POLYCENTRIC DRUG INNOVATION

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Abstract— *Our drug innovation ecosystem—the set of rules, actors, and institutions that influence the pace and direction of technological innovation in healthcare—is both complex and fragmented. Legal scholarship has begun to explore how incentives beyond patent rights influence the direction of innovation. But this scholarship is still largely focused on how policy levers–grants, patents, regulatory exclusivities and insurance reimbursement schemes–operate within specific institutions. In this Article, we argue that developing coherent drug innovation policies is all but*

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impossible without first understanding the interplay between policy levers and multiple institutional contexts. We set out to fill this gap in the literature by both synthesizing how institutional complexity and fragmentation impact drug development and by drawing on polycentric governance principles emerging from literature on commons management to develop a proposal that manages institutional fragmentation and optimizes drug innovation.

As a drug moves through our innovation ecosystem from conception to marketing, it encounters multiple institutional players with distinct mandates and priorities. These fragmented actors, working largely independently of each other, make policy decisions that, in the aggregate, encourage low-risk, incremental innovation and enable the marketing of only marginally effective or redundant treatments. This is the case despite individual institutional efforts to incentivize investment in risky, high social value innovation. Fragmentation has the undesirable effect of hindering institutional collaboration towards overarching innovation goals, allowing private actors to exploit knowledge and coordination gaps across institutions to maximize private gains–often at the expense of social welfare. Yet fragmentation also has benefits worth preserving, lessening the risk of regulatory capture and providing checks and balances.

Drawing from polycentric governance principles, we develop a new approach for managing institutional fragmentation that harnesses fragmentation's upside while managing its downside. We use a polycentric lens both descriptively and normatively. Descriptively, we identify emerging collaborations in our current drug innovation ecosystem as reflecting islands of beneficial polycentric governance. We describe in depth the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership as a case study illustrating how polycentricity is already at play in a limited way. While

traditional polycentric theory is descriptive, imagining polycentric arrangements as emerging organically, our proposal is also normative, exploiting these emerging collaborations to more intentionally engineer polycentric relationships among drug innovation institutions. Using lessons from ACTIV and other glimmers of polycentricity, we translate our polycentric framework into an actionable proposal: a special collaborative track that harnesses our complex and fragmented drug innovation ecosystem to optimize innovation in high-need drugs.

1. INTRODUCTION

Innovation in health care has significantly changed our world. Diseases that were once death sentences are now prevented by vaccines or managed with novel treatments. More than 300 million people died of smallpox before the advent of the smallpox vaccine.[2] Children diagnosed with type 1 diabetes were once expected to live only one to two years after their diagnosis[3] and patients diagnosed with HIV could expect to live just eight more years.[4] Health care innovation, and drug innovation in particular, has dramatically extended and improved our lives and is a major point of pride for Americans.

For all its virtues, the U.S. drug innovation system is also deeply imperfect and inequitable. Innovators devote the majority of their resources to solving problems that are of both high social value (the improvement of well-being) and high private value (the potential to generate revenue) while chronically underinvesting in treatments for problems that are of high social value but low private value. Research into rare diseases or diseases that afflict mostly poor populations, such as Chagas disease or toxoplasmosis[5], notoriously lags research into diseases that afflict

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[2] *See* Donald Henderson, *The Eradication of Smallpox – An Overview of the Past, Present, and Future*, 29 Vaccine D7 (2011), https://pubmed.ncbi.nlm.nih.gov/22188929/.

[3] Aaron M. Secrest, Raynard E. Washington & Trevor J. Orchard, *Mortality in Type 1 Diabetes* in Catherine C. Cowie et al., Diabetes in America (3d ed. 2018).

[4] *See* Caroline A. Sabin, *Do People with HIV Infection Have a Normal Life Expectancy in the Era of Combination Antiretroviral Therapy?*, 11 BMC Med. 251 (2013), https://doi.org/10.1186/1741-7015-11-251.

[5] Peter J. Hotez, *Neglected Infections of Poverty in the United States of America*, 2 PLoS Negl Trop Dis. e256 (2008).

primarily affluent socioeconomic groups, such as coronary heart disease.[6] The drug innovation system also over-incentivizes innovation that may not have high social value but nonetheless has high private value, such as me-too cancer drugs that modestly extend the lives of those with cancer. Me-too cancer drugs tend to be very expensive and only available to wealthier patients. Those patients end up having longer survival rates, even if the difference is relatively modest, from poorer patients who cannot access these luxury drugs.[7] In general, high drug prices make medicines inaccessible.

These two latter features are all the more pernicious when taken together because they amplify already-entrenched disparities in healthcare outcomes. One of the most pressing systemic consequences of the status quo system is intransigent health inequity. In the United States, life expectancy varies considerably by wealth and geography. In some affluent counties, a person lives on average 20 years longer than in comparable poor counties.[8] Life

[6] Although the binary classification of diseases into "diseases of the poor" and "diseases of the rich" is outdated (a significant proportion of individuals living below the poverty line in the U.S. suffers from chronic health conditions such as coronary heart disease) it is still a relevant distinction. *See* Majid Ezzati et al., *Rethinking the "Diseases of Affluence" Paradigm: Global Patterns of Nutritional Risks in Relation to Economic Development,* 2 PLoS Med. e133 (2005). Research spending is driven by whether a particular disease afflicts a sufficiently large number of individuals who are wealthy enough to pay for treatment.

[7] Medicaid covers many drugs in this category, but in states like Texas and Florida, many poor people do not qualify for Medicaid. Deductibles and out-of-pocket costs mean that poorer privately insured patients may be unable to afford these treatments.

[8] *See* Wendy Netter Epstein, *The Health Equity Mandate*, 9 J.L. & Biosciences 1 (2022) (citing Laura Dwyer-Lindgren et al.,

expectancy also varies starkly by skin color and education. This inequality can be traced directly back to both inadequate healthcare investments in diseases that afflict largely poor populations, and to access to the products produced for wealthier populations.[9] Combatting health inequity has become an urgent societal problem, leading the NIH to devote an entire institute (the National Institute on Minority Health and Health Disparities) to the analysis of healthcare outcomes in underrepresented populations.[10]

Scholars working in the innovation law and policy space have long recognized that current investment in drug innovation is misaligned with social welfare goals. For example, Peter Drahos has lamented what he calls the lack of "socially responsive" science and technology. [11] Peter Lee has similarly emphasized the "inability of science and technology to meet prevailing needs."[12] And a group of innovation scholars has recently published a scathing critique of the patent regime as harming overall patient welfare in the healthcare space. [13]

Inequalities in Life Expectancy among US Counties 1980 to 2014: Temporal Trends and Key Drivers, 177 JAMA INTERN. MED. 1003, 1005–06 (2017)).

[9] *See* Ruqaiijah Yearby, Brietta Clark & José F. Figueroa, *Structural Racism in Historical and Modern US Health Care Policy*, 41 Health Affs. 187, 188-92 (2022).

[10] The National Institute on Minority Health and Health Disparities (NIMHD), *About NIMHD*, (last updated Jan. 4, 2024), https://www.nimhd.nih.gov/about/

[11] Peter Drahos, *Responsive Science*, 14 Ann. Rev. L. & Soc Sci 327, 328 (2020).

[12] Peter Lee, *Enhancing the Broader Social Impacts of Innovation,* 104 B.U. L. Rev. (forthcoming 2024). *See also* Peter Lee, *Patent Law's Externality Asymmetry*; Peter Lee, *Toward a Distributive Commons in Patent Law*, Wisc. L. Rev. 917 (2009).

[13] Robin C. Feldman, David A. Hyman, W. Nicholson Price II

Despite copious writing about this misalignment, however, solutions have proven elusive. Part of the problem is that scholars have failed to identify theoretical tools to accurately understand and describe the root causes of this misalignment.

In this Article, we identify institutional fragmentation and complexity as two key, yet largely ignored, drivers of this misalignment between social welfare and investment in innovation. We then introduce a novel theoretical lens–polycentric governance–to describe the complex interactions among the institutions that make up our drug innovation ecosystem. Polycentric regimes have two features in common: (1) the existence of multiple, overlapping decision-making centers that enjoy some degree of autonomy and (2) these centers, though autonomous, choose to act in ways that take into account others (in the system) through processes of cooperation, competition, conflict, and conflict

& Mark J. Ratain, *Negative innovation: when patents are bad for patients*, 39 Nat. Biotech. 914 (2021). *See also* Mark A. Lemley, Ex Ante Versus Ex Post Justifications for Intellectual Property, 71 U. CHI. L. REV. 129, 129 (2004); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability,* 87 Tex. L. Rev. 503, 506 (2009); W. Nicholson Price II, *Regulating Secrecy*, 91 Wash. L. Rev. 1769, 1775 (2016) ("from a social welfare standpoint, innovators will tend to underinvest in innovation"); Alan Devlin & Michael Jacobs, *Anticompetitive Innovation and the Quality of Invention*, 27 Berkeley Tech. L.J. 1, 42 (2012) (describing the allure to pharmaceutical companies of product hopping); Bernard H. Munos, William W. Chin, *How to Revive Breakthrough Innovation in the Pharmaceutical Industry*, 89 Sci. Transl. Med. (2011), DOI:10.1126/scitranslmed.3002273 (arguing that "that more breakthrough therapeutics will reach patients only if the industry ceases to pursue 'safe' incremental innovation, reengages in high-risk discovery research, and adopts collaborative innovation models that allow sharing of knowledge and costs among collaborators").

resolution. Drawing from these polycentric governance principles, we develop a new approach for managing institutional fragmentation that harnesses fragmentation's upsides while managing its downsides.

The complexity and fragmentation of the drug innovation ecosystem—the set of rules, actors, and institutions that influence the pace and direction of technological innovation[14]—makes designing policy interventions to maximize social welfare particularly challenging. Institutional fragmentation presents two big-picture problems: first, it prevents efficient information flow across institutional silos;[15] second, it hampers coordination around shared institutional objectives, such as promoting high social value breakthrough innovation. In turn, information siloing and disjointed policy initiatives set the stage for opportunism–allowing private parties to take advantage of information gaps for their own private benefit, often to the detriment of social welfare.[16]

But fragmentation also has benefits. The checks and balances it provides mitigate the potential dangers of agency capture. And while fragmentation has its own efficiency problems caused by siloed information and lack of coordination, it also has a key advantage: its

[14] *E.g.*, Rachel E. Sachs, *Integrating Health Innovation Policy*, 34 Harv. J.L. & Tech. 57, 58 (2020).

[15] *E.g.*, Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 347 (2007); *see also* Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307 (2018); Daniel Hemel and Lisa Larrimore Ouellette, *Valuing Medical Innovation*, STANFORD L. REV. (forthcoming 2023); Qiwei Claire Xue & Lisa Larrimore Ouellette, *Innovation Policy and the Market for Vaccines*, 7 J.L. & BIOSCIENCES 1 (2020).

[16] *See generally* Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 Yale L.J. 1900 (2013); Alberto Galasso & Mark Schankerman, *Patent Thickets, Courts, and the Market for Innovation*, 41 RAND J. ECON. 472 (2010).

nimbleness in allowing actors to creatively and flexibly experiment with novel solutions. In policy areas such as drug development, where technology often moves faster than law can adapt to new discoveries, it is important to maintain this benefit of fragmentation.

Drug innovation is also a complex system, where institutional players interact with each other in intricate ways. Take, for instance, the relationship between the FDA and the Centers for Medicare and Medicaid Services (CMS): in some circumstances (but not all) CMS is mandated by statute to reimburse FDA-approved drugs, complicating what many see as insurance's important role in negotiating drug prices.[17] Therefore, policy interventions must account for how changes in one domain may simultaneously influence other institutional players within the system. Put differently, designing effective policy interventions in health technologies requires an understanding of each individual institutional player and how all players fit together as a synergistic whole.

A few analyses have tackled the problems of fragmentation and complexity. These analyses, however, tend to see fragmentation as the enemy, advancing solutions that emphasize centralization through the creation of new independent agencies.[18]

Other analyses tend to be reductionist: focusing on individual legal doctrines as applied by individual policy institutions[19] or on how disembodied policy

[17] *See infra* Part I. *See also* Sachs, *supra* note 15.

[18] *See supra* Part II(A).

[19] *See, e.g.,* William Fisher & Talha Syed, *Global Justice in Healthcare: Developing Drugs for the Developing World*, 40 U.C. Davis L. Rev. 581 (2007); Amy Kapczynski, *The Cost of Price: Why and How to Get Beyond Intellectual Property Internalism*, 59 UCLA L. Rev. (2012); Madhavi Sunder, From Goods to a Good Life: Intellectual Property and Global Justice (2012).

levers–grants, patents, regulatory exclusivities and insurance reimbursement schemes–interact with each other outside their institutional contexts.[20] To be clear, ours is not a paper against such reductionism. It is useful to zero in on the nuances of specific legal doctrines. But such an approach, standing alone, is insufficient to design effective solutions to our drug innovation crisis.[21]

We make several crucial contributions to the

[20] *See, e.g.*, Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Policy Pluralism*, 128 YALE L.J. 544 (2019); Andres Sawicki, *Risky IP*, 48 Loy. U. Chi. L. Rev. 81 (2016); Benjamin Roin, *Intellectual Property versus Prizes: Reframing the Debate*, 81 U. Chi. L. Rev. 999 (2014).

[21] Scholarship that pays attention to the institutional context focuses on isolated institutions or institutional dyads. *E.g.*, Nicholson Price, *Grants*, BERKELEY TECH. L.J. (studying the National Institutes of Health); Eisenberg, *supra* note 15 (focusing on the FDA); Laura Pedraza-Fariña, *Understanding the Federal Circuit: An Expert Community Approach*, BERKELEY TECH. L. J. (2015); Paul Gugliuzza, *Rethinking Federal Circuit Jurisdiction*, 100 GEORGETOWN L. J., 1437 (2012) (focusing on the Federal Circuit); Rochelle Cooper Dreyfuss, *Giving the Federal Circuit a Run for Its Money: Challenging Patents in the PTAB*, 91 NOTRE DAME L. REV. (2015); Michael D. Frakes & Melissa F. Wasserman, *Is the Time Allocated to Review Patent Applications Including Examiners to Grant Invalid Patents? Evidence from Micro-Level Application Data*, 99 REV. ECON. STAT. 550 (2017) (focusing on the PTO); Rachel Sachs, *Prizing Insurance: Prescription Drug Insurance as Innovation Incentive*, 30 HARV. J. L. & TECH. 153 (2016) (focusing on CMS as an innovation institution). *But see* Rachel E. Sachs, *Administering Health Innovation*, 39 Cardozo L. Rev. 1991 (2018) (acknowledging that much scholarly attention "has so far focused on the capacities of single agencies, acting alone" but noting the "the potential for collaboration across agencies"); Sean Tu, *FDA Reexamination: Increased Communication Between the FDA and USPTO to Improve Patent Quality*, 60 Hous. L. Rev. 403, 407 (2022); David Simon, *Off Label Speech*, EMORY L. J. (forthcoming 2023).

literature. First, we re-frame the problem of inefficient investment in innovation as a problem rooted in institutional fragmentation and complexity. Second, we show how individual policy levers work within the institutional contexts of the NIH, PTO, FDA, CMS, and private insurance. Third, armed with such a reframing, we argue that understanding drug innovation institutions as players in a polycentric system offers a more accurate description of current institutional interactions. Descriptively, we show how polycentricity can help explain the emergence of what we term "islands of collaboration" in drug development–a set of nascent bottom-up collaborations nestled within an otherwise fragmented system. Finally, turning from the descriptive to the normative, we rely on polycentric principles to design a novel collaborative institutional arrangement to foster innovation in high-need, high social benefit drugs.

Our normative proposal seeks to manage, rather than eliminate, institutional fragmentation. By maintaining institutional autonomy, a polycentric approach mitigates the danger of regulatory capture that plagues centralized regimes. By creating networks of information sharing, a polycentric regime lessens opportunities for private parties to take advantage of information gaps between institutions. Polycentric coordination also preserves the bottom-up creativity of autonomous institutions while simultaneously creating communication channels across institutions to minimize unintended consequences and scale creative ideas into systemic solutions.

We begin in Part I by reviewing the traditional approach to drug innovation that foregrounds understanding how to optimize policy levers such as grants, patents, FDA regulatory exclusivities, and

insurance reimbursement schemes. We then introduce emerging scholarship that shifts its focus to how these policy levers operate within individual institutional contexts. We close Part I with a brief description of the key institutions that participate in drug development: NIH, PTO, FDA, private and public insurance.

Parts II and III represent the core of our theoretical contribution. In Part II, we illustrate in detail how fragmented institutional actors, working largely independently of each other to fulfill their individual mandates, have made policy decisions that, in the aggregate, encourage only incremental innovation while insufficient resources are devoted to high social value breakthrough innovations.

We introduce polycentric governance theory in Part III and explain its key organizing principles. We describe how polycentric design principles have been successfully deployed in other domains outside the drug innovation context where semi-autonomous decision makers have successfully pursued a common goal. We also describe existing collaborations that display emerging polycentric features, paying particular attention to the emergence of novel multi-institutional partnerships in the wake of the Covid-19 pandemic. We explore in depth the operation of the "Accelerating COVID-19 Therapeutic Interventions and Vaccines" (ACTIV) consortium.

Part IV concludes with the description of a novel remedy to the failures of the current ecosystem to promote socially desirable innovation: a special collaborative track for high-need drugs. Bringing insights from polycentric governance theory, and using the ACTIV consortium as a blueprint, we argue for a collaborative innovation infrastructure that brings together the NIH, FDA, PTO and CMS in cases

of drugs with potentially high social benefits but low or uncertain private benefits. This collaborative track contemplates an expanded role for the NIH in drug development, going beyond basic research funding to provide more applied grant funding, infrastructure to bring together multiple institutional players, and independent laboratories and biostatisticians to create more transparent and accessible clinical data repositories for high-needs drugs.

I. CURRENT APPROACHES TO DRUG INNOVATION

A. Policy Levers in Innovation

One familiar way to conceptualize innovation incentives is to divide them into two categories of "policy levers": technology-push and demand-pull.[22] The "push" and "pull" concepts give rise to two ways to incentivize innovation. First, under a "push" model, governments can directly incentivize the creation of new information by reducing the private cost of producing such information, for instance, through grants and investments in training and research infrastructure.[23] Second, under a demand "pull" model, governments can increase the payoffs of successful innovation by providing intellectual property protection, granting market exclusivities or guaranteeing insurance reimbursement to successful innovations.[24]

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[22] *See* Christopher Buccafusco, *Disability and Design*, 95 N.Y.U. L. Rev. 952, 961 (2020) (giving a primer on innovation policy levers).

[23] *E.g.*, Nicholson Price, *Grants*, Berkeley Tech. L.J. (2015); Brett Frischmann, *Infrastructure: The Social Value of Shared Resources* (2012); Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Policy Pluralism*, 128 Yale L.J. 544 (2019).

[24] *E.g.*., Benoit Godin & Joseph P. Lane, *Pushes and Pulls: Hi(S)tory of the Demand Pull Model of Innovation*, 38 Sci., Tech., &

In this part, we canvas the traditional approach, summarizing existing work on two types of push levers (grants and infrastructure) and four types of pull levers (patents, FDA regulatory exclusivities, FDA novel approval pathways, and insurance reimbursement schemes). In the next Part, we introduce a second approach that, rather than focus on disembodied policy levers, foregrounds the institutional environments where drug innovation decisions take place.

1. Push Incentives: Grants and Infrastructure

Push incentives correct the misalignment between private and social value in the production of scientific knowledge—a basic input in drug innovation. In a now landmark paper, Richard Nelson frames the problem of incentivizing basic scientific research as one in which "private-profit opportunities do not adequately reflect social benefit."[25] In other words, basic scientific research will be underincentivized by market signals because it is almost always impossible to recoup the initial upfront investment in basic research by selling a product on the market. Figure 1 illustrates this insight that optimal innovation signals require alignment between social and private value. Basic scientific research falls under the top right quadrant in Figure 1: a high social value innovation that nonetheless will be underincentivized by market signals because of its low private value.

Advances in basic scientific knowledge in the healthcare field, such as knowledge about signal

Hum. Values 621 (2013).

[25] Richard R. Nelson, *The Simple Economics of Basic Scientific Research*, 67 J. Pol. Econ. 297, 298 (1959).

transduction and metabolic pathways, can significantly lower invention costs by, for example, helping drug developers predict which types of molecules will have a therapeutic effect. From this perspective, private and social value appear to be aligned: inventors invest in basic scientific knowledge to lower their invention costs, and society gains both new drugs and new scientific knowledge. But this perspective ignores a crucial characteristic of basic scientific research: its enormous spillover effects (or external economies) and the inability of a single private party to capture these externalities.

Because scientific research generates both unpredictable and wide-ranging societal benefits, it would be best if results of basic research were freely and openly disseminated so that they could reach those unpredictable areas of the economy where they may bear fruit. But a private firm will only want to invest in basic research if it can capture the value of this new knowledge.[26] Other misalignments between social and private value, however, extend beyond basic scientific research. As we describe in our section on patents below, there is no relevant market to foster investment in therapies for diseases in the developing world, despite their large social burden.

Grants represent the paradigmatic push incentive, encouraging high social value innovation

[26] Two other characteristics of basic scientific research also contribute to this misalignment between social and private value. First, many cash-strapped firms will be focused on short-term investment. For these firms, the long time horizon between basic science investment and a marketable product means they will underinvest in basic research from a societal perspective. Second, risk-averse firms that cannot spread risk among many research projects may underinvest in basic research due to its uncertain payoffs to any individual project. *See* Nelson, *supra* note 25.

that would otherwise be underincentivized.[27] By making information free, grants also facilitate the coordination, indexing, archiving, and repurposing of data. As Nicholson Price has argued, grants often create infrastructures for the coordination of research from multiple groups.[28] In fact, rather than represent a simple instrument to transfer government money to an individual researcher, grants can be structured in sophisticated ways to enable the formation of data-sharing infrastructure and the collaboration across private-public boundaries. For example, grants can enable the creation of scientific consortia, or of data exchange repositories.[29]

But despite their multifaceted role as engines for data generation and coordination, grants–and grant-making agencies–traditionally occupy a somewhat limited role in the drug development process. In contrast, our proposal, which we develop in Part IV, envisions a more robust engagement by grant-making institutions at multiple stages in the drug development pipeline.

2. Pull Incentives: Patents

Like grants for push incentives, patents represent the paradigmatic pull incentive. Patents both incentivize future investment in innovation by preventing free riding, and influence the direction of innovation by tying patent rewards to an inventor's ability to monetize her invention. In other words, patents rely on market signals to align private benefits with social welfare. This alignment is widely

[27] *See* Price, *supra* note 21 at 10.

[28] *Id.*; *see also* Pierre Azoulay & Danielle Li, *Scientific Grant Funding* (Nat'l Bureau of Econ. Rsch., Working Paper No. 26889, 2020), http://www.nber.org/papers/w26889.

[29] *Id.*

considered a key advantage of patents over push incentives, which require organizations other than the market to prioritize investment areas.[30]

But markets suffer from well-known failures that make patents alone an insufficient policy lever, in particular in the drug innovation space.[31] There is no large-enough market to foster investment in many rare diseases or in diseases that affect the developing world. As a consequence, patents will systematically under-incentivize these types of high social benefit but low private benefit inventions. The converse is also true: patents will over-incentivize some high private benefit but low social benefit inventions. Theoretically, if markets produced perfect signals, patents would channel most innovation into high social benefit innovations. But both patent law doctrine and the fragmented structure of the market for drugs make private investments into low social welfare innovation all too common. Examples of this type of investment are so-called "me-too" drugs,[32] the "evergreening" of drug patents,[33] and over- investment in cancer treatments whose benefit is life extension by only a matter of months.[34] This type of investment can yield

[30] *See* Brian D. Wright, *The Economics of Invention Incentives: Patents, Prizes, and Research Contracts*, 73 Am. Econ. Rev. 691, 691 (1983).

[31] Roger Allan Ford, *The Patent Spiral*, 164 U. Pa. L. Rev. 827 (2016).

[32] *See, e.g.*, Jeffrey K. Aronson & A. Richard Green, *Me-Too Pharmaceutical Products: History, Definitions, Examples, and Relevance to Drug Shortages and Essential Medicines Lists*, 86 BR. J. CLIN. PHARMACOL. 2114 (2020).

[33] *See, e.g.*, Robin Feldman, *Understanding 'Evergreening': Making Minor Modifications Of Existing Medications To Extend Protections*, 41 HEALTH AFFS. (2022).

[34] *See, e.g.*, Eric Burdish, Benjamin Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044 (2015).

very high private returns despite its relatively lower social welfare effect.[35] (See Figure 1, lower left quadrant.)[36]

In contrast to analyses of push incentives, legal scholarship is replete with excellent articles that examine how to better align patent doctrine with social welfare.[37] This scholarship focuses largely on making it harder for innovators to obtain patent protection, therefore decreasing private rewards for low social value innovation.[38] But this work pays insufficient

[35] *See, e.g.*, Michael A. Carrier & Steve D. Shadowen*, Product Hopping: A New Framework*, 92 Notre Dame L. Rev. (2016) (describing the phenomenon of "product hopping" where firms encourage doctors to prescribe marginally improved versions of existing products to extend market monopoly and avoid generic competition).

[36] Theoretically, there are two (non-exclusive) ways to bridge this gap between private and social value. The first focuses on increasing investment in high social value/low private value innovation by increasing private rewards (the "incentivizing breakthroughs" approach) (*Figure 1*, upper right quadrant). The second focuses on discouraging investment in low social value/ high private value innovation by decreasing existing private rewards for low social value innovation (the "discouraging incrementalism" approach) (*Figure 1*, lower left quadrant). We will return to these strategies.

[37] *See, e.g.*, Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 Tex. L. Rev. 989 (1997); Michael Risch, *Reinventing Usefulness*, 2010 B.Y.U. L. Rev. 1195, 1227 (2010).

[38] Such doctrinal changes include, raising the bar for findings of non-obviousness (*See, e.g.*, Rebecca S. Eisenberg, *Pharma's Nonobvious Problem*, 12 Lewis & Clark L. Rev. 375 (2008)); a more stringent application of doctrines that narrow claim scope (*see, e.g,* Mark A. Lemley, Michael Risch, Ted Sichelman & R. Polk Wagner, *Life After Bilski*, 63 Stan. L. Rev. 1315 (2011)); or changes to patent-adjacent doctrines such as antitrust law (*see, e.g.,* Carrier & Shadowen *supra* note 35) (arguing for more stringent antitrust analysis of product-hopping cases)). *See also* Mark Schankerman & Florian Schuett, *Patent Screening, Innovation, and Welfare*, 89 REV. ECON. STUD. 2101 (2022).

attention to the institution that operationalizes these levers–the Patent and Trademark Office (PTO)--and to how multi-institutional relationships shape how these policy levers ultimately impact innovation.

3. Pull Incentives: FDA Regulatory Exclusivities and Accelerated Approval Pathways

Market and data exclusivities make up another important pull lever in the drug innovation ecosystem. While patents are filed relatively early in the drug development process, getting a drug to market also requires conducting clinical trials to test its safety and efficacy in humans. Clinical trials are lengthy and costly—simultaneously increasing the time elapsed from patent grant to marketing approval, and decreasing effective patent length.[39] In part to counteract patent term erosion, and also to direct investments into high-social-need innovation, the FDA has enacted a series of so-called "exclusivities" for applicants. Market exclusivities prevent others from marketing a product for a prescribed time period.[40] Data exclusivities prevent others (usually generic manufacturers) from relying on drug developers' original clinical trial data to seek FDA approval.[41]

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[39] *See* Eisenberg, *supra* note 15, at 347 (describing the "competition" view of the patent law/ FDA intersection, in which "patents promote innovation by making it profitable, while drug regulation deters innovation, in furtherance of the competing goal of public health, by making it costly).

[40] For example, under the orphan drug market exclusivity, the FDA cannot approve another application for the same drug for the same disease or condition for 7 years. The orphan drugs market exclusivity program seeks to incentivize the production of high social/low private value drugs through the promise of a longer market exclusivity period.

[41] *See* Eisenberg, supra note 15.

Market and data exclusivities highlight the FDA's role in innovation policy. Exclusivities incentivize original filers to invest in producing clinical trial data for new chemical entities and new biologics—the lynchpins of breakthrough drug therapies.[42] They also foster R&D investment in new chemical entities and biologics by acting as what amounts to an "extension" of the patent monopoly during the market exclusivity period.

The FDA's primary mission, however, is ensuring production of safe and efficient medicines—a function that can be at odds with its innovation function.[43] Stringent quality and safety controls add a monetary burden to the already costly clinical trial process, delay patient availability of new interventions, or even prevent investment in them altogether. Responding to these concerns the FDA has, since 1992, created a number of approval pathways that lower the costs of drug approval and shorten a drug's time to market by, for example, accepting so-called "surrogate clinical trial endpoints" through its accelerated drug approval pathway.[44]

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[42] *Id.*

[43] *See, e.g.,* Thomas R. Fleming, *Surrogate Endpoints And FDA's Accelerated Approval Process*, 24 Health Affs. 67 (2005); Jeanne Lenzer & Shannon Brownlee, *Feature, Should regulatory authorities approve drugs based on surrogate endpoints?*, 374 BMJ n2059 (2021), http://dx.doi.org/10.1136/bmj.n2059; Rachel E. Sachs, W. Nicholson Price II & Patti Zettler, *Rethinking Innovation at FDA*, Boston University L. Rev. (forthcoming 2024) & Patricia J. Zettler, Rethinking the Role of Innovation at FDA (2023, draft on file with authors).

[44] As opposed to "clinical endpoints," "surrogate endpoints" are indirect markers of drug efficacy that typically take less time (and therefore less money) to monitor. *See* 21 C.F.R. §§ 314.500-.560 (2009) (for drugs); id. §§ 601.40-.46 (for biologics); *see also* Barbara J. Evans, *Seven Pillars of A New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 Notre Dame

Taken together, these two FDA interventions (exclusivities and accelerated approval pathways) represent one strategy to align private and social welfare: increasing private rewards in areas of high social need. These interventions, however, are not uncontroversial. Rather, they have sparked heated debates between those who maintain the FDA is sacrificing its watchdog role and acting against the public's interest, and those who defend accelerated approval pathways as necessary to improve fast access to promising new therapeutics.

We expand upon the interaction between the FDA's mission as safety and efficacy watchdog and its innovation-promoting mission when we describe the FDA as an institution in Part II.A.3 below.

4. Pull Incentives: Insurance Reimbursement Policies

Reimbursement incentives are also important pull-drivers of innovation.[45] Profit-maximizing pharmaceutical companies,[46] and the investors that

L. Rev. 419, 454 (2010) (discussing the use of surrogate endpoints).

[45] *See, e.g.,* Lisa Larrimore Ouellette, Nicholson Price, & Jacob Sherkow, *Innovation Law and COVID-19: Promoting Incentives and Access for New Healthcare Technologies*, in COVID-19 AND THE LAW: DISRUPTION, IMPACT AND LEGACY (eds. I. Glenn Cohen, Abbe Gluck, Katherine Kraschel, & Carmel Shachar) (Cambridge University Press 2022, forthcoming); Mark A. Lemley, Lisa Larrimore Ouellette & Rachel E. Sachs, *The Medicare Innovation Subsidy*, 95 N.Y.U. L. REV. 75 (2020); Rachel E. Sachs, *Prizing Insurance: Prescription Drug Insurance As Innovation Incentive*, 30 Harv. J.L. & Tech. 153 (2016).

[46] Fred D. Ledley et al., *Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies*, 323 J. AM. MED. ASS'N 834, 834 (2020) ("Virtually all of the US Food and Drug Administration–approved medicines in the United States were developed by for-profit corporations"); Brian Bruen et al., *The Impact of Reimbursement Policies and Practices on Healthcare Technology Innovation*, HHS (Feb. 2016),

finance them, strive to bring products to market that will bring them (and their shareholders) the greatest return on investment.[47] Return on investment, however, is highly dependent on payer decisions about reimbursement.[48]

For most consumer goods, the decision about whether to invest in a product turns on an estimate of consumer demand for the product at a particular price point compared to the cost to bring the product to market.[49] A company deciding whether or not to introduce a new tech gadget to the market will only do so if it can garner a price, and sell enough gadgets at that price, to justify the investment.

The pharmaceutical market is far more complicated than the market for most other consumer products. Patients cannot just decide to purchase a prescription drug. A provider—who does not bear, and may not even know, the cost—has to decide to prescribe it. In most cases, that can only happen if an insurer or government payer has agreed to cover the drug.[50] Payers are gatekeepers that control access to the

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https://aspe.hhs.gov/sites/default/files/private/pdf/188741/ImpactofReimbursementonInnovation.pdf.

[47] Lawrence Perkins, *Pharmaceutical Companies Must Make Decisions Based on Profit*, 175 WEST J. MED. 422, 422 (2001), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1275981/.

[48] Craig Solid, *Placing Return on Investment Analyses into a Value-based Context in Health Care*, JHEOR (Jan. 07, 2021), https://jheor.org/post/807-placing-return-on-investment-analyses-into-a-value-based-context-in-health-care/.

[49] Galina Merkuryeva et al., *Demand Forecasting in Pharmaceutical Supply Chains: A Case Study*, 149 PROCEDIA COMPUT. SCI. 3, 4 (2018) available at https://www.sciencedirect.com/science/article/pii/S1877050919301061.

[50] Patti Neighmond, *When Insurance Won't Cover Drugs, Americans Make 'Tough Choices' About Their Health*, NPR (Jan. 27, 2020, 5:05 AM), https://www.npr.org/sections/health-

product by making coverage decisions.[51] They also determine patient cost-sharing responsibilities, and in some circumstances, set prices.[52] Payers therefore have a lot of power to affect demand for a prescription drug.

Much like FDA regulation, reimbursement schemes can also influence the type of data that innovators create about a therapeutic compound. Institutions that pay for healthcare put a premium on cost/benefit analyses—seeking to cover drugs that represent an optimal balance between social benefit and cost. In this sense, insurance players are uniquely placed to incentivize breakthrough innovation–the type of high social benefit innovations described in Figure 1. Theoretically, reimbursement schemes could also discourage high private value/low social value innovation by refusing to cover drugs with minimal benefits over existing therapeutic regimes or by covering them at much lower reimbursement rates than those for products that represent breakthrough innovation. As we explore in more detail in Part II, however, our current innovation ecosystem makes it difficult for payers to use reimbursement levers as drivers of socially beneficial innovation, although private payers have more options available.

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shots/2020/01/27/799019013/when-insurance-wont-cover-drugs-americans-make-tough-choices-about-their-health; Scott Howell, *Quantifying The Economic Burden Of Drug Utilization Management On Payers*, Manufacturers, Physicians, And Patients, 40 HEALTH AFFS. 40 (2021), available at https://doi.org/10.1377/hlthaff.2021.00036.

[51] Brian Bruen et al., *The Impact of Reimbursement Policies and Practices on Healthcare Technology Innovation*, HHS (Feb. 2016), https://aspe.hhs.gov/sites/default/files/private/pdf/188741/ImpactofReimbursementonInnovation.pdf.

[52] *Id.*

Figure 1. Interactions between Private and Public Value in Innovation

Social Value Private Value	Low	High
Low	**Low-priority Innovation** (Largely) Not incentivized	**High-priority Innovation** (e.g. rare diseases, diseases with unknown/complex etiology, diseases prevalent only in developing world, basic research, comparative clinical data) Under-incentivized
High	**Low-priority Innovation** (e.g. me-too drugs, drug formulation changes) Over-incentivized	**High-priority Innovation** Incentivized

High social impact innovations in green.
Low social impact innovations in red.[53]

B. Key Institutions Participating in Drug Development

The policy-levers perspective on innovation is incomplete. It neglects to consider that policy levers are not disembodied initiatives but rather are

[53] *See* Jonathan S. Masur, *Costly Screens and Patent Examination*, 2 J. Legal Analysis 687 (2010).

implemented by actors who work within particular organizations. In turn, these organizations often have conflicting missions, priorities, and constraints that impact how effectively they can deploy these policy levers and how all levers–taken together–impact the overall direction of innovation. Developing coherent healthcare innovation policies is all but impossible without understanding the interplay between policy levers and the many institutional contexts where those levers operate.

There is no single U.S. institution charged with promoting health care innovation. Rather, a complicated innovation ecosystem has emerged somewhat piecemeal and haphazardly. Here, we briefly summarize the key innovation institutions–the NIH, PTO, FDA and insurance reimbursement players–and their stated roles in the innovation process. This description sets the stage for our analysis, in the next Part, of how siloed institutional solutions to foster breakthrough innovation, by failing to take into account their systemic effects on other players, have led to the exact opposite result: increasing *ex ante* uncertainty and further discouraging research into breakthrough therapies.

First, the National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the nation's largest funder of biomedical research. The NIH is organized into 27 specialized Institutes and Centers. Each institute specializes in a "specific disease area, organ system, or stage of life."[54] The Office of the NIH Director is responsible for coordinating work across all the NIH components, and

[54] NIH Grants & Funding,, *Understand NIH: Finding the Right Fit for Your Research,* National Institutes of Health, https://grants.nih.gov/grants/understanding-nih.htm (last updated May 24, 2016).

for setting broader NIH policy.[55]

More than 80% of NIH funding goes to its extramural program–awards to universities, medical schools, and other research institutions around the country. The system relies on individual scientists to apply for grants, which are then assessed for scientific merit by a panel of volunteer experts working in related fields. Reviewers ignore budgetary issues, assessing only scientific and technical merit. A unit's fixed budget is then allocated, with the projects ranked highest in merit by the panel being funded first, until funds are exhausted.

The NIH's stated mission is to "seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."[56] And its peer-review system has produced many successes, including more than 75 Nobel prizes awarded for extramural NIH-supported research.

Second, the U.S. Patent and Trademark Office (PTO) relies on a cadre of examiners to evaluate and issue patents to inventors. These examiners work in specialized art units organized according to technology areas. In the past few years, the process of patent examination has grown both in volume and complexity, with the PTO's annual budget increasing from approximately 3 billion in 2014 to 4 billion in 2022.[57] Formally, the PTO's central mission is to

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[55] National Institutes of Health: Office of Strategic Coordination- The Common Fund, https://commonfund.nih.gov/

[56] National Institutes of Health, *Mission and Goals*, National Institutes of Health, https://www.nih.gov/about-nih/what-we-do/mission-goals (last reviewed July 27, 2017).

[57] Glenn J. McLoughlin, *U.S. Patent and Trademark Office Appropriations Process: A Brief Explanation*, Cong. Rsch. Serv. (Aug. 28, 2014), https://sgp.fas.org/crs/misc/RS20906.pdf.

represent the public interest by granting patents to those inventions that promote social welfare, while weeding out "bad" patents. While there is no universally-accepted measure of what constitutes a "bad" patent, conceptually, bad patents occupy the bottom left quadrant in Figure 1: they represent those inventions for which the social costs of the patent monopoly exceed the social gains derived from the invention.

Third, the FDA's mandate is to receive a "reasonable assurance of safety and effectiveness" before it can authorize a drug to be sold.[58] The FDA has put into place what many consider to be a rigorous evaluation process, which typically entails preclinical research,[59] Phase I through III clinical trials, FDA review and approval, and post-marketing studies. Manufacturers have to provide "substantial evidence" that their products are effective before they can obtain approval from the Food and Drug Administration (FDA) to market drugs. The phrase "substantial evidence" is generally understood to mean at least one "adequate and well-controlled" study showing that a drug has a claimed effect.[60]

Finally, the last key institutional player in the innovation ecosystem is payers, whose reimbursement policies and practices exert considerable influence in which products are brought to market.[61]

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[58] 21 U.S.C. §§301-395.

[59] Kefauver-Harris Amendment, Pub. L. No. 87-781, 76 Stat. 780 (1962) ("to assure the safety, effectiveness, and reliability of drugs.").

[60] *Id.*

[61] *See, e.g.,* Brian Bruen et al., *The Impact of Reimbursement Policies and Practices on Healthcare Technology Innovation*, HHS (Feb. 2016), https://aspe.hhs.gov/sites/default/files/private/pdf/188741/Impac

Reimbursement decisions that are opaque and unpredictable cause innovators to be more risk-averse, whereas drugs for which reimbursement is assured tend to be prioritized.[62]

Payers as a group are heterogeneous: the two large public insurers, Medicare and Medicaid, have much more regulated and transparent insurance policies, whereas private payers' reimbursement processes are often kept as trade secrets and therefore inaccessible to the public.[63] For most drugs to have market success, however, they must clear the hurdle of being approved for reimbursement by both government and private payers.

We represent drug innovation institutions and their mandates in Figure 2 below.

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tofReimbursementonInnovation.pdf (in a survey of experts "there was broad agreement that reimbursement is a critical factor in determining which products reach the market").

[62] There does not seem to be empirical evidence to tie reimbursement policy to resultant innovation. This Section draws largely on economic theory.

[63] *See, e.g.,* Katherine L. Gudiksen, Samuel M. Chang, & Jaime S. King, *The Secret of Health Care Prices: Why Transparency Is in the Public Interest*, Cal. Health Care Found. (Jul. 2019),

https://www.chcf.org/wp-content/uploads/2019/06/SecretHealthCarePrices.pdf.

Institution	Core Mission	Institutional Priorities
NIH	"Seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."[64]	Fund high-social impact scientific research Fund efforts to translate basic science into therapies
PTO	"Foster innovation, competitiveness and economic growth, domestically and abroad, by providing high quality and timely examination of patent and trademark applications, guiding domestic and international intellectual property (IP) policy, and delivering IP information and education worldwide."[65]	Issue patents to non-obvious advances over prior art

FDA	"Protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices."	Ensure marketing of safe medicines (Regulation function) Foster data production about medicines (Innovation function)
Centers for Medicare and Medicaid Services (CMS)	"Provide access to high quality care and improved health at lower costs."	Equity Cost/benefit analysis
Private Health Insurance	Differs by carrier, but e.g. "Anthem is dedicated to delivering better care to our members, providing greater value to our customers and helping improve the health of our communities"	Cost/benefit analysis

Figure 2: Drug Innovation Institutions and their Mandates

II. DRUG DISCOVERY DISTORTIONS IN A FRAGMENTED AND COMPLEX SYSTEM

The theoretical description of the drug innovation ecosystem described in Part I, however, is idealized. We need to better understand how institutional mission impacts the pace and direction of innovation in the real world. Fragmented institutional actors, working largely independently of each other to fulfill

their individual mandates, make policy decisions that, in the aggregate, tend to encourage only incremental innovation while insufficient resources are devoted to high social value breakthrough innovations.

This is the case despite individual institutional efforts to incentivize investment in risky, high social value innovation. The result is a fragmented and complex system, ripe with important disadvantages, but also benefits we should not ignore.

a. A. Institutional Incentives Driving Incrementalism

1. THE NATIONAL INSTITUTES OF HEALTH (NIH)

The NIH's peer review system, which governs how it awards 80% of grants, impacts the pace and direction of innovation in notable ways. For one, science is increasingly specialized, making it difficult to find appropriate "peers" to evaluate more novel research. Legacy fields tend to benefit and receive an outsized percentage of fund awards.

NIH standards also emphasize the feasibility of research proposals and have high bars for preliminary data.[66] These institutional hallmarks have been criticized for rewarding "incremental research at the expense of work that could be more innovative."[67] Peer review groups ranking the merit of proposals are notoriously risk-averse.

Grant funding indisputably contributes to the

[66] Pierre Azoulay, Joshua S. Graff Zivin & Gustavo Manso, *NIH Peer Review: Challenges and Avenues for Reform*, NBER Working Paper 18116, (2012) https://www.nber.org/system/files/working_papers/w18116/w18116.pdf

[67] *Id.*

vast foundation of knowledge about disease mechanisms and pathways that enable private actors to more effectively develop targeted therapeutics. Yet only 25 percent of drugs approved from 2007 to 2017 credit NIH-grant recipients with a drug's initial discovery, synthesis, or key intellectual property. This percentage narrows to 15 percent if we focus on patents issued to NIH-funded researchers or crediting NIH funding. NIH's funding impact is more pronounced, however, if we focus only on breakthrough therapeutics.[68]

In all of these cases, NIH involvement happens very early in the drug development timeline and is relatively hands-off. Grant funding agencies pick which research projects to fund, and ensure researchers meet their research goals for continued grant funding but–with the exception of some Common Fund projects–there is no continuous NIH involvement in translating basic research findings into actual therapeutics or in ensuring patient access. That role is widely believed to belong, first, to patent instruments and, later in the development process, to clinical trials under FDA's regulatory authority, and even later on, to reimbursement decisions by insurance companies. In this timeline sense, the NIH is the "first" actor in a development process that reflects discrete interventions by fragmented actors with different specific goals and purposes, despite all of them participating in the overarching project of drug innovation. (See Figure 3.)

[68] *See* Price, supra note 21, at 20.

2. The Patent and Trademark Office (PTO)

Institutional design features of the PTO make it hard for the PTO to serve as the guardian of the public interest it was ostensibly designed to be. Indeed, both lawmakers and academic commentators have criticized the PTO for granting too many bad patents. In the healthcare innovation sector, too many bad patents on drugs translates into delayed market entry of generic competitors and higher prices for medicines.[69] The reasons for the PTO's inability to guard against bad patents are multifaceted, but many of them boil down to its institutional design. First, rather than be funded by general tax revenues, the PTO funds itself through application and maintenance fees.[70] This funding structure puts pressure on the PTO to solicit more "business" in the form of more patent applications. It also somewhat awkwardly puts patent applicants in the role of customers before the PTO.[71] While more applications generate more revenue, they also incentivize the patent examination corps to work faster, potentially lowering the quality of their work.

Second, adding to this time pressure is the fact that examiners are already given a limited amount of time to review a patent application. As Melissa Wasserman and Michael Frakes have shown,[72] on

[69] *See, e.g.*, Aaron S. Kesselheim & Jonathan J. Darrow, *Hatch-Waxman Turns 30: Do We Need A Re-Designed Approach for the Modern Era?*, 15 Yale J. Health Pol'y, L. & Ethics 293 (2015).

[70] Leahy-Smith, *America Invents Act* , 125 Harv. L. Rev. 1290, 1293 (2012).

[71] *See* Michael D. Frakes & Melissa F. Wasserman, *Does Agency Funding Affect Decisionmaking?: An Empirical Assessment of the PTO's Granting Patterns*, 66 Vand. L. Rev 67, 70, 78 & n 35 (2013).

[72] Michael D. Frakes & Melissa F. Wasserman, *Is the Time*

average, an examiner spends only nineteen hours reviewing an application. Because patent examination places the burden on examiners to articulate a proper basis to reject a patent, examiners may be inclined to allow applications simply because they did not have enough time to fully search the prior art or consider potential arguments against patentability.[73]

Third, examiners and applicants have vastly asymmetric information: examiners, while familiar with the broad technological area to which the patent pertains, are not experts in the prior art like the inventor is. As relative non-experts under time constraints they lack the type of knowledge and resources to rigorously vet patent applications that would be available in an adversarial proceeding. The increasing complexity of technological innovation, including the rise of innovation that spans multiple technological areas, further amplifies this information asymmetry.[74]

In contrast to the FDA, which has implemented a series of expedited review pathways and designed special exclusivities to influence the direction of drug development towards those high social value innovations in the top-right quadrant in Figure 1, the PTO has not made wide use of administrative levers to regulate the flow and priority of patent applications.[75]

Allocated to Review Patent Applications Including Examiners to Grant Invalid Patents? Evidence from Micro-Level Application Data, 99 REV. ECON. STAT. 550 (2017).

[73] *Id.*

[74] Sean B. Seymore, *Patent Asymmetries*, 49 U.C.D. L. REV. 963 (2016).

[75] Responding in part to all of these deficiencies, the America Invents Act established a set of adversarial proceedings known as "Inter-Partes Review" that allows third parties to challenge issued patents before the PTO.

As long as an invention clears the, by many accounts quite low, threshold of patentability, the PTO does not differentiate between breakthrough and incremental inventions.[76] As we discuss in more detail in Part III, in a polycentric and collaborative healthcare ecology, the PTO could be more proactive and collaborative in generating signals for other players, namely FDA and insurance reimbursement, about the strength of the patents it issues.[77]

3. The Food and Drug Administration (FDA)

The FDA is at the center of a number of debates that pit its function as a promoter of innovation and facilitator of access to novel therapeutics against its original role as enforcer of drug safety and efficacy standards.[78]

The FDA is influenced by a constantly evolving chorus of public sentiment. In the two decades following the passage of the Kefauver-Harris Drug Amendments in 1962, concerns about drug safety dominated the drug approval process. An unlikely

[76] There is one accelerated approval pathway at the PTO reserved for a small category of inventions, including those that increase environmental quality. 708.01 List of Special Cases [R-10.2019].

[77] Proposals for "gold-plating" patents or to create expedited approval pathways for truly novel or breakthrough inventions have thus far not borne fruit. Mark Lemley et al., *What to Do about Bad Patents?*, REGULATION, Winter 2005, at 10, 12; *see also* Doug Lichtman & Mark A. Lemley, *Rethinking Patent Law's Presumption of Validity*, 60 STAN. L. REV. 45, 61-63 (2007); Ana Santos Rutschman, *Regulatory Malfunctions in the Drug Patent Ecosystem*, 70 Emory L.J. 347 (2020).

[78] *See, e.g.* Rachel E. Sachs, W. Nicholson Price II & Patricia J. Zettler, *Rethinking the Role of Innovation at FDA* (draft on file with authors) (arguing that "that FDA should not weigh innovation in decisions about a product's safety and effectiveness").

coalition of patient advocates, free market enthusiasts and pharmaceutical companies criticized the FDA as being overly risk-averse and pushed for faster pathways for drug approval. Those forces incentivized the FDA to progressively loosen its safety and efficacy requirements in favor of faster access to therapeutics as reflected in a number of FDA initiatives, such as the accelerated approval process with surrogate endpoints for clinical trials[79], the Real-World Evidence initiative[80], fast-track and breakthrough therapy designations[81]; and the Result Act[82], which seeks speedy review of drugs approved in other countries.

This set of "looser" standards for drug approvals have put pressure on other healthcare system players, most importantly both public and private insurance payers. Although, as we discuss below, the relationship between FDA approval and reimbursement is complex—with reimbursement in public insurance programs often following FDA approvals— relaxed FDA approval standards have pushed insurers to take a more active role in performing cost/benefit analysis of approved drugs, and basing more reimbursement decisions on the outcome of these analyses

4. Payers: Private Insurers and the Centers for Medicare and Medicaid Services (CMS)

Finally, it is harder to describe the general motivations and incentives that influence payer decision-making across heterogeneous private and

[79] 21 C.F.R. 58; Aaron S. Kesselheim et. al., Pharmaceutical Policy in the United States in 2019: An Overview of the Landscape and Avenues for Improvement, 30 STAN. L. & POL'Y REV. 421, 431 (2019).

[80] 21 U.S.C. § 355(d).

[81] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[82] *See, e.g.,* Eisenberg, *supra* note 15.

public insurance programs.

Private insurers themselves are a diverse group, including both group and individual-focused businesses, traditional insurance and self-funded plans, and for-profit/not-for-profit/mutual insurers. Although opaque, private insurer decision-making is undoubtedly influenced by economic incentives– insurers determine whether the health and economic benefits of a product compared to the standard of care are sufficient to justify the product's price–and legal requirements. But payers have every incentive to be risk averse. It follows that manufacturers may be hard-pressed to get a favorable reimbursement decision on a new, expensive drug, with a limited evidence base, rather than a more modest extension of an already existing/proven drug.

Medicare, a federally-funded health insurance that primarily covers Americans aged 65 and older, and is the single largest health care benefits provider in the country,[83] is in some ways differently situated.

Unlike private payers, Medicare is not seeking to maximize profit and it is prevented by law from explicitly considering cost or comparative efficacy in making coverage determinations.[84] In reality, while CMS cannot refuse to cover a new drug due to high cost,[85] CMS has an incentive to control cost in its coverage decisions without appearing to run afoul of legal dictates.[86] Similarly, Congress, which must come

[83] CMS Roadmaps Overview, Ctrs. for Medicare & Medicaid Servs., https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualityinitiativesgeninfo/downloads/roadmapoverview_oea_1-16.pdf (last visited Feb. 14, 2022).

[84] Jacqueline Fox, *The Hidden Role of Cost: Medicare Decisions, Transparency and Public Trust*, 79 U. Cin. L. Rev. 1, 15 (2010).

[85] 42 U.S.C.A. § 1395y(l)(1) (West).

[86] *See, e.g.*, Fox, supra note 87, at 8; David McAdams & Michael

up with the funding that Medicare requires, does not have the incentive to engage in much oversight of CMS's cost-relating decision-making.

On the other hand, health care coverage is an important issue to seniors.[87] And Medicare is politically very popular.[88] CMS must carefully thread the needle to keep seniors happy and as healthy as possible. Refusing to cover drugs that could potentially save lives or improve quality of lives is politically (if not also morally) perilous.

The final payer to consider is Medicaid, a public health insurance program serving low-income Americans that is jointly administered and funded by the states and federal governments. Because of its status as a social welfare program, it is governed by strict coverage parameters. While states are not required to cover outpatient prescription drugs, all states do, and in turn must agree to cover all FDA-approved drugs with only limited exceptions. Contrary to private payers and Medicare, innovators can typically be assured that a new drug that wins FDA approval will also win coverage under the Medicaid program.[89]

Schwarz, *Perverse Incentives in the Medicare Prescription Drug Benefit*, 44 Inquiry: J. Health Care Org., Provision, & Fin. 133 (May 1, 2007), https://doi.org/10.5034/inquiryjrnl_44.2.157.

[87] Ashley Kirzinger et al., *KFF Health Tracking Poll – October 2021: Home and Community Based Services and Seniors' Health Care Needs*, Kaiser Fam. Found. (Oct. 15, 2021), https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-october-2021/.

[88] Data Note: 5 Charts About Public Opinion on Medicaid, Kaiser Fam. Found. (Mar. 30, 2023), https://www.kff.org/medicaid/poll-finding/data-note-5-charts-about-public-opinion-on-medicaid/.

[89] Some state Medicaid programs have asked to not have to cover drugs approved on accelerated pathways that do not have

However, the big question when it comes to Medicaid is how utilization controls–such as preauthorization requirements or pre-claim review initiatives–will affect access to new drugs and technologies, and what sort of price an innovator will be able to garner. Medicaid is an entitlement program, giving states a strong interest in containing cost.

In sum, while cost-benefit analysis dictates many reimbursement decisions in the private insurance marketplace, FDA approval plays a big role in coverage decisions, although Medicare retains some discretion that it is able to deploy in cases where cost greatly exceeds benefit. CMS utilized this authority to refuse reimbursement in most instances of the Alzheimers drug, Adulhelm.[90] In recent years, CMS has been more willing to deploy this policy lever, in part to counteract what many perceive as the weakening of the FDA's watchdog role in ensuring drug safety and efficacy. In general, risk-averse payers seem more likely to refuse reimbursement for expensive, not yet proven, breakthrough therapies.

proof of efficacy. See, e.g., https://www.oregon.gov/oha/HSD/Medicaid-Policy/Documents/2022-2027-Waiver-Application-Final.pdf.

[90] CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (April 7, 2022), https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment.

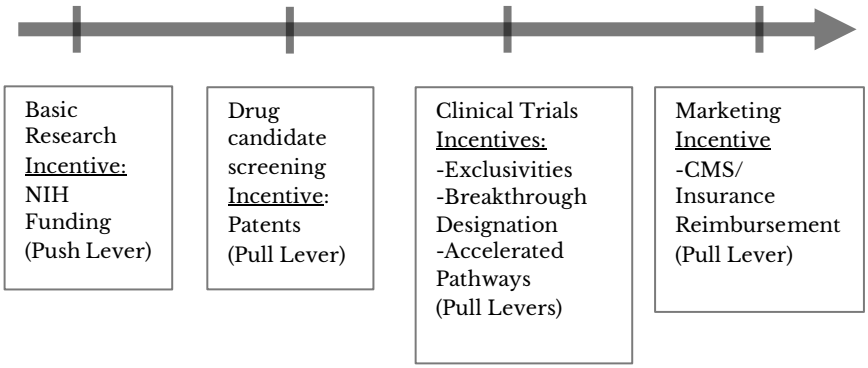

Figure 3. Innovation Institutions and Their Policy Levers Through the Pharmaceutical Lifecycle

Taken together with Part I, the preceding sections illustrate the fragmented and complex nature of our drug innovation ecosystem. To recap: at least five institutional players (NIH, PTO, FDA, CMS and private insurers), subject to public demands, private lobbying and legal constraints, deploy a wide variety of push and pull signals that influence the direction of drug innovation–in both direct and indirect ways. The next two sections work through the consequences of this fragmentation for drug development.

There are two big-picture problems with a fragmented innovation ecosystem. First, fragmentation prevents efficient information flow across institutional silos. Second, fragmentation hampers coordination around shared institutional objectives, such as promoting breakthrough innovation and minimizing incrementalism. Making matters worse, because individual institutional initiatives do not take into account their impact on the whole innovation ecosystem, isolated regulatory efforts can often have unintended consequences that paradoxically push private parties towards incrementalism.

In brief, rather than create a set of coherent policies designed to minimize the high risk inherent in breakthrough innovation, patent law doctrine, FDA

practice, and insurance reimbursement policies[91] all combine to reinforce incentives towards incrementalism and create opportunities for private parties to "game the system."[92] In this Part we delve into the details of how this fragmented system of checkpoints favors incrementalism.

These limitations of a fragmented innovation ecosystem may appear to inevitably point to centralization as the logical policy solution. After all, a centralized administration is nothing if not powerful to implement and enforce coherent innovation policies and facilitate information sharing. But fragmentation is not without its upsides. A full analysis of our current innovation ecosystem requires recognizing these upsides, which include flexibility to experiment with creative policy solutions and avoidance of regulatory capture, and asking how they measure up to a centralized organizational structure. This Part acknowledges those benefits, reflecting the nuanced nature of this problem.

In the final analysis, we argue that we need a better vocabulary to describe governance in a complex innovation system, a vocabulary that goes beyond the centralization/fragmentation dichotomy. In the next Part, drawing on political theory literature on commons governance, we propose a third way to

[91] Nicole M. Gastala, et al., *Medicare Part D: Patients Bear The Cost Of 'Me Too' Brand-Name Drugs,* 35 Health Affs. (2016), https://doi.org/10.1377/hlthaff.2016.0146.

[92] We do not mean to suggest that incrementalism is per se undesirable. Breakthroughs can happen through incremental improvements. See, e.g., Mario Coccia, *Problem-driven innovations in drug discovery: Co-evolution of the patterns of radical innovation with the evolution of problems*, 5 Health Policy and Technology 143, 145 (2016), https://doi.org/10.1016/j.hlpt.2016.02.003. Nonetheless, the impediments to risk-taking that we discuss in this Part tend to burden the pace of socially desirable innovation.

analyze our innovation ecosystem: as an emerging polycentric governance regime. We show how polycentric governance provides a particularly good framework not just for describing on-the-ground practices, but also for normatively addressing fragmentation's negative impact on innovation, while maintaining its benefits.

B. Fragmentation's Downsides: Opportunism and Incrementalism

One persistent issue in drug innovation policy is the over-proliferation of follow-on drugs that represent only marginal (if any) improvements over existing therapies.[93] This trend undermines what should be the main goal of drug development—to develop effective active medicinal agents, for those diseases with the highest social burden, and at the lowest possible cost.

Developing follow-on therapies that rely on minor product reformulations is a low-risk, low-cost, and relatively high reward proposition for pharmaceutical firms. Examples of such reformulations include changes in delivery mechanisms to decrease dosing frequency, slight chemical alterations, and combinations of multiple active ingredients.[94] Although new formulations can improve patient adherence through dosing frequency reductions, increased tolerability, and convenience, new formulations are often not clinically superior to

[93] *See* Christopher Buccafusco & Jonathan S. Masur, *Drugs, Patents, and Well-Being*, 98 Wash. U.L. Rev. 1403 (2021); Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 Iowa L. Rev. 1129 (2019).

[94] *Id.*

the original drug formulation.[95] And their potential convenience benefits (when present) are quite often outweighed by their cost.

Slight chemical alterations to design around an existing chemical patent or to extend patent protection for a product line[96], while preserving the chemical's mechanism of action, have led to the proliferation of me-too drugs that are often indistinguishable (in terms of clinical benefits) from the first in class drug.[97] For

[95] *See, e.g.,* Jane L. Tarry-Adkins et al., *Efficacy and Side Effect Profile of Different Formulations of Metformin: A Systematic Review and Meta-analysis*, 12 Diabetes Therapy 1901 (2021); Walid F. Gellad et al., *Assessing the Chiral Switch: Approval and Use of Single-Enantiomer Drugs, 2001 to 2011*, 20 Am. J. Managed Care e90-e97 (2014); Andrew Sumarsono et al., E*conomic Burden Associated with Extended-release vs Immediate-release Drug Formulations Among Medicare Part D and Medicaid Beneficiaries*, 3 JAMA Network Open e200181 (2020).

[96] Both patent holders and competitors can develop me-too drugs for the original compound covered by a product patent.

[97] Me-too drugs can be broadly defined as chemically related to the prototype, or having an identical mechanism of action. Recent studies suggest that many me-too drugs do not arise from imitation but rather from patent races in which many pharmaceutical companies' R&D target the same signal transduction pathway and have near-simultaneous discoveries of similar active ingredients. That parallel innovation takes place in the pharmaceutical industry is undoubtedly true, and many me-too drugs may have real advantages over first-in-class drugs. *See* Joseph A. DiMasi & Laura B. Faden, *Competitiveness in Follow-on Drug R&D: A Race or Imitation?* 10 Nature Rev. Drug. Discovery 23 (2011). This observation, however, does not negate the existence of an also broad category of duplicative me-too drugs that focus on a very narrow subset of molecular targets, as is the case with the PD-1 and PD-L1 story. And formulation changes often represent efforts by individual companies to extend patent protection for often trivial changes. *See, e.g.,* Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLoSOne (2012) ("Independent secondary patents tend to be filed and issued later than chemical compound patents, and are also

example, in the field of oncology three blockbuster cancer-immunology drugs (Keytruda (marketed by Merck), Opdivo (marketed by Bristol Myers Squibb), and Tecentriq (marketed by Roche)) although slightly different in terms of their chemical structure, target the same protein, PD-1, that tumors use to evade the immune system.[98] Another set of closely related drugs (Tecentriq, Bavencio, and Imfinzi) target the protein PD-L1, which works by binding to PD-1 and dampening the body's immune response against cancer cells.[99]

Although there are benefits to having more than a single compound that targets the same protein, over-focusing clinical efforts on a single molecular target is likely socially inefficient. In the field of cancer immunology, in 2018 there were about 2,250 clinical trials underway for PD-1 or PD-L1 agents[100]—a number that is difficult if not impossible to justify in terms of societal need.[101]

A close look at FDA approvals confirms this

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more likely to be filed after the drug is approved."); Feldman W, Bloomfield D, Beall RF & Kesselheim AS, Patents and Regulatory Exclusivities on Inhalers for Asthma and COPD, 1986–2020, 41 Health Affs. 787 (2022).

[98] *See Immune Checkpoint Inhibitors and Their Side Effects*, American Cancer Society (Nov. 17, 2022), https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html; *See also* Hyun Tae Lee, Sang Hyung Lee, & Yong-Seok Heo, *Molecular Interactions of Antibody Drugs Targeting PD-1, PD-L1, and CTLA-4 in Immuno-Oncology*, 24 Molecules 1190 (2019).

[99] *Immune Checkpoint Inhibitors and Their Side Effects*, American Cancer Society (Nov. 17, 2022), https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html;

[100] Jun Tang et al., *The Clinical Trial Landscape for PD1/PDL1 Immune Checkpoint Inhibitors*, 17 Nature Revs. Drug Discovery 854 (2018), https://doi.org/10.1038/nrd.2018.210.

[101] Id.

trend: the more novel a drug is, the less likely it is to receive regulatory approval, further underscoring the risk of investing in novel drugs.[102] At the same time, novel drug candidates are more socially valuable.[103] In short, pharmaceutical firms are risk-averse: preferring to invest in follow-on drugs with an already-established market.[104]

By forcing firms to negotiate multiple institutional contexts, fragmentation amplifies this risk aversion. A truly new drug faces a series of administrative hurdles with each new agency it must confront. A "no" at any stage can end its path to marketability, and accordingly, profitability. With no coordination between agencies, there is very little assurance that research funded by the NIH will, for instance, ultimately be covered by private payers. It might be worth the risk to a manufacturer if the upside is greater, but drugs resulting from incremental innovation can be very profitable, even absent comparative effectiveness over existing formulations.

Various institutions in the innovation ecosystem

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[102] Joshua Krieger, Danielle Li & Dimitris Papanikolaou, *Missing Novelty in Drug Development*, The Review of Financial Studies 35 636, 638 (2022), https://doi:10.1093/rfs/hhab024. ("[R]elative to other drug candidates developed in the same quarter for the same disease indication, a one-standard-deviation increase in novelty is associated with a 24% decrease in the likelihood that a drug candidate receives regulatory approval from the FDA.")

[103] *Id.* at 639. ("[T]he key patents associated with novel candidates generate significantly greater contributions to stock market value and receive more citations: a one-standard-deviation increase in novelty is associated with approximately a 10% increase in the estimated value of associated patents and an 8%–18% increase in future citations.").

[104] *Id.* at 642. ("[W]hat limits innovation in established firms is risk aversion, that is, concerns about future cash shortfalls, rather than the lack of financial resources at the present.")

have attempted to discourage incrementalism and incentivize breakthroughs. And yet, policy levers currently deployed within individual institutions do little to discourage the tendency to incrementalism, precisely because they fail to take into account the consequences of such policies on other institutional actors in the ecosystem.

Concerns about incrementalism are not new, and several other scholars in multiple disciplines have described the perils of incremental innovation in drug development.[105] What is new in our analysis is the insight that interlocking policy levers and institutional decisions in a fragmented environment have tended to make the problem worse.

In the next paragraphs we focus on single institutional solutions (in the order in which a drug faces them as it moves through the institutional ecosystem) and their overall effects on innovation.

PTO

Patent law as currently structured makes it relatively easy to patent incremental follow-on innovations, creating an incentive for pharmaceutical companies to extend their monopoly over a product through such minor modifications, or to patent me-too drugs that design around a competitor's patent to take

[105] *See*, e.g., Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 532-45 (2009); Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 San Diego L. Rev. 419, 480 (2014); Buccafusco & Masur, *supra* note 96. *But see* Albert Wertheimer et al., *Too Many Drugs?: The Clinical and Economic Value of Incremental Innovations, in Investing in Health*, The Social and Economic Benefits of Health Care Innovation 77, 79-82 (Irena Farquhar et al. eds., 2005) (arguing that me-too drugs provide useful patient choice).

advantage of an established market. The most important doctrinal lever in patent law to police the patenting of minor technological improvements is the nonobviousness doctrine, which is designed to require a patentable invention to show a non-trivial technological improvement over the existing prior art.[106] In the area of pharmaceuticals, however, recent Federal Circuit decisions have all but eliminated the nonobviousness doctrine as a barrier for patentability for follow-on chemical improvements.

Institutional incentives help explain why the PTO has not taken a stronger stance on incrementalism. The PTO sees itself largely as an agency in charge of issuing patents to specific inventions that clear patent law's doctrinal hurdles as articulated by relevant caselaw, not as an agency in charge of shaping innovation policy or of conducting cost/benefit analyses of patent policy–despite the important innovation role it nonetheless plays.[107] In other words, the PTO does not concern itself with how its own patent policies impact the amount and direction of overall drug innovation.

The PTO as an institution could do more to

[106] *See* Jason Rantanen, Lindsay Kriz, & Abigail A. Matthews, *Studying Nonobviousness,* 73 Hastings L.J. 667 (2022); *see also* Karen I. Boyd, *Nonobviousness and the Biotechnology Industry: A Proposal for a Doctrine of Economic Nonobviousness*, 12 BERKELEY TECH. L.J. 311 (1997).

[107] Jonathan Masur, *CBA at the PTO*, 65 Duke L. J. (2016) (criticizing the PTO for lack of capacity to conduct cost/benefit analysis, even in cases where such analysis is required by Executive Order). The one exception to this trend is the emergence of the Post-Grant Review and Inter-Partes Review proceedings as fora to challenge weak patents. Jonathan Stroud, Linda Thayer & Jeffrey C. Totten, *Stay Awhile: The Evolving Law of District Court Stays in Light of Inter Partes Review, Post-Grant Review, and Covered Business Method Post-Grant Review*, 11 Buff. Intell. Prop. L.J. 226 (2015).

discourage the patenting of incremental reformulations.[108] It could deploy other policy levers, such as patent application[109] and renewal fees,[110] accelerated review tracks,[111] patent gold-plating[112], and administrative patent review processes[113] to nudge pharmaceutical companies away from wasteful incrementality and towards more socially beneficial drugs. Yet, the PTO by and large does not use administrative policy levers outside of patent doctrine itself to nudge patentees away from incrementalism and toward breakthrough medical therapies.

Scholars and policymakers have proposed various single institutional solutions.[114] But these

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[108] See Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495, 1495 & n.1 (2001); Adam B. Jaffe & Josh Lerner, Innovation And Its Discontents: How Our Broken Patent System Is Endangering Innovation And Progress, And What To Do About It 12 (2004); Joseph Farrell & Robert P. Merges, *Incentives to Challenge and Defend Patents: Why Litigation Won't Reliably Fix Patent Office Errors and Why Administrative Patent Review Might Help*, 19 BERKELEY TECH. L.J. 943, 944-46 (2004); Roger Allan Ford, The Patent Spiral, 164 U. Pa. L. Rev. 827, 842 (2016). *See* Patent Quality, USPTO, https://www.uspto.gov/patent/patent-quality (explaining the PTO's approach to better ensuring patent quality).

[109] *See, e.g.*, Neel U. Sukhatme, *Loser Pays in Patent Examination*, 54 Houston L. Rev. 165 (2016).

[110] Brian J. Love, *To Improve Patent Quality, Let's Use Fees to Weed Out Weak Patents*, 2016 BTLJ COMMENT (2016).

[111] *See generally* Advancement of Examination, 37 C.F.R. § 1.102(a) (2010); *see also* U.S. Patent & Trademark Office, U.S. Dep't of Commerce, Manual of Patent Examining Procedure § 708.02 (8th ed., Rev. 8, July 2010), available at http://www.uspto.gov/web/offices/pac/mpep/index.htm.

[112] *See supra* note 71.

[113] David Orozco, *Administrative Patent Levers*, 117 PENN ST. L. Rev. 1 (2012).

[114] *See, e.g.,* Michael D. Frakes & Melissa F. Wasserman, *Is the Time Allocated to Review Patent Applications Inducing Examiners to*

solutions all leave out the administrative expertise housed in the many other institutions that take part in the pharmaceutical lifecycle. (See Figure 2). Put differently, these solutions fail to consider the costs of information siloing.

The costs of this omission can be high. For example, in the process of granting market approval for a new drug, the FDA routinely gathers crucial technical information about patented compounds or processes–information that is often relevant to a patentability analysis but that is inaccessible to the public.[115] As Sean Tu documents, lack of communication between the PTO and the FDA may in fact create perverse incentives for patentees to frame a discovery as "unexpected" before the PTO to clear the nonobviousness hurdle, and as "routine" to the FDA to facilitate market approval.[116] Recent proposals for closer collaboration between the FDA and the PTO[117],

Grant Invalid Patents? Evidence from Microlevel Application Data, 99 Rev of Econ & Stats 550 (2017), doi: https://doi.org/10.1162/REST_a_00605; Ryan Whalen, *Complex Innovation and the Patent Office*, 17 Chi.-Kent J. Intell. Prop. 226 (2018); Lauren Cohen, John M. Golden, Umit G. Gurun & Scott Duke Kominers, *"Troll" Check? A Proposal for Administrative Review of Patent Litigation*, 97 B.U. L. REV. 1775, 1808 (2017); Nat'l Research Council of the Nat'l Acad., A Patent System for the 21st Century 18-19 (Stephen A. Merrill, Richard C. Levin & Mark B. Myers eds., 2004); *see* 35 U.S.C. §§ 301-307 (2010) for ex parte patent reexamination procedures and 35 U.S.C. §§ 311-318 (2010) for inter partes reexamination.

[115] Clinical data disclosed to the FDA during the market approval process are subject to data protections, and are therefore kept confidential.

[116] *See* Tu *supra* note 28.

[117] Kathi Vidal & Robert M. Califf, *The Biden Administration is acting to promote competition and lower drug prices for all Americans*, USPTO Dir.'s Blog (July 6, 2022), https://www.uspto.gov/blog/director/entry/the-biden-

backed by President Biden's executive order calling for inter-agency collaboration to control drug prices,[118] make this a crucial moment of political will to design inter-agency collaborative arrangements.

FDA

FDA policy also incentivizes incrementalism. FDA clinical trial requirements, which require only placebo-controlled studies but do not include comparative effectiveness studies,[119] all but guarantee that these incremental innovations will quickly gain market approval. And because reformulations of established and well-understood drugs do not require extensive R&D, the time from patent grant to market approval is significantly shorter for drug reformulations than for first-in-class drugs–therefore maximizing monopoly profits.[120]

On the marketing side, because follow-on innovations can capitalize on an already existing patient market, they provide an almost guaranteed return on investment.

Notwithstanding its incrementalism-favoring

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administration-is-acting

[118] Exec. Order No. 14,036, 86 Fed. Reg. 36,987 (July 14, 2021).

[119] *See, e.g.,* Randall S. Stafford, Todd H. Wagner & Philip W. Lavori, *New, But Not Improved? Incorporating Comparative Effectiveness Information into FDA Labeling*, 361 New England J. Med. 1230, 1231 (2009) *but cf.* Scott Gottlieb, The FDA Should Not Mandate Comparative Effectiveness Trials, https://www.aei.org/wp-content/uploads/2011/10/HPO-2011-05-g.pdf?x91208.

[120] Michael D. Frakes & Melissa F. Wasserman, *Irrational Ignorance at the Patent Office*, 72 Vand. L. Rev. 975 (2019); Carrier & Shadowen *supra* note 35; *but see* Kristina Acri & Erika Lietzen, Solutions *Still Searching for a Problem: A Call for Relevant Data to Support "Evergreening" Allegations*, 33 FORDHAM INTEL. PROP., MEDIA & ENT. L. J. 788 (2023).

clinical trial requirements, the FDA has not ignored the problem of incrementalism. To the contrary, among the institutions in a drug's development path, the FDA has focused the most intensely on trying to solve the twin problems of incrementalism and lack of breakthrough innovation. This is perhaps unsurprising, since the FDA stands at a key juncture in the innovation process, tasked both with ensuring the public gets safe and effective drugs, but also concerned with fostering the development of breakthrough therapeutics for unmet needs.

The FDA's main approach has been to incentivize breakthrough innovation by lowering the cost of getting a breakthrough drug through the FDA approval process–and therefore theoretically lowering the risk of investing in breakthrough therapeutics. Two levers are foundational to the FDA's efforts: (1) "breakthrough therapy" designation and (2) the accelerated approval pathway. These policy levers share a central design principle: they both trade off greater certainty about a drug's efficacy for faster approval and therefore faster public access.

The FDA awards "breakthrough therapy" designation to drugs that "are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint."[121] A breakthrough therapy drug designation expedites the development and review of drugs by providing intensive FDA guidance, "organizational commitment" regarding clinical trial design, and speedy review through "fast track"

[121] Breakthrough Therapy, U.S. Food & Drug Admin., https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (last visited Aug. 13, 2023).

designation.[122]

The accelerated approval process is perhaps the most important of these novel pathways. It hastens approval of "drugs that treat serious conditions, and that fill an unmet medical need."[123] Under the accelerated approval process, the FDA grants marketing approval for therapeutic interventions when they have been shown to have compelling effects on surrogate endpoints (as opposed to clinical endpoints), where these effects are "reasonably likely to predict clinical benefit."[124]

Clinical endpoints represent measures that unequivocally reflect a real benefit to patients, such as life extension or relief of disease-related symptoms. In an ideal world, clinical trials would measure clinical benefit directly. But for many drugs, gathering data on clinical endpoints such as life extension can require trials that are large, very costly and take many years to finish. In contrast, surrogate measures are measures that are supposed to be correlated with clinical endpoints. When a study uses surrogate endpoints, those endpoints "stand in" for the expected clinical benefit.

Because of uncertainty about whether surrogate endpoints signal a real clinical benefit, however,

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[122] *See id.*

[123] U.S. Food & Drug Admin., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 25 (2014) [hereinafter FDA GUIDANCE FOR INDUSTRY].

[124] The FDA defines "surrogate endpoints" as "a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit." Public Law 114-255; Framework for FDA's Real-World Evidence Program, U.S. Food & Drug Admin. (Dec. 2018), https://www.fda.gov/media/120060/download#:~:text=Real%2D World%20Data%20(RWD),derived%20from%20analysis%20of%20 RWD.

obtaining accelerated approval commits the sponsor to conduct post-approval clinical trials to confirm the predicted relationship between the surrogate endpoint and the expected clinical benefit.[125] The FDA retains its authority to revoke market authorization if these studies cannot confirm a therapy's clinical benefit.

In practice, however, there are few incentives for pharmaceutical companies to invest in speedy confirmatory clinical trials. Confirmation of a clinical benefit may marginally increase sales, but the opposite result—failure to confirm a benefit—is much more likely to diminish sales. Accordingly, many validation trials drag on for years, often with dismal patient enrollment rates.[126] The penalties for this delay are mild, if any: influenced by political pressures from both patients and manufacturers, the FDA rarely withdraws drug approval, even though some confirmatory trials are not run at all and only a small fraction confirm a clinical benefit.[127]

The development of drugs to treat Duchenne muscular dystrophy (DMD) illustrates this. In 2016, the

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[125] FDA GUIDANCE FOR INDUSTRY, supra note 74.

[126] *See, e.g.,* Stephanie Diu, *Slowing Down Accelerated Approval: Examining the Role of Industry Influence, Patient Advocacy Organizations, and Political Pressure on FDA Drug Approval,* 90 Fordham L. Rev. 2303, 2315 (2022).

[127] *See* Reciprocity Ensures Streamlined Use of Lifesaving Treatments, Act of 2019, S. 2161, 116th Cong. § 2 (2019). Accelerated Approval Program, U.S. Food & Drug Admin., https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program (last visited Aug. 16, 2023); *see also* Review of the FDA's Accelerated Approval Pathway, HHS-OIG, https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp(last visited Aug. 16, 2023). *See also,* Ravi B. Parikh et al., *Exposure to US Cancer Drugs With Lack of Confirmed Benefit, After US Food and Drug Administration Accelerated Approval*, JAMA Onc. (2023).

FDA approved the drug Eteplirsen for DMD.[128] In a subset of DMD cases, muscle loss is mediated by mutations in a gene that codes for the protein dystrophin.[129] In theory, restoring dystrophin function should prevent or reverse DMD in this patient subpopulation.[130] Eteplirsen was developed specifically to restore dystrophin function in this subset of cases.[131]

Eteplirsen's approval, however, through its accelerated approval pathway, proved extremely controversial.[132] The FDA approved Eteplirsen using restoration of dystrophin function as a surrogate endpoint, despite objections from an advisory committee and its own scientific staff. Eteplirsen's accelerated approval controversy centers precisely on whether restoration of dystrophin function reflects real clinical benefits. In fact, the same clinical trial of Eteplirsen that showed a small increase in dystrophin levels failed to show statistically significant benefits in validated clinical tests for DMD such as the "six minute walk test."[133]

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[128] FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy, U.S. Food & Drug Admin., https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy (Sept. 19, 2016).

[129] Dongsheng Duan et al., *Duchenne Muscular Dystrophy,* 7 Nature Revs. Disease Primers 13 (2021). https://doi.org/10.1038/s41572-021-00248-3.

[130] *Id.*

[131] Kenji Rowel Q Lim, Rika Maruyama & Toshifumi Yokota, *Eteplirsen in the Treatment of Duchenne Muscular Dystrophy*, 11 Drug Design, Dev. & Therapy 533 (2017), https://doi.org/10.2147/DDDT.S97635.

[132] *See, e.g.,* Derek Lowe, *Opening the Lid on Sarepta's Drug Approvals*, Science (Jan. 22, 2020), https://www.science.org/content/blog-post/opening-lid-sarepta-s-drug-approvals.

[133] *See* Kenji Rowel Q Lim, Rika Maruyama & Toshifumi

Perhaps even more concerning, at least to skeptics of FDA's Eteplirsen approval, is the agency's willingness to continue approving DMD drugs under its accelerated review pathway that use the exact same, and still unvalidated, surrogate endpoint.[134] Further amplifying these concerns is the lack of political will, on the part of FDA, to impose meaningful penalties for delays in conducting confirmatory trials.[135] These observations have led some critics to equate the accelerated approval pathway to receiving full approval under a much more lenient standard.[136]

Although these concerns are valid, we do not view them as an example of inefficient policy-making at the FDA. Rather, they illustrate how FDA–acting alone–is limited in the array of policy tools it can deploy to incentivize breakthrough therapies and in its

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Yokota, Eteplirsen in the Treatment of Duchenne Muscular Dystrophy, 11 Drug Design, Dev. & Therapy 533 (2017), https://doi.org/10.2147/DDDT.S97635.

[134] Golodirsen was approved despite relying on the same surrogate endpoint as the prior approval for Exondys, despite the confirmatory trial not being completed.

[135] Bishal Gyawali, Spencer Phillips Hey & Aaron S. Kesselheim, *Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval,* 179 JAMA Internal Med. 906 (2019); Bishal Gyawali, Benjamin N. Rome & Aaron Kesselheim, *Regulatory and Clinical Consequences of Negative Confirmatory Trials of Accelerated Approval Cancer Drugs: Retrospective Observational Study,* 374 British Med. J (2021) https://doi.org/10.1136/bmj.n1959.

[136] *See, e.g.,* Mike Mitka, *Oversight of Fast-track Drug Approval by FDA Stuck in Low Gear, Critics Say*, 304 JAMA 1773 (2010). Derek Lowe, Opening the Lid on Sarepta's Drug Approvals, Science (Jan. 22, 2020), https://www.science.org/content/blog-post/opening-lid-sarepta-s-drug-approvals ("The idea is that the FDA evaluates things on the basis of safety and efficacy, but it can apparently throw both of those out the window when it feels like it? This is infuriating, and it damages things in all directions: not only the health of suffering Duchenne patients, but also the integrity of the whole regulatory process and the reputation of the FDA").

authority to efficiently enforce penalties. Lowering the regulatory approval bar for potential breakthroughs (or what the FDA has termed "increasing regulatory certainty"[137]), facilitates not only breakthrough but also ineffective therapies. Approving therapeutics with lower-quality data may simply kick the buck down the road–leaving insurance companies to deal with the problem of paying for potentially useless therapies.

Medicare and Medicaid spending data bears out this prediction: from 2018 to 2021, both agencies spent an estimated $18 billion on therapies that were past their originally scheduled confirmatory trial completion date.[138] And although the FDA has the institutional authority to revoke regulatory approval for failure to conduct confirmatory trials, in practice, the process is costly, lengthy, and politically fraught (due largely to opposition from powerful constituencies such as patient-advocacy groups and pharmaceutical companies).[139]

Conversely, as the FDA itself has lamented, increasing regulatory certainty may not be enough to

[137] *See* Kristina Fiore, *FDA 'Leans In' to Accelerated Approval for Rare Disease Drugs — CBER Director Says "Moment is Tender for Gene Therapy," Sees Opportunity to "Salvage" Treatments*, MedPage Today (May 19, 2023), https://www.medpagetoday.com/special-reports/exclusives/104594 (quoting Peter Marks, MD, PhD, director of the Center for Biologics Evaluation and Research (CBER) at the FDA).

[138] Off. of Inspector Gen., U.S. Dep't of Health & Hum. Serv., OEI-01-21-00401, Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns (2022).

[139] *See* Rachel E. Sachs et al., *Medicaid and Accelerated Approval: Spending on Drugs with and without Proven Clinical Benefits*, 47 J Health Polit Policy Law 673–690 (2022), https://read.dukeupress.edu/jhppl/article/47/6/673/316038/Medicaid-and-Accelerated-Approval-Spending-on (noting that the FDA may be beginning to increase enforcement under the pathway).

bring to market programs with promising clinical data but uncertain commercial viability.[140] In other words, FDA cannot create a market for low private value but high social value innovation. In a 2023 talk, Peter Marks, director of the Center for Biologics Evaluation and Research (CBER) at the FDA, framed this problem succinctly: "I can think of 5 or 10 programs [with] promising clinical data where they're not that far off but they've been put on the back burner or transferred back to academics because of the commercial viability issues," . . . "So we can try to get over some of those issues and get things back on track to some form of commercial viability, either by reducing manufacturing costs, increasing regulatory certainty, decreasing the costs of preparing regulatory submissions, or a combination of all of the above for these relatively small niches that are not commercially viable currently."[141]

As such, breakthrough therapy designation and accelerated approval pathways are insufficient to foster significant investment in low private value but high social value innovation–this type of innovation often represents drugs for rare diseases or for diseases that afflict poor populations. Breakthrough therapy designation will nudge private parties to invest in more high social value innovation at the margins. Nevertheless, the current FDA structure, with very lax oversight of confirmatory trials, creates an additional social cost: the cost of approving an ultimately ineffective treatment. For these reasons, the effects of breakthrough therapy designation on overall social welfare are unclear.

Finally, breakthrough therapy designation does

[140] *See* Gyawali et al, *supra* note 138 (finding that only in one case did the FDA revoke an approved indication).

[141] *See* Fiore, *supra* note 140.

not address, either directly or indirectly, the problems with incrementalism. As a business strategy, it is still much more certain and profitable for drug developers to invest R&D dollars on small improvements in established therapies. Given these advantages, it is unlikely that breakthrough therapy designation will significantly reroute dollars towards breakthrough therapeutics that would otherwise have gone towards incremental innovation.

Payers

Theoretically, health insurance schemes could also disincentivize incremental, inefficient drugs from entering the market by tailoring reimbursement amounts to clinical efficacy data.

Our earlier example of DMD therapies illustrates the private insurance approach to reimbursement. Disagreements around the quality of the data in the accelerated approval process led several private insurance companies to refuse coverage of Eteplirsen altogether or to impose additional restrictions, such as requiring patients to be ambulatory or under a particular age threshold.[142]

Some private insurance companies took a similar approach to the drug Spinraza[143] approved through the accelerated pathway for the treatment of spinal muscular atrophy (SMA)–a rare and often deadly disorder affecting motor neurons. FDA granted

[142] Katie Thomas, *Insurers Battle Families Over Costly Drug for Fatal Disease*, The New York Times (June 22, 2017), https://www.nytimes.com/2017/06/22/health/duchenne-muscular-dystrophy-drug-exondys-51.html.

[143] FDA label for SPINRAZA (nusinersen) injection, for intrathecal use, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf

Spinraza's maker (Biogen) a broad label that included its use for all adult and pediatric patients with the disease.[144] But at least one large insurance company, Kentucky-based Humana, determined that available data supported reimbursement only for pediatric patients with the most severe form of the disease.[145] More recently, private payers excluded the controversial Alzheimer disease drug adulcanumab (Aduhelm) from reimbursement.[146]

Medicaid programs, on the other hand, are legally required to cover all FDA-approved drugs, irrespective of their paths to approval. These constraints in effect tie Medicaid reimbursement to FDA-approval and render Medicaid unable to engage in the type of efficacy data analysis that takes place in the private insurance marketplace. Medicaid spends an important percentage of its annual budget on accelerated approval drugs (6.4 % in 2015), especially

[144] *Id.* The FDA granted fast track designation, priority review, and orphan drug designation for this therapy.

[145] Suzanne Elvidge, *Another US Insurer Places Limits on Spinraza Coverage*, BioPharmaDive (Feb. 10, 2017), https://www.biopharmadive.com/news/humana-spinraza-coverage-insurer-biogen/435923/. Biogen's only Phase III clinical trial data was a randomized clinical trial for patients with infantile onset of SMA. Only open label trial data (i.e. lower quality data) supported the broad label extending Spinraza's use to populations with less severe forms of the disease. *See* U.S. FDA Approves Biogen's SPINRAZA™ (nusinersen), The First Treatment for Spinal Muscular Atrophy (Dec. 23, 2016), https://investors.biogen.com/news-releases/news-release-details/us-fda-approves-biogens-spinrazatm-nusinersen-first-treatment.

[146] Howard Gleckman, *Medicare Won't Pay For Controversial Alzheimer's Drug Aduhelm Without A New Trial*, Forbes (Jan. 11, 2022, 5:47 PM), https://www.forbes.com/sites/howardgleckman/2022/01/11/medicare-wont-pay-for-controversial-alzheimers-drug-aduhelm-without-a-new-trial/?sh=186aee792069.

given that these drugs make up a very small fraction of all outpatient prescription drugs paid for by Medicaid (between 0.2% and 0.4%).[147] Crucially, a significant share of Medicaid's spending on accelerated approval drugs covers drugs whose confirmatory trials use surrogate endpoints with no demonstrated clinical validity.[148] In other words, Medicaid may be grossly overspending on ultimately ineffective drugs.

Medicare occupies a middle ground between the relatively unconstrained private insurance marketplace and the tightly constrained Medicaid programs. Medicare retains some discretion to refuse to cover drugs that it deems not reasonable and necessary.[149] It has started to deploy this power recently.[150]

We can think about this web of legal restrictions around Medicare and Medicaid as interfering with their ability to do what insurers often do best: conduct careful cost/benefit analyses and tie reimbursement schemes to these cost/benefit calculations. This framing also suggests a solution: as Rachel Sachs has proposed, we could untie Medicaid's and Medicare's hands by delinking their reimbursement decisions from FDA approval.[151] But delinking is not without

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[147] Rachel E. Sachs, Kyle A. Gavulic, Julie M. Donohue & Stacie B. Dusetzina, *Recent Trends in Medicaid Spending and Use of Drugs With US Food and Drug Administration Accelerated Approval*, 2 JAMA Health Forum e213177 (2021), https://jamanetwork.com/journals/jama-health-forum/fullarticle/2784982.

[148] *See* Sachs et al., supra note 150.

[149] C. Joseph Ross Daval & Aaron S. Kesselheim, *Authority of Medicare to Limit Coverage of FDA-Approved Products*, JAMA Internal Med. (2023), https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2808074.

[150] *See* discussion of Aduhelm, Gleckman, supra note 149.

[151] Xavier Becerra, U.S. Dept. Health & Hum. Servs., A Report

costs. While delinking would allow both Medicare and Medicaid to serve a watchdog role against the marketing of ineffective drugs and to encourage data production about effectiveness and safety, it will also increase uncertainty ex ante for drug makers, patients, and doctors.

This, in fact, has been the effect of the private insurance marketplace: its complex web of requirements to cover a particular drug has made access unpredictable for patients.[152]

Delinking may also fall short of achieving the often elusive balance between incentivizing breakthroughs, disincentivizing incrementalism, and ensuring robust safety and efficacy data for marketed products. For an important subset of breakthrough drugs–those that struggle with commercial viability–a collaborative model that takes advantage of the expertise not only of the FDA and insurance companies, but also of the PTO and the NIH, is best situated to develop policies that create a clear and predictable ex ante plan for reimbursement.

C. Fragmentation's Upsides: Independence and Experimentalism

The downsides of the fragmented drug innovation ecosystem seem to suggest that centralization is preferable. But fragmentation also has important benefits. In this Part, we briefly review these benefits, presenting them as counterpoints to a centralization narrative.

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in Response to the Executive Order on Lowering Prescription Drug Costs for Americans 10, 14 (2023).

[152] Nikoletta M. Margaretos, *Patients' Access to Rare Neuromuscular Disease Therapies Varies Across US Private Insurers*, Orphanet J. Rare Diseases (2022), https://doi.org/10.1186/s13023-022-02182-3.

The few scholars in the drug and healthcare innovation space who have analyzed fragmentation tend to view it as the enemy.[153] The same tends to be true in other policy contexts–notably in international law-making–where the proliferation of institutional players has been held responsible for lack of leadership, democratic accountability, and weak policy enforcement. The traditional narrative favoring centralization emphasizes a centralized bureaucracy's efficient ability to both draft *and* enforce coherent policies to advance a singular mission.[154] Theoretically, in the context of drug innovation, a centralized agency would be able to conduct comprehensive cost/benefit

[153] *See, e.g.,* Stuart Minor Benjamin & Arti K. Rai, *Fixing Innovation Policy: A Structural Perspective*, 77 Geo. Wash. L. Rev. 1 (2008).; Einer Elhauge, ed. The Fragmentation of US Health Care: Causes and Solutions, (2010). *See also,* Gary E. Marchant, *Governance of Emerging Technologies as a Wicked Problem*, 73 Vand. L. Rev. 1861, 1876 (2020) (acknowledging the fragmentation of the healthcare system and advocating for the "some type of multistakeholder entity or forum for providing the necessary coordination" between governance initiatives.); David C. Szostak, *Vertical Integration in Health Care: The Regulatory Landscape*, 17 DePaul J. Health Care L. 65, 70, 2015 (offering vertical integration, meaning "one type of provider's acquisition of a different type of provider," as the solution to the problem of fragmentation.); Terry L. Corbett, *The Case for a Health Care Benefit Corporation*, 47 Cap. U. L. Rev. 183, 259-60, 2019 (in response to fragmentation, "The arguable solution is to hire a "general contractor" to control the actions of the electricians and plumbers- just as in health care it would be to hold "someone accountable for the totality of care given to patients."); Elenore Wade, *Health Injustice In the Laboratories of Democracy,* 29 Geo. J. On Poverty L. & Pol'y, 177, (2022) (proposing a federal-based single-payer healthcare program as what is needed to appropriately address healthcare fragmentation.)

[154] *See e.g.,* Eyal Benvenisti & George W. Downs*, The Empire's New Clothes: Political Economy and the Fragmentation of International Law*, 60 Stan. L. Rev. 595 (2007-2008).

analyses of individual policy changes at each innovation agency, design a system that maximizes benefits while minimizing costs, and force agencies to implement its comprehensive innovation blueprint.

One obvious problem with centralization, however, is that setting up such an agency would require the type of political will that is simply unavailable in the U.S. political system. In fact, the many historical failures that prevented setting up an agency to govern the admittedly broader area of healthcare delivery, suggest these hurdles are close to unsurmountable.

But even setting aside political constraints, centralization suffers from two key drawbacks: regulatory capture and stagnation. In fact, the concentration of political authority is a double-edged sword as it simultaneously enables robust enforcement *and* efficient lobbying by private interests.

Regulatory capture is a well-known phenomena that affects all regulatory agencies with a single mission and a defined constituency. Although individual agencies in our innovation ecosystem are also susceptible to capture, fragmented institutional actors can work as a system of checks and balances. Put differently, despite private efforts to capture individual institutions, their different missions generate lobbying constituencies and interests that do not perfectly overlap, reducing capture of the system as a whole. A good example of this system of check-and-balances in action is private insurers' rejection of reimbursement claims for drugs approved through the FDA's accelerated approval pathway, when those drugs were found not to offer a significant clinical benefit.[155]

[155] See, e.g., Daniel L. Shaw, Sanket S. Dhruva, & Joseph S. Ross, Coverage of Novel Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval, 24 J. Managed

Private insurers balance the influence of pharmaceutical and patients' groups lobbying for accelerated drug approval with a concern for cost-cutting.[156]

The second important drawback of centralization is ossification. Centralized regimes can be slow to respond to technological changes, precisely because they must take in and consider broader swaths of information, and seek to synthesize (and reach consensus) across multiple types of expertise. In the context of drug development, there is a danger that a centralized innovation agency, in an effort to reach consensus among multiple expertises (scientific, technological, ethico-medical and economic) would be both slow to respond to technological progress and conservative in its policy proposals.

While fragmentation has its own efficiency problems caused by siloed information and lack of coordination, fragmentation has a key advantage, as well: its nimbleness in allowing actors to creatively and flexibly experiment with novel solutions. In policy areas such as drug development, where technology

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Care & Specialty Pharmacy (2018), https://doi.org/10.18553/jmcp.2018.24.12.1230.

[156] The experience with Aduhelm, the Alzeheimers treatment, is another example. After the FDA's decision to grant accelerated approval, overruling an advisory panel that had recommended against it, a subsequent Congressional investigation found "irregularities" in the FDA's process. C. Joseph Ross Daval, Theodore W. Teng, Massimiliano Russo & Aaron S. Kesselheim, Association of Advisory Committee Votes With US Food and Drug Administration Decision-Making on Prescription Drugs, 2010-2021, 4 JAMA Health Forum (2023), doi: 10.1001/jamahealthforum.2023.1718. Ultimately, CMS provided necessary checks and balances by deciding only to provide Medicare reimbursement for individuals involved in clinical studies.

often moves faster than law can adapt to new discoveries, it is important to maintain this benefit of fragmentation.

Fragmentation also allows more types of on-the-ground expertise to participate in policy-making, generating and implementing a wider variety of policy solutions to any given problem. In the context of drug innovation, the myriad reimbursement schemes in private payer insurance, as well as the multiple initiatives (both by the PTO and the FDA) to foster breakthrough innovation, are examples of this fragmented creativity. Although unbridled experimentalism is no panacea, especially when efforts are not coordinated across fragmented units, the dangers of ossification and slowness should give us pause to reconsider proposals for a centralized overhaul of our innovation ecosystem.

* * *

So far, we have described the drug innovation ecosystem as a series of unconnected institutions that make fragmented, sequential decisions that have complex effects on innovation. This description, while capturing much of the current drug innovation landscape, is not entirely accurate. In fact, budding collaborative institutional arrangements have already emerged as islands of collaboration that operate within the larger fragmented and complex healthcare ecosystem.

Players in these islands of collaboration can be conceptualized as part of an emerging polycentric innovation ecosystem. In this type of ecosystem, many centers of decision-making that are formally independent of each other nevertheless enter into

various contractual and cooperative undertakings.[157]

We summarize the key principles of polycentric governance systems in the next Part. A polycentric lens has both descriptive and normative implications. Descriptively, it allows us to understand the emergence and operation of what we call "islands of collaboration" between institutional players in the healthcare ecosystem. Turning from the descriptive to the normative, we take these early glimmers of polycentricity in drug innovation as case studies for a new, and more ambitious, collaborative pathway for drug development, which we develop in more detail in Part V.

III. THEORIZING COMPLEXITY: POLYCENTRIC HEALTHCARE GOVERNANCE

A. Polycentric Governance Theory

What is polycentricity? The concept was first defined by Michael Polanyi in his book, The Logic of Liberty, in 1951, to mean "a social system of many decision centers having limited and autonomous prerogatives and operating under an overarching set of rules."[158] Polanyi drew on scientific success and observed that there was no centralized authority dictating a rigid scientific method. Rather, researchers enjoy freedom to make contributions in the way they deem fit, subject to the pursuit of a common goal, which is a pursuit of objective truth.[159] The system

[157] Vincent Ostrom, Charles M. Tiebout & Robert Warren, *The Organization of Government in Metropolitan Areas: A Theoretical Inquiry*, *55* Amer. Pol. Sci. Rev. 831 (1961).

[158] Michael Polanyi, The Logic of Liberty: Reflections and Rejoinders 170 (1951); *see also* Lon L. Fuller, *The Forms and Limits of Adjudication*, 92 Harv. L. Rev. 353, 394 - 405 (1978).

[159] *See* Paul D. Aligica & Vlad Tarko, *Polycentricity: From Polanyi*

works because it empowers individuals and promotes creativity and progress, but systemic success depends on autonomous entities learning from–and building–on each other's work.

The concept of polycentricity was imported into many domains. Most prominently, in 1961, Vincent Ostrom, Charles Tiebout, and Robert Warren published "The Organization of Government in Metropolitan Areas,"[160] which introduced polycentricity to the governance context. The influential article explored the "organized chaos" of metropolitan government.[161] The authors noted that there was no single entity charged with addressing the problems of a metropolitan region. Rather, various federal and state governmental agencies, counties, cities, and special districts all have overlapping authority and must combat a range of common problems. Prior work had described this governance system as pathological, criticizing its duplication of functions and the lack of a centralized authority as inefficient and costly.[162] Critics also assumed that each unit in such a system would act independently and without regard to the others–therefore engendering inefficient transaction costs and unpredictable policy outcomes.[163]

Ostrom et. al's insight was that despite their formal independence, each autonomous decision-maker may actually take the others into account through both competitive and cooperative interactions. In turn, these two types of interactions would lead metropolitan government units to actually

to Ostrom, and Beyond, 25 Governance 237 (2012).

[160] Ostrom et al., *supra* note 161.

[161] *Id.*

[162] *See, e.g.,* Robert C. Wood, The New Metropolis: Green Belts, Grass Roots or Gargantua, 52 Am. Pol. Sci Rev. 108 (1958).

[163] *See* Ostrom, *supra* note 161.

"function in a coherent manner with consistent and predictable patterns of interacting behavior,"[164] as opposed to the unpredictable and inefficient behavior theorized in prior scholarship.

The authors posited that whether a centralized system or a polycentric system is desirable should be an empirical question. Indeed, there may be many advantages to polycentric governance. Among them are increased flexibility and responsiveness arising from competition between decision-makers, and bottom-up experimentalism with different policy solutions to any given problem, due to redundancy among decision-making centers.

Through the continued work of Victor Ostrom and Elinor Ostrom, the first woman to win a Nobel Prize in economics, among others, a modern definition of polycentric governance emerged and has come to be characterized by the following elements.

First, a polycentric governance system has multiple, overlapping decision-making centers that enjoy some degree of autonomy, although there is a debate in the literature about how much autonomy is enough. These decision-making centers can also rely on other actors, such as private entities or NGOS, to play a "critical supporting role" in designing shared policy solutions.[165]

Second, the decision-making centers in a polycentric system "choose to act in ways that take into account others (in the system) through processes of cooperation, competition, conflict, and conflict

[164] Michael D. McGinnis, Costs and Challenges of Polycentric Governance, Workshop on Analyzing Problems of Polycentric Governance in the Growing EU, Humboldt University, Berlin. 2005.

[165] *See, e.g,* Keith Carlisle & Rebecca L. Gruby, *Polycentric Systems of Governance: A Theoretical Model for the Commons*, 47 Pol'y Stud. J. 927 (2019).

resolution."[166] Institutions can choose to cooperate with each other, often creating stable cooperative arrangements. Crucially, through cooperative processes actors can enhance their collective capacity or outsource functions to more capable decision-making centers or supporting actors.[167]

But actors can also compete or clash with each other. In a polycentric system, conflict is not necessarily detrimental to the shared goals of the system so long as entities are capable of resolving conflicts; rather, conflict can be an idea-generating, learning process so long as it doesn't involve institutional competition about resources and it doesn't turn into dysfunctional bickering—a balance that may be hard to achieve in some fraught institutional contexts.

Normatively, a key advantage of polycentric decision making lies precisely in the ability of the system (or of the institutions that make up the system, collectively) to learn and nimbly adapt to new situations. Semi-autonomous institutions can simultaneously experiment with different approaches to solve common problems, and learn from each others' experience through processes of information sharing.[168] Meanwhile, some cognitive distance is a

[166] *Id.*

[167] *See* Ramiro Berardo & Mark Lubell, *Understanding What Shapes a Polycentric Governance System*, 76 Pub. Admin. Rev. 738 (2016), https://doi.org/10.1111/puar.12532.

[168] Yochai Benkler, in his pioneering work on commons-based production, has also analyzed how cooperation can emerge without formal (legal) coordination. *See, e.g.,* YOCHAI BENKLER, WEALTH OF NETWORKS (2006); Yochai Benkler, *Coase's Penguin, or, Linux and The Nature of the Firm*, 112 YALE L.J. 369 (2002). His work draws inspiration from earlier work by Elinor Ostrom on natural resources commons. *See, e.g.,* ELINOR OSTROM, GOVERNING THE COMMONS: THE EVOLUTION OF INSTITUTIONS FOR COLLECTIVE ACTION (1990). *See also*

necessary ingredient for innovation that avoids groupthink.[169]

Polycentric governance instantiates such an adaptive system by bridging the gap between representative and deliberative models of democracy. In other words, polycentric governance places intrinsic value on individual self-governance (a feature of representative models of democracy) without prescribing specific outcomes from the process of governance (a feature of deliberative models).[170]

Copious work has now explored examples of polycentric governance in practice and has sought to empirically assess how polycentricity performs compared to more centralized and hierarchical governance systems. For instance, Elinor Ostrom, Roger B. Parks, and Gordon P. Whitaker tested the performance of polycentric governance units in comparison to more centralized units. In their renowned work, Patterns of Metropolitan Policing,[171] they conducted studies of police department performance in Indianapolis, Chicago, St. Louis, and in eighty U.S. metropolitan areas.[172] Their data showed that the most effective police governance systems used smaller police departments to provide direct services including patrols and 911 response and larger departments to provide indirect services such as

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Stephanie Plamondon Bair, Laura G. Pedraza-Fariña, *Anti-Innovation Norms*, 112 Nw. U. L. Rev. 1069, 1136 (2018); *See* Matthew Jennejohn, *The Private Order of Innovation Networks*, 68 STAN. L. REV. 281, 313 (2016).

[169] *See, e.g.,* Laura Pedraza-Farina & Ryan Whalen, *A Network Theory of Patentability*, U. Chi. L. Rev. (2020).

[170] *See* Josephine van Zeben & Ana Bobić, Polycentricity in the European Union (Cambridge, Cambridge University Press 2019).

[171] Elinor Ostrom, Roger B. Parks & Gordon P. Whitaker, Patterns of Metropolitan Policing (1978).

[172] *Id.*

training, forensics, and radio communications. When larger departments consolidated both direct and indirect tasks, they realized neither gains in performance nor lower costs.[173]

Polycentric governance systems have also been studied or proposed in myriad other contexts, including natural resource management,[174] global climate change,[175] cybersecurity,[176] healthcare delivery,[177] and most recently in an edited volume,[178] which both identified current polycentric features of the EU but also made the case for why a polycentric governance model would be more successful than existing EU governance theories.

A common theme in this work is that polycentric governance systems often bring the advantage of enhanced adaptive capacity due to the promotion of learning and trust between autonomous decision-makers.[179] As such, polycentricity is particularly well-

[173] *See also* Michael Dean McGinnis, Polycentricity and local public economies: Readings from the workshop in political theory and policy analysis (University of Michigan Press 1999) (arguing that solving complex urban policing problems is better done by polycentric systems than the simple, centralized solutions advocated by many social scientists); Elinor Ostrom, *The Institutional Analysis and Development Framework and the Commons,* 95 Cornell L. Rev. 807, 808 (2010).

[174] *See, e.g.,* Krister Andersson & Elinor Ostrom, *Analyzing Decentralized Resource Regimes from a Polycentric Perspective*, 41 Pol'y Scis. 71 (2008).

[175] Elinor Ostrom, *A Polycentric Approach for Coping with Climate Change*, 15 Annals of Econ. & Fin. 97 (2014).

[176] Scott Shackelford, *Toward cyberpeace: Managing cyberattacks through polycentric governance*, 62 Am. UL Rev. 1273 (2012).

[177] Michael McGinnis, D. H. Cole & M. D. McGinnis. "Commons, Institutional Diversity, and Polycentric Governance is US Health Policy." *Elinor Ostrom and the Bloomington School of Political Economy* 4 (2018): 279-308.

[178] van Zeben & Ana Bobić, *supra* note 174.

[179] *See, e.g.,* Peter J. Boettke, *Introduction to Polycentric Political*

suited to deal with complex, evolving problems. Empowering decision-makers and allowing them to set the rules of interaction in pursuit of a common goal leads to creative problem solving.

In addition, the redundancy in a decentralized system that was once considered a pathology also has important advantages, namely in mitigating risk. Maintaining a degree of fragmentation and expecting that autonomous units will find ways to collaborate and even challenge each other through competition, makes errors–and particularly errors borne of capture–less likely.

But common pitfalls of polycentricity have also emerged. Transaction costs can be high–not only of maintaining separate governance units but also for collaboration and coordination. The dispersion of authority can also make it hard to hold actors accountable when things go wrong. For this reason, careful empirical evaluation of any polycentric governance model is important, with an eye toward monitoring for cost and accountability.

B. Glimmers of Polycentric Governance: Islands of Institutional Collaboration in Drug Innovation

It is only partially accurate to describe our innovation ecosystem as "entirely piece-meal,"[180] as Benjamin and Rai put it, and infected with siloed

Economy, 57 J. Econ. Behav. & Org. 141 (2005) in Polycentric Political Economy: A Festschrift for Elinor and Vincent Ostrom; Michael D. McGinnis & Elinor Ostrom, *Reflections on Vincent Ostrom, public administration, and polycentricity*, 72 Pub. Admin. Rev. 15 (2012); Elinor Ostrom, *Beyond markets and states: polycentric governance of complex economic systems*, 100 Amer. Econ. Rev. 641 (2010).

[180] *See* Benjamin & Rai *supra* note 156.

decision-making. In fact, as the case studies below illustrate, institutional actors and private players interact formally (to a limited degree) and informally with each other as a drug moves from a basic research idea to Phase III clinical trials. These islands of institutional collaboration look much like institutions engaged in polycentric governance.

In the following sections we describe two types of emerging polycentric arrangements in drug innovation: bilateral collaborations between two institutions ("institutional dyads"); and a novel multilateral collaboration among FDA, NIH, Biomedical Advanced Research and Development Authority (BARDA) and private firms that emerged from the COVID-19 pandemic.

1. Institutional Dyads

Institutions are increasingly working together to solve problems at their overlapping institutional boundaries. For example, the FDA-CMS Parallel Review mechanism allows FDA and CMS to simultaneously review clinical data to help decrease the time between FDA's approval of a premarket application and the subsequent CMS national coverage determination (NCD). The FDA and the NIH have also launched a collaboration to fast-track innovations to the public.[181] More recently, in an executive order, President Biden called for closer collaboration between the FDA and the PTO, leading to several proposals for joint efforts.[182]

[181] Nat'l Inst. of Health, NIH and FDA Announce Collaborative Initiative to Fast-track Innovations to the Public, News Release (Feb. 24, 2010), https://www.nih.gov/news-events/news-releases/nih-fda-announce-collaborative-initiative-fast-track-innovations-public.

[182] What Are the USPTO-FDA Collaboration Initiatives?

One way to conceptualize these collaborative agreements between FDA and CMS, FDA and NIH, or FDA and PTO is as constituting a limited polycentric governance arrangement nestled within autonomous institutions with overlapping mandates. Interestingly, every single one of these arrangements involves the FDA collaborating with a different partner, as illustrated in Figure 4 below. Because of its gate-keeping role in drug approvals, the FDA has increasingly assumed the role of a collaboration-hub in current institutional arrangements. While these collaborations are promising, this hub-and-spoke design doesn't fully reap the benefits of polycentricity, as all information is filtered through a single actor (the FDA). As a consequence, other actors in the system, the NIH, PTO and CMS, do not have opportunities to directly interact with each other and share relevant information. Below, we summarize key aspects of these FDA-led institutional dyads.

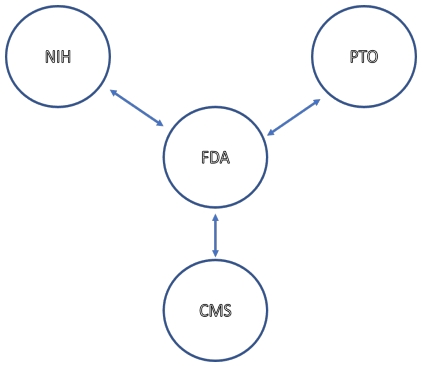

Figure 4 *Institutional Dyads in Drug Innovation*

USPTO (2021), https://www.uspto.gov/initiatives/fda-collaboration/what-are-uspto-fda-collaboration-initiatives

1. FDA/CMS Parallel Review

The FDA-CMS Parallel Review mechanism allows FDA and CMS to simultaneously review clinical data to help decrease the time between the FDA's approval of a premarket application and the subsequent CMS national coverage determination (NCD). In a parallel review process, both agencies meet with the manufacturer to provide feedback on clinical trial design, but evaluate the resulting data independently to assess whether it meets each agency's standards.[183]

The FDA-CMS parallel review process has several attributes of a polycentric system–and reaps many of its rewards. First, both agencies ultimately retain their autonomous decision-making authority while also collaborating in the design of clinical trials. Involving both agencies at the clinical trial stage can enhance idea-generation, learning, and problem-solving. In the traditional model, CMS would not be involved at this stage, but might later raise concerns about the evidence generated by the trials, at a time when it would not be feasible to fix the problems CMS identifies. In theory, this collaboration should lead to better, early decision-making. CMS's involvement at the clinical trial stage should also enhance trust in the process and the related data generated by it.

But this is also a very limited application of polycentricity in the sense that it does not involve other key actors in the innovation ecosystem and addresses only one limited (albeit important) component of the innovation process – the clinical trials.

[183] Pilot Program for Parallel Review of Medical Products, 76 FR 62808 (Oct. 11, 2011).

2. FDA/NIH Collaboration

The FDA and the NIH also coordinate some of their activities through the FDA-NIH Joint Leadership Council Charter.[184] The purpose of the collaboration is to "provid[e] new methods, models or technologies that will inform the scientific and regulatory community about better approaches to evaluating safety and efficacy in medical product development."[185] The Leadership Council has made modest funding available to support its efforts.

The Charter works as a quasi-polycentric governance institution. The FDA and NIH share a common goal of improving public health, and this common goal is clearly articulated in the Charter's mission. They collaborate to ensure that the basic science funded by the NIH ultimately proves helpful in innovating medical products and therapies that can pass the FDA's safety and efficacy bars. Their collaboration has resulted in aligning terminology and streamlining processes to enhance efficiency as science moves from the realm of the NIH into that of the FDA.

However, the Leadership Council's work has not been groundbreaking. One hurdle is that the NIH and FDA fulfill complementary roles and have therefore focused most of their attention on improving the handoff of information from one agency to the next. But their work has not had significant impact on the

[184] FDA-NIH Joint Leadership Council Charter, U.S. Food & Drug Admin., https://www.fda.gov/science-research/advancing-regulatory-science/fda-nih-joint-leadership-council-charter (Mar. 29, 2018).

[185] Nat'l Inst. of Health, NIH and FDA Announce Collaborative Initiative to Fast-track Innovations to the Public, News Release (Feb. 24, 2010), https://www.nih.gov/news-events/news-releases/nih-fda-announce-collaborative-initiative-fast-track-innovations-public.

overall pace or success of innovation.[186] While the collaboration does take into account the work of the other agency, the non-overlapping relationship between these two agencies only provides limited opportunity for progress through competition or conflict resolution. The main purpose of polycentric governance, to leverage shared expertise, has only been modestly accomplished.

3. FDA/PTO Collaboration

In 2021, President Biden issued an executive order to "promote competition in the American Economy."[187] The order called on the Commissioner of Food and Drugs to write a letter to the Under Secretary of Commerce for Intellectual Property and to the Director of the United States PTO "enumerating and describing any relevant concerns of the FDA."[188] This executive order set in motion a series of communications between the FDA and the PTO, announcing their intent to collaborate more closely. As outlined in a PTO publication, the collaboration will focus on both training and informational exchanges between PTO examiners and FDA staff to "protect against the patenting of incremental, obvious changes

[186] More recently, NIH and FDA have targeted efforts to address the dearth of drugs for rare neurodegenerative diseases by launching a new public-private partnership. https://www.fda.gov/news-events/press-announcements/fda-and-nih-launch-public-private-partnership-rare-neurodegenerative-diseases.

[187] Executive Order on Promoting Competition in the American Economy (July 9, 2021), https://www.whitehouse.gov/briefing-room/presidential-actions/2021/07/09/executive-order-on-promoting-competition-in-the-american-economy/.

[188] *Id.*

to existing drugs that do not qualify for patents."[189]

Because this is such a new initiative, its scope as well as its potential impact are still unclear. To the extent that this new collaboration will center only on informational exchanges and training seminars, it risks replicating the non-overlapping nature of the FDA-NIH collaboration. In other words, it will fall short of a true polycentric relationship because the FDA and the PTO will not work cooperatively or competitively to solve a shared problem, but rather, each player will be limited to sequentially providing its expert input. In its blog, however, the PTO hinted at a potentially broader and more ambitious scope for this collaboration– reaching beyond training seminars and informational exchanges to joint policymaking.[190] This overture provides an opening for a true polycentric partnership between the PTO and the FDA, one in which staff from both agencies come together to both define shared goals and solve conflicts in areas of overlapping expertise.

More recently, new collaborative models, some

[189]Kathi Vidal & Robert M. Califf, *The Biden Administration is acting to promote competition and lower drug prices for all Americans,* DIRS. BLOG (Jul. 6, 2022), https://www.uspto.gov/blog/director/entry/the-biden-administration-is-acting.

[190] Kathi Vidal & Robert M. Califf, Director's Blog: the latest from USPTO leadership (July 6, 2022), https://www.uspto.gov/blog/director/entry/the-biden-administration-is-acting#:~:text=The%20USPTO%20and%20the%20FDA%20will%20further%20collaborate%20to%20develop,outreach%20events%20and%20listening%20sessions.

("The USPTO and the FDA will further collaborate to develop policies aimed at protecting and promoting U.S. innovation while advancing competition that can lower drug prices for all Americans.").

of them catalyzed by the Covid-19 pandemic, have further disrupted the traditionally fragmented and sequential role of individual institutions in drug innovation. The Covid-19 pandemic spurred the emergence of multi-institutional collaborations catalyzed around the common problem of preventing the spread of Covid-19 worldwide. The next section delves in detail into one case study of a multi-institutional collaboration that most closely resembles an existing polycentric model: the COVID-19 ACTIV Consortium.

2. Emerging Polycentricity: The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Consortium

The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership was one of the most ambitious multi-institutional initiatives, both in scope and membership, to emerge from the COVID-19 pandemic.[191]

ACTIV was formed in April 2020, with the NIH, CDC, FDA, and Biomedical Advanced Research and Development Authority (BARDA) all participating, along with other U.S. government agencies such as the

[191] We highlight ACTIV as the case study, here, and not OWS, because ACTIV is a better illustration of networked connections across public and private divides, with a focus on making information widely accessible. OWS, which ultimately replaced ACTIV, was a well-funded, centralized operation based largely on bilateral, secret contracts with pharmaceutical companies, making it a less promising model for wider adaptation. Moncef Slaoui & Matthew Hepburn, *Developing Safe and Effective Covid Vaccines — Operation Warp Speed's Strategy and Approach*, 383 NEW ENG. J. MED., 1701 (2020).

https://www.nih.gov/research-training/medical-research-initiatives/activ. Francis S. Collins & Paul Stoffels, *Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) An Unprecedented Partnership for Unprecedented Times*, 323 JAMA 2455 (2020).

Department of Defense (DOD) and Department of Veterans Affairs (VA).[192] Because of the global nature of the pandemic, the European Medicines Agency (EMA) also participated, as did representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies.[193] ACTIV's stated goal was to "develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines" for Covid-19.[194] In the words of ACTIV's founders, "there was no true overarching national process in either the public or private sector to prioritize candidate therapeutic agents or vaccines, and no efforts were underway to develop a clear inventory of clinical trial capacity that could be brought to bear on this public health emergency."[195]

Rather than act solely as a funding entity, in ACTIV, the NIH also played a scaffolding role: helping to identify coordination gaps and providing needed infrastructure to center collaboration across multiple players. The ACTIV initiative identified three gaps in the global vaccine and therapeutics response to COVID-19: (1) defining adequate surrogate and clinical endpoints; (2) comparing the efficacy of vaccines across clinical trials; and (3) coordinating the global response.[196] Rather than reflect COVID-19-specific

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[192] ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV), https://www.nih.gov/research-training/medical-research-initiatives/activ (last accessed Aug. 16, 2023).

[193] *Id.*

[194] *Id.*; *see also* Bhaven N. Sampat & Kenneth C. Shadlen, *The COVID-19 Innovation System*, Health Affairs (2021).

[195] *Id.*

[196] Lawrence Corey, John R. Mascola, Anthony Fauci & Francis Collins, *A Strategic Approach to COVID-19 Vaccine R&D*, Science (2020).

issues, these gaps reflect long-standing concerns with drug development more broadly, concerns that we explored at length in Parts II and III. What is particularly remarkable about the ACTIV initiative is that it developed targeted solutions to these long-standing gaps–solutions that emerged from a process of debate and consensus-building across multiple stakeholders. This process was polycentric in nature and provides a blueprint that, we argue, should be replicated in other drug-development contexts.

As we explored in Parts II and III, the use of surrogate trial endpoints stands at the center of a yet-unsettled debate at the FDA. This debate pits those who celebrate the use of surrogate endpoints as a tool to decrease drug approval costs (therefore increasing approval speed and access to drugs), against those who criticize recent approvals of potentially ineffective and harmful drugs based on surrogate endpoints. The second gap, comparing the efficacy of vaccines across different vaccine trials, similarly reflects concerns that go beyond the development of COVID-19 vaccines and therapeutics. Indeed, one of the key critiques of the proliferation of me-too drugs to treat the same disease is that there is at present no incentive for pharmaceutical companies to sponsor trials that help determine their comparative effectiveness. Finally, although the need for global coordination may not be necessary for all drugs, it is an increasingly crucial element in the development of drugs for infectious diseases.

In response to these three gaps, the ACTIV consortium arrived at four interlocking solutions. The first was the creation of a public/private forum to house collaboration. The explicit role of the ACTIV consortium was to bring together multiple actors focused on discussion and consensus seeking.

The three remaining solutions emerged from agreement among forum members. In addition to creating a public/private space, ACTIV introduced three additional innovations in clinical trial design: (1) harmonized master protocols, (2) harmonized testing, and (3) harmonized monitoring. In the context of ACTIV, harmonization meant not that every clinical trial used the same exact protocols, but that clinical trials were designed with an eye toward allowing easy comparisons across trials, and generating public trust in the outcome of these comparisons. More broadly, harmonization makes it easier (and therefore more efficient) to compare different drugs in the same disease category and to validate surrogate endpoints.

In practice, achieving these harmonization goals required, first, early collaboration and agreement on trial components such as sample size, clinical sampling design (including diversity, equity and inclusion considerations),[197] and surrogate endpoints. Second, willingness on the part of trial sponsors to share samples across clinical trials–something that ACTIV achieved through the creation of clinical trial networks.[198] Third–and arguably ACTIV's central

[197] *See, e.g.,* Vivek Murthy, et al., *Participation in Cancer Clinical Trials: Race-, Sex- and Age-Based Disparities,* JAMA (2004) (finding lower enrollment fractions in clinical trials for minorities (black and latinx) when compared to white trial participants, a gap which *widened* in the 2000-2002 study period); Versavel et al., *Diversity, equity, and inclusion in clinical trials: A practical guide from the perspective of a trial sponsor*, 126 Comtemp. Clin. Trials (2023); Igwe et al, *Opportunities to Increase Science of Diversity and Inclusion in Clinical Trials: Equity and the Lack of a Control*, J. Am. Heart Assoc. (2023) (showing that "participants enrolled in clinical trials still do not accurately represent the racial and ethnic composition of patients nationally or globally");

[198] Nat'l Inst. Health, Virtual Biorepository for Researchers, ACTIV (July 25, 2023), https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-

innovation–the operation of government-supported central laboratories and independent biostatisticians "as key resources for efficacy trials, thereby providing a standardized way to assess the relative immune responses of different types of vaccines."[199]

ACTIV's creation of publicly available data repositories and infrastructure for data-sharing, as well as its codification of tacit knowledge, are likely to have social spillover effects (in the form of best practices for future therapeutic candidate selection processes and clinical trials) that extend well into the future and greatly outweigh the NIH's initial investment.[200] As such, it represents a promising example of NIH involvement in innovation beyond basic research funding.

ACTIV's structure reflects polycentricity in action. First, it brings together multiple and diverse types of organizations from the public and private realms. The public organizations involved, NIH, FDA, CDC, BARDA, and EMA, all have overlapping mandates along multiple dimensions. For example, EMA and FDA overlap fully in their substantive mandates (drug regulation and approvals) but occupy different jurisdictional niches (the U.S. and European markets, respectively). The remaining organizations, NIH, BARDA and CDC all interact with the drug development process, although their core expertises reside at different points in a drug's lifecycle, with the NIH focusing more heavily on early stage research, BARDA on developing manufacturing and procurement capacity, and the CDC on

therapeutics-prioritized-testing-clinical-trials#virtual-biorepository.

[199] Lawrence Corey et al., *A Strategic Approach to COVID-19 Vaccine R&D*, 368 SCIENCE 948, 950 (2020).

[200] Laura G. Pedraza-Fariña, *Covid-19 and Boundary-Crossing Collaboration* (draft on file with authors).

epidemiological surveillance. Crucially, through ACTIV, these overlapping decision-making centers interact with private actors and NGOs to form a polycentric governance system: a collection of autonomous, yet overlapping, decision-making centers that enter into stable cooperative agreements to share information and resources with each other and with supporting actors with relevant expertise, and that are able to resolve conflicts arising from their overlapping mandates.

The creation of clinical trial networks, agreements to share samples across clinical trials, and the use of independent laboratories and biostatisticians to collate and analyze clinical trial data are all examples of collaborative arrangements that maximize the efficiency of each overlapping unit, while being nimble enough to respond to changing circumstances.

In the next and final Part, we bring together insights from our case studies and polycentric design principles to sketch a polycentric solution that, rather than seek to eliminate fragmentation, capitalizes on its benefits while proposing flexible structures to foster collaborative decision-making.

IV. SOLUTIONS: OPTIMIZING COLLABORATIVE DECISION-MAKING IN A POLYCENTRIC ECOSYSTEM

The current fragmented innovation ecosystem, with its checks and balances, has the potential to prevent harm by fostering creative experimentation with diverse solutions to the incremental innovation problem. Institutional fragmentation can also avoid the type of regulatory capture that plagues centralized governance regimes. But fragmentation's two key drawbacks–information siloing and inefficient coordination around shared goals–have hamstrung individual institutional efforts to foster socially

desirable, breakthrough innovation, where market signals are inadequate.[201] More importantly, in a fragmented system, individual institutional efforts to address incrementalism, no matter how creative, cannot scale up to systemic solutions. As we illustrated in Part III with the example of FDA's accelerated approval pathway, isolated institutional solutions can also have unintended consequences that paradoxically increase *ex ante* uncertainty and risk for innovators. As a result, we see too many high-priced drugs of limited social utility and too few socially desirable but less profitable drugs.

Scholars have started to explore how an institution-focused approach could address the social welfare/innovation mismatch. But addressing the problems wrought by fragmentation and complexity has remained elusive. We explore proposals by existing scholars before turning to our proposed polycentric model.

A. Emerging But Incomplete Institutional Perspectives

Innovation scholars have begun to focus on how institutional contexts influence innovation outcomes. The bulk of these studies, however, tend to focus either on single institutional players or on agency dyads, such as the FDA and CMS, or the FDA and the PTO. For example, Rachel Sachs has studied the relationship between FDA and insurance companies, arguing that delinking CMS reimbursement decisions from FDA

[201] *See* Rachel E. Sachs, *Administering Health Innovation*, 39 Cardozo L. Rev. 1991 (2018) (suggesting that agencies acting together could achieve better social value.)

approval can promote socially valuable innovation, including more information about comparative effectiveness and the long term effects of drugs.[202] Rebecca Eisenberg has long emphasized the FDA's often neglected role in promoting investment in drug trials and fostering the creation of information about drugs.[203] Rebecca Eisenberg and Nicholson Price have also studied what they call "demand side" innovation – emphasizing health insurers' potential to produce new knowledge about the provision and effects of healthcare through access to healthcare records.[204] Focusing on the interaction between the PTO and the FDA, Arti Rai and Nicholson Price argue for more coordination[205] and Sean Tu argues that closer cooperation, including by granting PTO access to information acquired by FDA in the drug approval process, can lead to better patentability decisions.[206] David Simon proposes closer collaboration between CMS and FDA to evaluate evidence to support off-label drug uses.[207]

A few analyses take a broader view. Tackling our "entirely piece-meal" innovation ecosystem, Stuart Benjamin and Arti Rai propose the creation of an Executive Agency, the Office of Innovation Policy—an

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[202] *See* Sachs, supra note –; see also Sachs, supra note – (discussing the possibility of wider agency collaboration).

[203] Eisenberg, *supra* note 15.

[204] Rebecca Eisenberg & Nicholson Price, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & Bioethics 3 (2017), doi:10.1093/jlb/lsw062.

[205] Arti Rai & Nicholson Price, *An administrative fix for manufacturing process patent thickets*, 39 Nature Biotechnology 20 (2021), https://doi.org/10.1038/s41587-020-00780-9.

[206] Tu, *supra* note 28.

[207] David Simon, *Off Label Speech*, 72 Emory L.J 549 (2023); *see also* David Simon, *Off Label Innovation*, 56 Georgia L. Rev. 701 (2022).

entity focused entirely on evaluating regulation's effect on the direction and volume of technological innovation.[208] Benjamin and Rai focus more broadly on the impact of regulation on technological innovation writ large rather than squarely on innovation in the healthcare space, as we do, but their overall project is concerned with the problem of institutional fragmentation. We share their concerns with our fragmented innovation ecosystem, including their emphasis on its particular pathologies, such as short-termism, conflicting institutional priorities, and siloed decision-making.[209] Our proposal differs from theirs, however, both in its theoretical grounding and in its scope. Our proposal eschews the creation of a new coordinating agency in favor of a polycentric model, which maintains fragmentation's key upsides discussed below.

Rachel Sachs also acknowledges the potential for collaboration among the key innovation institutions, focusing mostly on the agencies.[210] She proposes that HHS could facilitate interagency collaboration either by creating a position of Chief Innovation Officer or by requiring each agency to set collaboration priorities and report on progress towards achieving those priorities. She also suggests that the executive branch could serve a coordination role, perhaps through the Office of Information and Regulatory Affairs (OIRA), or that Congress could get involved. We agree with the general focus on the need for collaboration and the

[208] Benjamin & Rai *supra* note 156; *see also* Tejas N. Narechania, *Patent Conflicts*, 103 Geo. L.J. 1483, 1526 (2015) (suggesting both a hierarchical model where a new entity would coordinate between agencies or "an administrative interface for interagency dialogue.").

[209] *Id.*

[210] Rachel E. Sachs, *Administering Health Innovation*, 39 Cardozo L. Rev. 1991, 2044-2045 (2018).

promise of procedural options to support collaboration. But we are skeptical of the promise in hierarchical approaches, as we explore further below.

Finally, at a theoretical level, Brett Frischmann, Michael Madison and Katherine Strandburg have developed a novel lens to understand innovation systems: their commons approach develops a methodology to study how multiple nestled actors and incentive structures interact with each other to produce new knowledge.[211] Polycentric governance theory, which we introduce in Part III, is a close relative of theories of the commons. The key difference between these two approaches is that polycentric governance theory squarely focuses on relationships between institutions and emphasizes the role of law, government, and regulation. In contrast, commons theory takes a bottom-up approach that seeks to understand the emergence of arrangements (public or private, mediated by either law or informal norms) to share information resources. In the context of our drug innovation ecosystem, polycentricity is a better theoretical fit to describe emerging patterns of institutional cooperation that can be marshaled to improve upon incipient collaborative decision-making.

Indeed, there are several problems that a new model designed to prompt upper right quadrant innovation would need to address. As the prior sections have highlighted, the fragmented innovation ecosystem is rife with uncertainty and inefficiency. Innovators designing socially beneficial but novel treatments must navigate various required, usually sequential, approvals. Innovators may be left

[211] Michael Madison, Brett Frischmann & Katherine Strandburg, *Constructing Commons in the Cultural Environment*, 95 Cornell L. Rev. 657 (2009).

wondering how they can adequately test treatments on small patient populations, what to do when primary outcome measures on disease modification are hard or time-inefficient to track, and whether private insurers and CMS will agree to cover a drug or a treatment with a high price tag. This uncertainty often prompts drug companies to focus on the surer (and quicker) profits that come from incremental innovation. At the same time, centralized solutions risk losing the checks and balances that the current system of autonomous decision-makers provides.

Innovators are also underincentivized to contribute data to the benefit of science and innovation more generally, beyond clinical trial data required to gain market approval. From a social welfare perspective, data beyond that required for FDA approval can generate enormous positive externalities. Post-market approval studies, comparative efficacy research, and work to validate surrogate clinical trial endpoints can generate enormous positive externalities: helping us understand long-term efficacy and side-effects of drugs, verifying the clinical significance of surrogate endpoints, and comparing multiple drugs against each other. But they generate little private value once the FDA has cleared a product for market entry, therefore creating an ever-expanding clinical data gap.

Finally, much like the vaccine-development landscape prior to ACTIV, our current system lacks a coordinated mechanism to identify and prioritize promising drug therapies at an early stage, and marshal resources to test and bring those therapies to market.

These problems are ripe to be solved using a polycentric governance approach that brings together multiple institutions (or "decision-making centers" in the language of polycentric governance) for

coordination and conflict resolution around a shared problem. A polycentric solution mitigates those risks inherent in both fragmented *and* centralized regimes. By maintaining institutional autonomy, a polycentric approach mitigates the danger of regulatory capture that plagues centralized regimes. By creating networks of information sharing, a polycentric regime lessens opportunities for private parties to take advantage of information gaps between institutions. Polycentric coordination also preserves the bottom-up creativity of autonomous institutions while simultaneously creating communication channels across institutions to minimize unintended consequences and scale creative ideas into systemic solutions.

As Lon Fuller has said, "a polycentric problem is one that comprises a large and complicated web of interdependent relationships, so that a change in one factor produces an incalculable series of changes in other factors." Here, more than four separate innovation institutions, each with separate missions, and separate standards, are united–to a degree–by the common goal of getting effective products to market. This is why we have seen glimmers of polycentricity emerging organically. But it is not enough. This Part describes how polycentricity could be thoughtfully engineered through a new collaborative track for high-need drugs. Our proposal is more of a high-level sketch of the possibilities of such a novel track than a fully detailed blueprint–a task that would require a separate paper. Many additional details will remain to be worked out to implement this proposal in practice.

B. A New Collaborative Track for High-Needs Drugs

Where polycentricity has evolved organically, there has been a common–and often urgent–goal.

Most obviously, in the case of ACTIV, the Covid-19 emergency provided the goal and the urgency. In the other case studies, at least one of the innovation institutions was motivated to bring together others to solve an important problem. But in the larger context that this Article explores–prompting socially desirable breakthrough innovation when market signals provide insufficient incentive–polycentric governance has not occurred organically.

Polycentricity can, however, be prompted or engineered. We propose a pathway that would create a collaborative track for high-need drugs. We envision that a private party (either a laboratory investigator, a biotechnology start-up or a pharmaceutical company) would apply to be part of the new track, which would consist of a multi-institutional partnership among NIH, FDA, PTO, CMS, private insurers and potentially other players. By defining which categories of innovation are eligible to partake of the new pathway, the new framework crystalizes a common goal for institutions that all have somewhat different roles in the overall process, just as ACTIV created a common goal of getting COVID vaccines and treatments to the market. While ACTIV was COVID-specific, the model, here, would define eligibility criteria that map to incentivizing upper right quadrant innovation.

Eligibility criteria could be defined in a number of different ways. Perhaps the most appealing, consistent with the dictates of polycentricity, would require a working group of the NIH/PTO/FDA/CMS and private payers to collaborate and agree on eligibility criteria. In a smaller way, something similar was done when Congress passed the Advancing Breakthrough Therapies for Patients Act to expedite clinical development of potential "breakthrough" drugs. The Act defined a breakthrough as "treat[ing] a

serious or life-threatening condition and [where] preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."[212] The statute required the FDA to issue guidance detailing criteria for Breakthrough Therapy designation, which it subsequently did.[213]

At the basic science level, the NIH, through its Common Fund, has also created a "Transformational Science and Discovery" research track that seeks to identify novel areas of research likely to lead to scientific breakthroughs. As we elaborate further below, we propose that the NIH take on an expanded role in this novel collaborative track for high-needs drugs. This new role would capitalize on the NIH's experience in designing ACTIV and its ability–through the Common Fund– to connect researchers from many different disciplines to solve roadblocks and identify new areas of research with high impact potential.

The PTO also has the capacity to collaborate with the NIH and the FDA in identifying promising breakthrough patents. Currently, a patent grant is an on/off switch: an invention either gets a patent or is denied one. But the PTO can marshall its expertise to identify, among all granted patents, those patents that are likely to represent breakthrough innovation. In the

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[212] Frequently Asked Questions: Breakthrough Therapies, U.S. Food and Drug Admin, https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies#:~:text=A%20breakthrough%20therapy%20designation%20is,(s)%20over%20available%20therapies.

[213] FDA, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), https://www.fda.gov/media/86377/download.

language of patent law, the PTO could identify patents that clear the non-obviousness hurdle by a wide margin, or patents that fill a long-felt need in our innovation landscape. One of us has advanced a proposal, and a measure, of breakthrough patents that could serve as a rough proxy.[214] Alternatively, the PTO could open a breakthrough patent designation option that relies on individual parties' application. PTO breakthrough designation could guarantee priority consideration for the high-need drugs collaborative track, and "gold plate" breakthrough patents by providing an enhanced presumption of validity.[215]

Finally, CMS and private insurance can bring their expertise in cost/benefit analysis to the table– identifying those innovations whose social benefit is expected to largely exceed its cost of development. Bringing all of these actors together, the FDA, NIH, PTO, CMS and private insurance, would enable the identification of promising research at an early translational stage and subsequently help shepherd that research from bench to bedside.

Many scholars have also suggested definitions and criteria that might fit. For instance, Horning et al., defined qualitative criteria marked by three main eligibility categories: "1. Drugs that address conditions with poor outcomes, which may be defined by clinical or biologic subsets of disease, for which no established [Standard of Care] SoC or available concurrent control exist. . . 2. Drugs that provide substantial therapeutic improvement over existing, established SoC for conditions with poor outcomes, which may be defined by a clinical or biologic subset of disease. . . 3. Drugs that provide a substantial therapeutic index advantage

[214] [omitted]

[215] *See* Mark Lemley, Douglas Lichtman, Bhaven N. Sampat, *What to Do about Bad Patents?*, 28 Regulation, 10 (2005).

over a SoC with well characterized efficacy and safety in a similarly defined population . . . ."[216]

Once a drug is deemed to qualify for the collaborative track, what would that mean? Perhaps most importantly, innovators whose projects fall within the scope of the collaborative track would get the advantage of a working group comprised of representatives from all relevant innovation institutions (NIH, PTO, FDA, CMS, and private insurers). The primary purpose of this working group would be to address uncertainty, jointly problem-solve, and provide feedback from various stakeholders when feedback can still influence the approach. The group would be able to address *ex ante* those areas where the interests of private actors acting alone do not align with public welfare. Below, we elaborate on specific areas of high-needs drug development that could particularly benefit from such a collaborative approach.

Innovators would benefit from working with the NIH, FDA, and CMS on designing their clinical trials. While CMS would not ordinarily be involved in that process, the data that the trials generate will need to later be used to satisfy the "reasonable and necessary" standard. In recent examples, CMS determined that drugs that passed FDA screens didn't pass CMS screens. As such, getting CMS feedback on trial design so that trials produce the data that CMS will later need for approval, is important. Similarly, private insurers have created a reimbursement minefield for many patients with rare diseases. Recall the fractured reimbursement landscape for Duchenne Muscular Dystrophy discussed above: disagreements about whether a

[216] Sandra J. Horning et al., *Developing standards for breakthrough therapy designation in oncology*, 19 Clin Cancer Res.4297 (2013), doi: 10.1158/1078-0432.CCR-13-0523.

surrogate endpoint is adequate, or whether clinical data is sufficient to warrant coverage of particular subpopulations has denied many patients access to potentially life-saving drugs. Ex ante, nuanced conversations about clinical trial design–including the use of surrogate endpoints, sample sizes, sample composition (including whether it equitably represents the affected population), and additional testing for sub-populations with the disease–could reduce risk and uncertainty while closing the clinical data gap by creating valuable data for patients, prescribers, and future innovators.

In addition, consider that usually a manufacturer doesn't engage with CMS or insurers until after the drug has already been patented and received FDA approval. But concerns over reimbursement could easily deter manufacturers from pursuing the development of a particular product. The risk that reimbursement at a satisfactory level may ultimately be denied can deter researchers from even starting down the long and expensive path required to get there. A collaborative pathway would permit CMS to be involved at an earlier stage, so that payment hurdles could be timely anticipated and resolved. The Alzheimers drug Aduhelm, which the FDA approved but then CMS refused to cover, tells a cautionary tale. If CMS had advised earlier in the process that it would not greenlight coverage on the basis of surrogate endpoint data, Biogen may have made different decisions at the clinical trial stage.

Beyond designing clinical trials, the new collaborative track for high-need drugs could also provide needed infrastructure to enable data-sharing and data harmonization. Such data can be used in future research, for example, to evaluate the comparative efficacy of multiple drugs that treat the

same disease. Although pharmaceutical companies may be hesitant to freely share clinical trial data, we can envision a number of work-arounds. First, this type of data sharing would not be unprecedented: the ACTIV consortium built precisely the same type of infrastructure. Second, there are mechanisms to make this type of data semi-private: allowing independent government laboratories to carry out comparative effectiveness analysis without releasing raw data to the broader public. Capitalizing and expanding upon its experience in the ACTIV consortium, the NIH should step in to provide such infrastructure. More specifically, the NIH could replicate its key role in the ACTIV consortium through the operation of government-supported central laboratories and independent biostatisticians to provide independent validation of clinical trial results and carry out comparative effectiveness analysis.

Perhaps more controversially, the NIH could also provide targeted R&D funds to complement private investments. These additional R&D funds could be conditioned on, for example, making clinical trial data freely available, or agreeing to insurance reimbursement schemes that make the drug more broadly accessible. Supplemental R&D funding may be particularly crucial to incentivize the validation of surrogate endpoints–for which there is currently little incentive. Alternatively, because validating a surrogate endpoint has welfare benefits that extend beyond any specific drug, collaborative track members may decide to validate surrogate endpoints in government-funded laboratories, thereafter making this data freely available to other drug makers working on the same disease. Indeed, public subsidies have already played a critical role in the validation of surrogate endpoints. For example, the Framingham Heart Study–a

publicly-run clinical trial spanning many decades–was crucial in validating blood pressure or LDL (low-density lipoprotein) cholesterol as surrogate markers for heart failure. This finding enabled the development and marketing of many life-saving heart medications.[217]

A related benefit of bringing all innovation institutions together is the possibility for parallel review and getting drugs to market faster. While some steps need to be sequential, for instance the FDA needs clinical trial data to determine whether or not to approve a drug, CMS's review could happen concurrently with the FDA's.

The collaborative nature of this model and the expectation that it will expedite products to market, opens it up for criticism. When it was revealed that the FDA was intimately involved in the design of Aduhelm's clinical trials and in shepherding its application for approval, scholars and policymakers worried about objectivity or capture. An investigation suggests that the FDA was unduly influenced by pressure from industry and patients' groups to approve a drug it should not have. But involving all innovation institutions in one collaborative process means that the FDA would not be out on an island with Biogen. The opportunity to coordinate and resolve conflicts lessens the possibility that one institution will fall prey to capture without backup.

Expedited pathways have also been subject to criticism, particularly in concerns that thorough enough testing could not have been conducted prior to approval. The collaborative model, however,

[217] *See*, Eric Burdish, Benjamin Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044 (2015).

contemplates that the working group would stay in place as a monitor through the post-market study phase. Indeed, as suggested above, the NIH could stay involved to advise and even provide funding for required post-market studies. Many Phase 4 trials don't currently get completed, and the FDA has been criticized for oversight failure. In general, the collaborative track could ensure continuing post-market collaboration.

An ideal model is one that would (1) identify high-need areas, (2) fund research in those areas, (3) produce the data necessary to satisfy the differing standards of all individual innovation institutions, and (4) provide an efficient pathway to approval to get treatments to vulnerable populations that need them. The ACTIV experience illustrates the potential that a new, collaborative track could have to both incentivize and expedite innovation, while still maintaining safeguards to protect from harm. (Figure 5)

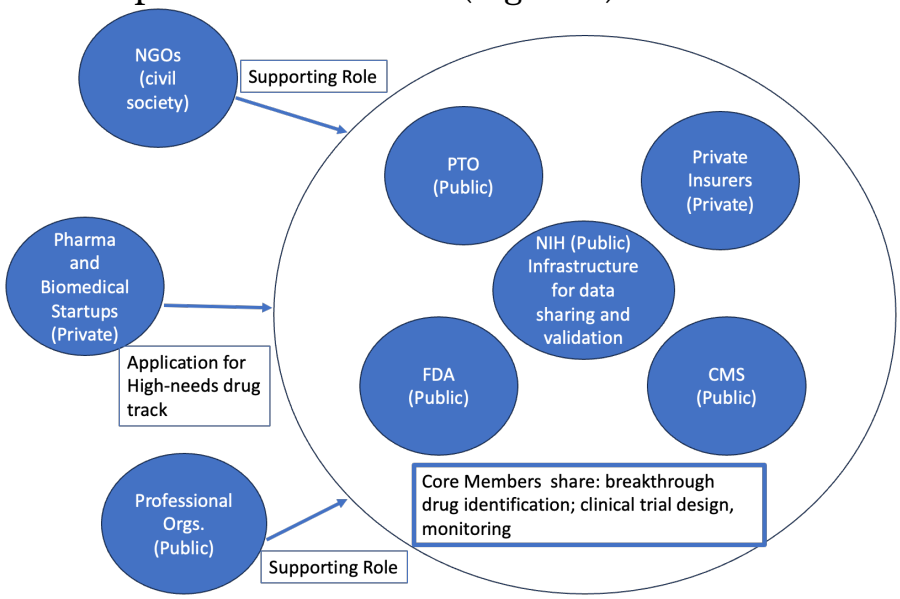

Figure 5 *Polycentric Drug Innovation*

5. CONCLUSION

Innovation in drug development has been the subject of intense academic and public scrutiny. As drug prices continue to rise and drug makers over-focus on me-too drugs, investment in therapies for high social burden diseases lags. Two institutional features of our healthcare ecosystem–complexity and fragmentation–have emerged as largely responsible for our drug innovation crisis. In this Article, we provided a novel perspective on these twin problems, grounded in polycentric governance theory. Polycentricity, in contrast to traditional analyses of innovation, is well suited for understanding complex systems with multiple interacting parts, such as the drug innovation ecosystem.

Traditional analyses of innovation, we argued, are incomplete: they tend to focus on understanding how individual policy levers, such as patents, regulatory exclusivities, or reimbursement schemes, influence the pace and direction of innovation but neglect the institutional contexts where these levers operate. In contrast, a new wave of legal scholarship on innovation has begun to analyze the problem from an institutional lens: focusing on understanding–and addressing–how specific institutions in the healthcare system use policy levers to influence drug development. We situate our contribution squarely within this emerging body of scholarship. But in contrast to prevailing institutional views that see centralization–either through the creation of a new innovation agency or through giving more power to existing agencies–as a cure for fragmentation, we build upon polycentric governance theory to develop a proposal that harnesses the benefits of fragmentation

while minimizing its downsides.

We made three key contributions to the literature. First, we synthesized how individual policy levers work within the institutional contexts of the NIH, PTO, FDA, CMS, and private insurance. Individual institutions, most notably the FDA, have used policy levers to encourage private investment in high private risk/high social need areas. These individual institutional efforts to increase breakthrough innovation and decrease incrementalism, however, have fallen short precisely due to a lack of coordination among these institutional players.

Second, we introduced polycentric governance theory as a novel approach to harness fragmentation's upside (its flexibility) while managing its downside (the inability to individual players to coordinate their actions towards a shared goal). We argued that core principles of polycentricity–(i) multiple, overlapping decision-making centers with some degree of autonomy; (ii) choosing to act in ways that take account of others through processes of cooperation, competition, conflict, and conflict resolution–help describe and understand the emergence of islands of collaboration in healthcare innovation. We describe some collaborative initiatives in depth, including the "Accelerating COVID-19 Therapeutic Interventions and Vaccines" (ACTIV) initiative, as representing polycentricity in action, and as blueprints for our normative proposal: a new collaborative track for high-need drugs.

Third, we apply principles of polycentric governance to engineer a new collaborative track for high need drugs. Modeled upon ACTIV's multi-institutional collaboration, this novel proposal brings together the NIH, PTO, FDA, CMS and private

insurers, with the NIH serving a novel, and key, scaffolding role. Our core insight is that pooling this institutional expertise early in the process of drug development can address ex ante those areas where the interests of private actors acting alone do not align with public welfare. A collaborative track that brings together institutions with their own independent mandates, agendas, and ways of framing innovation problems harnesses the benefits of fragmentation. In other words, building a scaffold for collaboration– rather than creating a new centralized institution– allows each institution to experiment with different approaches to solve common problems, and learn from each others' experience through processes of information sharing, while simultaneously minimizing the risk of capture.

Getting innovation right is one of the most important issues of our time. It is time to experiment with a new solution to this well-documented problem.