt prescription drug subsidy. • E.g., testing rate for the lowest poverty quintile was 10% lower than that of the highest poverty quintile.	Receipt of targeted therapy was less likely for patients residing in lower-income areas. Decreasing neighborhood SES was associated with decreasing likelihood of targeted therapy.
Lower testing rates associated with public insurance • Patients with public insurance (Medicare, Medicaid, or dual Medicare/Medicaid) were less likely to get tested than patients with commercial insurance. • Patients with dual Medicare/Medicaid were less likely to get tested than patients with Medicare alone.	Patients with public insurance (Medicare or Medicaid) less likely to receive targeted therapy than those with private insurance.
Race	
Testing rates vary by race, with most studies reporting highest testing rates in Asian patients and lowest in Black patients. • E.g., Kehl et al. reported testing rates of 14.1% Black, 26.2% White, 32.8% Asian. (18)	Receipt of targeted therapy varies by race, with most studied reporting higher rates in Asian patients.
Access (geography)	
Higher testing rates were associated with residence in urban or metropolitan areas in several studies.	Higher rates of targeted therapy were associated with residence in urban or metropolitan areas

Testing	Targeted Therapy
Higher testing rates observed in proximity to NCI testing center.	Higher targeted therapy rates observed in proximity to NCI testing center.
Regional differences, e.g., lower testing rates in non-Western states reflect concentration of urban areas in West Coast.	
Other characteristics (Age, sex, smoking status, comorbidity status)	
Lower testing rates were associated with younger age, male sex, current smoker, and higher comorbidity scores.	Lower targeted therapy rates were associated with older age, male sex, current smoker, and higher comorbidity scores.

Disparities in Immunotherapy Treatment

A 2019 study of the National Cancer Database, which covers ~70% of the US population, identified racial and socioeconomic inequalities in administration of immunotherapy. Racial disparities persisted in analyses stratified by insurance type. (19)

This study identified 504,447 patients newly diagnosed with metastatic NSCLC from 2004-2015 and analyzed factors associated with receipt of immunotherapy-type compounds (including monoclonal antibodies, tumor vaccines, and viral/cellular therapies). (19) While many medical factors (age, comorbidity score, cancer stage and histology, receipt of chemotherapy or radiation) were associated with immunotherapy administration, multivariate analysis also yielded significant associations with race and socioeconomic factors. Patients were significantly less likely to receive immunotherapy if they were African American, had Medicaid or no insurance, lived in low-education areas, or lived within 20 miles of a treating facility. There were also regional differences. Compared to the Northeast region on the US, immunotherapy was more likely in the South Atlantic, South, and Intermountain West, and less likely in the Pacific. (19)

Racial disparities persisted in subgroup analyses stratified by insurance status, with African Americans significantly less likely to receive immunotherapy than Caucasians in all three insurance types (Private, Medicare, Medicaid). Among private and Medicare insured, Asian patients were more likely to receive immunotherapy, but this association was not statistically significant in the Medicare analysis. Statistically significant differences by race were not observed among the uninsured. (19)

Clinical Care Setting

While the studies described above evaluated geographical factors (e.g., region, urban vs. rural, proximity to NCI testing center) which might reflect clinical care setting, they did not specifically evaluate type of clinical care setting. Clinical care setting is an important consideration as it is often cited that 85% of cancer patients in the United States are treated in community-based practices where there is less awareness of clinical trials and cutting-edge testing and treatment. (20) In a recent study in the Flatiron Health Database, 91.6% of the 14,768 patients with advanced NSCLC received care in community settings. (10) In addition to finding racial disparities in genomic testing and clinical trial participation, the authors observed significant associations with practice size. Patients treated in low or medium sized clinical practices were significantly less likely to have genomic testing and significantly less likely to participate in a clinical trial than patients treated in a large sized clinical practice. (10)

Implications for Case Study: Mitigating Data-Related Bias in Predictive Models

Availability of large-scale datasets and advances in machine learning and artificial intelligence (AI) have led to a rise in health care algorithms. While this trend has led to many successes in health care, algorithms can not only reflect bias, but also reinforce biases through both clinical and algorithmic feedback loops.

Bracic et al. applied "exclusion cycles," a concept which originated in social interactions, to describe a framework within which medical practice and AI can create interacting exclusion cycles that reinforce discrimination of marginalized groups and disparities in health care. (21) Exclusion cycles are self-reinforcing cycles comprised of 4 steps. In a *clinical exclusion cycle*, biases against and differential treatment of a particular group are reinforced through misattribution of patient response strategies. In *AI exclusion cycles*, methods to develop and deploy health care algorithms can also act as a self-reinforcing exclusion cycle. Because the clinical and AI exclusion cycles interact, the use of AI can both reflect and reinforce system biases. (Figure 3)

Medical practice and AI create overlapping exclusion cycles

Around a generalized structure of the four-step cycle, we depict two interacting exclusion cycles: clinical encounters (blue) and artificial intelligence (AI) products that result from, and influence, data surrounding those clinical encounters (orange). Each cycle self-perpetuates, but the cycles also interact at various points.

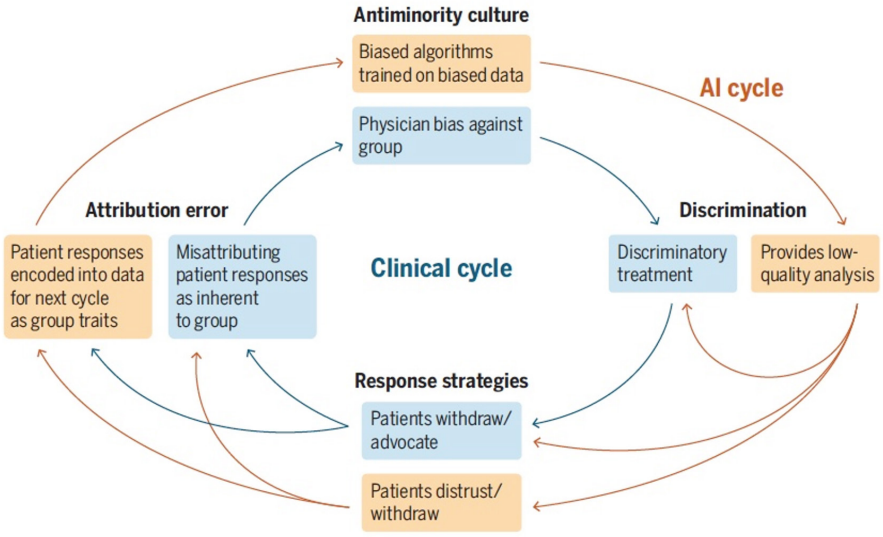

Figure 3. Exclusion cycles illustration from Bracic A, Callier SL, Price WN. Exclusion cycles: Reinforcing disparities in medicine. Science. 2022;377(6611):1158-60.

Bracic et al. illustrate the self-reinforcing concepts of exclusion cycles and interaction between *clinical exclusion cycles* and *AI exclusion cycles* using the perception and treatment of pain in Black patients as well as minoritized patient participation in clinical research as examples. (Table 2) While the examples are based on race, exclusion cycles can occur in groups based on other factors, e.g., gender identity, education, disability, as well as a combination of multiple factors.

Table 2. Exclusion Cycles in Medical Practice and AI from Bracic et al. (21)

Exclusion Step	Clinical Encounter	Clinical Research	AI Cycle
Antiminority culture Bias against group	Perception that Black patients feel less pain	Perception that minoritized patients are mistrustful of research and less interested in research participation	Algorithm trained on biased data. (Reflects biased system as well as underrepresentation in research data.)
Discrimination Discriminatory treatment	Physicians prescribe inadequate pain medication to Black patients	Less effort to recruit minoritized patients, use of convenient (but biased) samples	Provides low-quality health care recommendations *(feeds into clinical cycle)* and low-quality analyses *(feeds into AI cycle)* for underrepresented patients.
Response strategies Patients withdraw (or advocate)	In future encounters Black patients withdraw from relationship or self-advocate	Minoritized patients reluctant to participate due to lessened engagement.	AI is too new to observe response strategies, but underrepresentation may result in reluctance of minoritized patients to participate in research *(clinical cycle)* or to trust algorithm recommendations *(AI cycle)*
Attribution error Response behavior misattributed as inherent quality of group rather than response to discriminatory treatment.	Withdrawal or self-advocacy erroneously interpreted as Black patients being distrustful or non-compliant rather than response to inadequate pain medication.	Reluctance of minoritized patients to participate in research erroneously interpreted as inherent to group rather than result of lessened engagement.	Potential to attribute poor response or outcome to group status rather than system biases reflected in algorithm.
Feedback Attribution error feeds into next cycle with stronger antiminority culture.	Perception that Black patients are distrustful or non-compliant strengthens bias against groups.	Misattribution strengthens bias that minoritized patients mistrust/don't engage in research.	Potential for poor response/outcome to reinforce bias against group *(clinical cycle)* and encoded into data *(AI cycle)*

Challenges and Opportunities

Given the racial, socioeconomic, and geographic disparities observed in clinical research and disease management and treatment, there is a risk of exclusionary cycles in a predictive model of ICI response in patients with NSCLC perpetuating health disparities. Additionally, there are several

challenges, including, among others, data quality and availability as well as the complex nature of health disparities.

Identifying exclusion cycles is an important first step to examine methods with which to break the self-reinforcing cycle and reduce disparities. The ACCURE systems-based antiracism intervention (14) described above is an example of use of an intervention to break a *clinical exclusion cycle*.

Bracic et al. note that the impact of *AI exclusion cycles* is particularly concerning due to how they can amplify system biases under the guise of "algorithmic objectivity." (21) However, recognition of exclusion cycles helps identify how to address algorithmic bias, e.g., knowledge of biases in existing data, improving representation, identifying discriminatory outcomes before biases are encoded (i.e., "breaking the exclusion cycle"). (21)

For this methods innovation case study, we will explore ways in which to mitigate risk of bias through the front-end selection of data sources.

The development of a new equation for estimated glomerular filtration rate (eGFR) in chronic kidney disease (CDK) by Inker et al. is an example of mitigating algorithmic bias with this approach. (22) Current equations estimate eGFR using a filtration marker (e.g., serum creatinine or cystatin C) along with other factors such as race to account for previously observed racial variations in average serum creatinine concentrations. However, this approach has come under scrutiny with rising awareness for the potential of algorithmic bias and perpetuation of health disparities. Inker et al. developed new eGFR equations using data sets with greater racial diversity and explored inclusion of additional laboratory values. They found that an equation that used both serum creatinine or cystatin C without race was more accurate than the current single marker plus race equations and had less differential bias between race groups. (22)

A recent article by Cabreros et al. describes alternative methodologic approaches and opportunities for equitable health care algorithms with respect to race and ethnicity specifically, that could further inform this case study. While race and ethnicity data are often unavailable, incomplete, or incorrect, Cabreros et al. argue that explicitly acknowledging race and ethnicity in the development and use of health care algorithms is a better approach to algorithmic bias than attempting "race-blind" algorithms. They describe methodologic approaches that can be employed when race and ethnicity data is available, such as modifying upstream data inputs or downstream predictions to enforce a specific equity requirement. (23) When race and ethnicity data is not available, Cabreros et al. propose imputing race and ethnicity through validated methods such as the Medicare Bayesian Improved Surname Geocoding (MBISG) 2.0 so that identification of algorithmic bias and use of potential corrective measures is possible. They propose two applications of how imputed race and ethnicity could be used to mitigate algorithmic bias: 1) equitable disease screening algorithms using machine learning and 2) equitable pay-for-performance incentives. (23)

As with the multi-factorial aspects of tumor immunobiology and ICI response described in the June 2022 case materials, health and health disparities are driven by complex, interconnected, and diverse factors. Because of this, we see an opportunity for methods innovation through the exploration of a federated (machine) learning model that combines evidence from diverse data sources (socioeconomic, biologic, clinical, insurance claims, patient-generated, wearables, etc.). Whereas current approaches to mitigating the risk of bias in predictive modeling focus on assessing the probability of risk of models that have been/are being developed (24), we propose a

complementary approach focused on the front-end selection of data sources for developing the models. Specifically, selection would be guided by a structured assessment of sub-populations represented in each data set. Where gaps are illuminated, additional targeted data sets that feature the under-represented sub-populations would be identified to include in the development of the predictive models. Potential associated methodologic challenges (e.g., is it feasible to integrate multiple predictive models developed from different data sets) are now being explored by the LEAPS Methods Innovation Team.

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Appendix 1: Payment Innovation Framework

Next Generation Payment Innovation Roundtable

Payment Innovation Framework

For discussion only

September 21, 2022

GOAL

To catalyze next generation payment innovation to enable sustained patient access to transformative therapies

The landscape for market access continues to evolve as pharmaceutical companies launch novel products in an environment where payers are striving to manage treatment costs and affordability. NEWDIGS is focused on payment innovations that are independent of price setting, and that address multi-stakeholder needs through creation of sustainable payment systems that ensure patient access.

Need for payment innovation: Challenges to address

Appropriate, timely patient access can be inhibited by stakeholder incentive misalignment as each pursues their legitimate goals within their constraints. Payment innovation could both reduce that misalignment and improve goal attainment across stakeholders. To do so, payment innovations must address:

- **Patient benefit uncertainty:** Therapeutic performance uncertainty can cause mismatches between patient benefits received and payments made.
- **Actuarial risk:** Unpredictability of patients likely to be treated and surges can create financial strain
- **Operational efficiency:** Implementation mechanics can consume payment innovation benefits
- **Evidence creation:** Collection of post approval real-world data to reduce uncertainties and ensure patients will benefit, especially when labeled indications are broader than participants evaluated in the clinical trials.

Scope

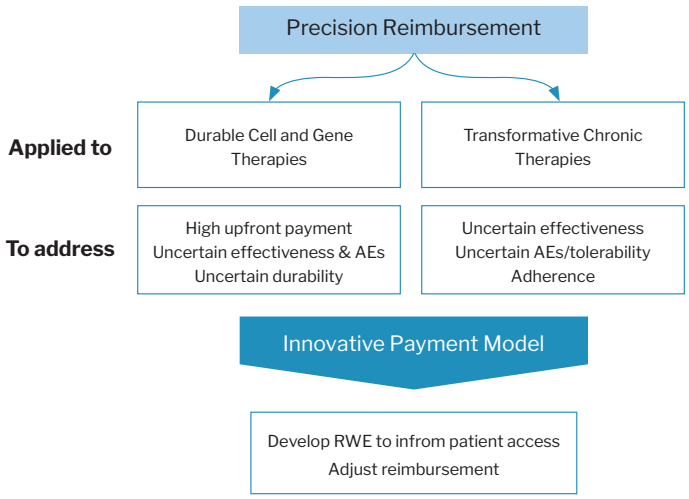
Payment Innovation occurs independent of the determination of the initial value/price of the therapeutic benefit. It may be implemented among a subset of stakeholders (such as payers and developers) but the impacts must be considered for all in the design: patients; providers; pharmacies and other channel participants; payers; and therapeutic developers.

Payment Innovation includes therapy-associated financial flows and related non-financial elements such as utilization management, coverage, reimbursement, benefit design and associated legal/regulatory structures.

Principles for payment innovation

1. Align incentives across stakeholders
2. Prioritize patient outcomes while simultaneously satisfying other stakeholder needs
3. Connect access and reimbursement to patient benefits received
4. Progressively reduce stakeholder-relevant uncertainties by leveraging payment-generated data/evidence.
5. Refine access and reimbursement over time as uncertainty diminishes through maturing evidence

Payment Innovation Application



6. Smooth financial volatility through financial instruments/ payment models
7. Achieve operational feasibility in a patient meaningful manner
8. Ensure payment innovations do not disadvantage patients or increase disparities of care

System changes to catalyze payment innovation
Payment innovation requires new capabilities and evolving regulations, including:

- Develop patient-centric, practical performance metrics through patient-driven, stakeholder inclusive processes for therapeutic areas.
- Streamline administration and measurement of patient outcomes across multiple contracts and therapeutic areas.
- Address patient mobility challenges with targeted data sharing.
- Evolve Federal policy regarding the Medicaid Drug Rebate Program and safe harbors in the Anti-Trust and Stark Law statutes.
- Refine health technology assessment methods to include payment innovation uncertainty reduction, both for initial evaluations and over time.
- Establish 'fit for purpose' RWE standards for reimbursement and clinical regimen uses.

Durable therapies and high investment chronic therapies present an opportunity for payment innovation
Situations that most need payment innovation meet these criteria:

- High uncertainty of potential patient benefit
- Uncertainty regarding treated patient population
- Large financial impact per patient or for the population

Durable cell and gene therapies with their high upfront costs and often uncertain long-term benefits are already experimenting with payment innovations such as multi-year performance-based payments, warranties, and subscriptions. The innovations are coming from multiple stakeholders including payers, stop loss and reinsurers, new financial start-ups in addition to the therapy developers.

High-investment chronic therapies for rare conditions and oncology across multiple therapeutic modalities are an emerging area for payment innovation as well. Mass population therapeutics may also benefit from next generation payment innovations.

Demonstrating payment innovation success for some therapies in these areas could then scale to broader adoption.

Actions to catalyze change
The following immediate collaborative activities would catalyze payment innovation implementation:

1. Define patient-centric health outcomes metric selection processes for key therapeutic areas
2. Improve outcomes data collection. Begin by exploring feasibility of HHS-wide effort to facilitate patient outcomes tracking
3. Develop guiding principles for multi-stakeholder engagement in innovative payment arrangements.
4. Continue to refine the Medicaid Drug Rebate Program to enable payment innovations such as subscription models, and efficient implementation

About NEWDIGS
The NEW Drug Development ParadIGmS (NEWDIGS) Initiative is an international "think and do tank" dedicated to delivering more value faster to patients, in ways that work for all stakeholders. NEWDIGS designs, evaluates and initiates advancements 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. For more information, visit http://newdigs.tuftsmedicalcenter.org.

GLOSSARY
Payment innovation: Contracting arrangements other than straight discount or volume-based rebates, such as warranties, pooling approaches, subscription models.

Durable therapies: Cell and gene therapies providing an expected benefit duration of at least 18 months from a single administration. Examples include CAR-T cell therapies and AAV-based therapies such as Zolgensma, but not vaccines.

Chronic therapies: Therapies administered on a recurring basis over time to treat an on-going condition. Includes small molecule, biologic, cell, and gene therapies for conditions ranging from ultra-orphan to large population, including oncology.

Appendix 2: Team Remits

Immuno-Oncology (IO) Team

Goal

Produce Landscape Analysis for the first case study for the Integrated Pilot Concept which focuses on improving our ability to predict which patients with metastatic non-small cell lung cancer (NSCLC) will respond to immune checkpoint inhibitors (ICIs). The Landscape Analysis will help to inform key strategy and design choices made by other teams involved in the Integrated Pilot Concept.

2022 Target Deliverables

1. **Develop the Landscape Analysis for the initial Case Study** (ICIs in NSCLC). The Landscape Analysis will be developed incrementally with each versions prepared to inform targeted discussions at specific Design Labs.
   a. V1.0 provides the broad landscape analysis for ICIs in NSCLC (June Design Lab)
   b. V2.0 provides background relevant to health disparities (November Design Lab)
2. **Building on #1, create a generalizable framework for a Landscape Analysis** for the LEAPS System Design Module for use with any future Case Study that we may evaluate in LEAPS.
3. **Provide case-specific expertise to the other LEAPS teams.** Where feasible and when needed, provide additional case-specific input and/or research support to other teams.
4. **Plan for extending the initial Landscape Analysis** to other related target areas (e.g., ICIs in earlier stages of NSCLC and other tumor types) if these are identified by the LEAPS Community as priorities for scaling the Integrated Pilot Concept.

Status

- The IO and Core Protocol Teams elected to meet jointly between the June and November Design Labs in 2022. These teams may resume meeting independently following the November Design Lab. Priorities for this team moving forward will be defined following the November 2022 Design Lab.

Team

- Associate Director, Center for Integrated Diagnostics, Massachusetts General Hospital
- Epidemiologist and Science Writer, Independent
- Executive Director, Center for Observational & Real World Evidence, Merck & Co., Inc.
- Global Head of Development, RWE, Sanofi
- Founder & General Manager, Princeton Healthcare Strategies, LLC
- Quality Improvement Medical Director, Kaiser Permanente National Transplant Services
- Vice President, Corporate Strategy, Flatiron Health
- Gigi Hirsch, Executive Director, NEWDIGS

Core Protocol Team

Goal

Building on the concept of Master Protocols for adaptive platforms trials , develop a set of generalizable frameworks/templates that we will for now call "Core Protocols" for real-world evidence (RWE) platforms. We anticipate that Core Protocols will need to be tailored to different "archetypes" of RWE platforms that address different types of distributed evidence production within a learning health system (e.g., hypothesis generation, hypothesis validation, predictive modeling, etc.). This team will begin by designing a Core Protocol for a Predictive Outcomes Platform (POP) that can undergo rapid cycle prototyping and refinement within the LEAPS system design module.

2022-2023 Target Deliverables

1. **June 2023:** V1.0 of the Core Protocol for the initial implementation planning for the Predictive Outcomes Platform (POP) for the first case study focused on immune checkpoint inhibitors for advanced NSCLC will be discussed at the June Design Lab 2023.
2. **November 2023:** Plan for refining the V1.0 Core Protocol as implementation planning advances through the work of other teams, especially the Immuno-Oncology, Methods, and METRICS Teams.
3. **June 2024:** Refining of Core Protocol with insights from initial implementation of the Predictive Outcomes Platform prototype in the first half of 2024.

Status

- The IO and Core Protocol Teams elected to meet jointly between the June and November Design Labs in 2022. These teams may resume meeting independently following the November Design Lab.
- Seeking new members with additional expertise in such areas as distributed research networks, adaptive study designs, observational study designs, epidemiology, informatics, machine learning.

Team

- Executive Director, Global Market Access, Merck & Co., Inc.
- Director, Center for Clinical Trials, Tufts Clinical and Translational Science Institute
- Senior Advisor in Research, Retired
- Director of Data Science, NEWDIGS
- Epidemiologist and Science Writer, Independent
- Gigi Hirsch, Executive Director, NEWDIGS

Precision Reimbursement Team

Goal

Produce Precision Reimbursement Frameworks that integrate across all NEWDIGS activities and provide Precision Reimbursement expertise to specific working teams.

2023 Target Deliverables

1. **Refining a practical Precision Reimbursement framework** by expanding the 2022 Payment Innovation framework beyond value-based arrangements for medicines to include provid-

ers, patient engagement and benefit design, channel participants, and secondary payers. The immediate deliverable could be one or more publications and multiple presentations at key venues. The longer-term goal would be catalyzing broad adoption of Precision Reimbursement payment innovations in practice and enabling policy changes as needed.

2. **Elucidate critical Precision Reimbursement designs via a portfolio of case studies.** Case studies in weight loss, NSCLC, accelerated approval and rare disease pooling have been identified to examine critical issues regarding:
   - Multi-stakeholder incentive alignment
   - Payment innovation in complex treatment settings
   - Reducing uncertainty using value-based arrangements connected to evidence generation
   - Spreading financial burdens sustainably

   These case studies will provide practical implementation insights and new models for sustainable patient access as well as inform the Precision Reimbursement Framework.
3. **Provide Precision Reimbursement expertise to the POP working teams** as opportunities arise. The Methods team and the Core Protocol team both are requesting multi-stakeholder input regarding the 'fit-for-purpose' evidence requirements and Precision Reimbursement decisions that the work of their teams must support.

Team

- CEO, Amaranthus
- Chief Clinical Officer, Real Endpoints, former IBM CMO
- Director Pharmaceutical Transformation, Point32 Health
- Former Humana VP, CMS, AMCP President
- Director, Global Oncology Value-Based Innovation at Takeda
- Former ISPOR President
- Former Principal of Specialty Innovations, MedImpact
- Global Healthcare Innovation, Pfizer
- Global Market Access RWE, Merck
- Director of Precision Medicine, Point32Health
- President HealthCore (Anthem)
- Quality Improvement Medical Director, Kaiser Permanente National Transplant Services
- VP Clinical Innovation Point 32 Health
- VP Policy and Outreach, Family Heart Foundation
- Mark Trusheim, Strategic Director, NEWDIGS

Status (expertise needed)

- Patient benefit design
- Patient reported outcomes (PROs)
- Provider risk sharing agreements
- Drug innovative payment models/Value-Based Purchasing Arrangements
- Real-World trial design/epidemiology

Methods Innovation Team

Goal

The Methods Team focuses on optimizing drug therapy regimens through the use of distributed networks of real-world evidence (RWE) generation partners and the application of machine learning tools.

Initial Focus

Developing a generalizable framework for a Predictive Outcomes Platform where machine learning tools are used to generate predictive models that improve the selection of targeted treatments for patient. The team will take a case-based approach to its design and prototyping, with Case Study #1 focused on improving our ability to predict which patients with metastatic non-small cell lung cancer (NSCLC) will respond to immune checkpoint inhibitors.

Methodologic Challenge

Integration of multiple predictive models from diverse and disparate data sets across the distributed network and demonstrating associated validity. Initial methodologic work is on applying federated machine learning, a promising technique of addressing data silos in healthcare. A summary of the strengths and limitations of machine federated learning will be reported.

Target Deliverables & Timeline

1. The development of a characterization matrix of data (including DARE: Data Assessment and Risk Engineering) and technical skills for consideration in the execution of the federated machine learning network prototype for Case Study #1
   - V1.0: December 2022
2. Discussion of a list of machine learning and statistical methods that can be applied to a series of case studies within LEAPS
   - V1.0: December 2022
3. Implementation of a federated learning network prototype for Case Study #1 (immune-checkpoint inhibitors in advanced NSCLC)
   - V1.0: December 2022
4. Refinement of V1.0 prototype with insights derived from portfolio of follow-on case studies, with goal of enhancing generalizability of the framework/template for future application outside of LEAPS.
   - 2023

Status

- Seeking additional expertise in distributed research networks

Team

- Senior Director, AI for Healthcare & MedTech, IQVIA
- Founder & General Manager, Princeton Healthcare Strategies, LLC
- Chief Medical Officer, Genesis Research
- Director, Digital and Data Sciences, Sanofi
- Director, Center for Clinical Trials, Tufts Clinical and Translational Science Institute
- Statistics team leader (Oncology Biomarker), Sanofi
- Biomarker statistician, Sanofi
- Associate Director for Machine Learning and Advanced Analytics, VA Boston Healthcare System
- Principal Data Scientist, U.S. Department of Veterans Affairs
- Senior Advisor in Statistics, Retired
- Student Researcher, ML & AI, MIT
- Fotios Kokkotos, Director of Data Science, NEWDIGS

Metrics for Evaluation Thresholds & Reimbursement for Incentive Correlation across Stakeholders (METRICS) Team

Goal

Identification of metrics and thresholds for predictive modeling and reimbursement of drug therapy regimens through a defined multi-stakeholder process. Outputs will focus on 3 areas:

1. Identification of condition-specific Clinical Outcomes Measures
2. Identification of systemic Impact Metrics for tracking overall pilots
3. Establishment of a Reproducible Process for development and refinement of pilot metrics and thresholds.

Target Deliverables

1. Identify clinical outcomes and impact metrics to support the LEAPS NSCLC Integrated system design module:
   a) Condition/treatment-specific outcome measures that are acceptable to key stakeholders and are technically feasible for predictive modeling- inputs for:
   - Precision Reimbursement contract design
   - Outcomes tracking
   - Target variables for predictive modeling

   b) Impact measures for tracking overall pilots that reflect the impact of the new integrated system capability (predictive models + payment models) on perceived benefits and risks for each stakeholder. Impact measures may be applicable to multiple pilots and apply at a societal level.
2. Apply the outcomes measures and impact criteria to predictive models by defining thresholds for stakeholder action
3. Codify a process for the development of integrated pilot metrics for use with any case study (pilot) that we may evaluate in LEAPS. This process should include development of thresholds for actionable application

Status

- Established overall metrics team and sub-team
- Drafted a process for metric and threshold development
- Identified potential clinical and outcomes metrics
- Applying process to refine metrics
- For the upcoming design lab
  - Validate proposed metrics with other work streams
  - Finalize metrics
  - Whiteboard thresholds with feedback on multi-stakeholder validation process.

Team

- Chief Medical Officer & Head of Research, Genesis Research
- Associate Director, Center for Integrated Diagnostics, Mass General Hospital
- Director of Pharmaceutical Transformation, Point32 Health
- Lead Clinical Analyst, Point32 Health
- Director of Global Evidence & Outcomes, Takeda
- Director of Global Oncology Value-Based Innovation, Takeda
- Sr. Director of Global Evidence and Outcome Research, Solid Tumor at Takeda Oncology
- Chief Technology Officer, Family Heart Foundation

- Strategic Director, NEWDIGS
- Director of Data Science, NEWDIGS
- Researcher and Science Writer, Independent
- Jane Barlow, Senior Advisor, NEWDIGS