AUTHORIZING BESPOKE THERAPIES

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ABSTRACT

Novel medical treatments that skip or mask genetic mutations are capable of solving previously incurable ailments. Genetic mutations are individually rare but collectively common, affecting 30 million individuals in the US alone.[2] *Genetic interventions provide treatments that save lives, particularly those of children. These interventions are developed for as few as one patient, earning the moniker "N-of-1 precision medicine."*

Such ultra-individualized treatments pose challenges for the existing system of 1) premarket regulation, 2) pharmaceutical incentives, and 3) tort compensation. First, the goals of N-of-1 precision medicine create legitimate concerns over whether precision medicine constitutes drug development, over which the FDA has authority, or the "practice of medicine," over which it does not. Moreover, the onerous and slow premarket approval process conflicts with the emergency circumstances in which N-of-1 treatments are currently used. Second, N-of-1 precision medicine treatments target too few individuals to justify the cost of drug development under the traditional patent system. Finally, patients seeking tort compensation for injuries caused by such treatments face significant hurdles for both products liability and medical malpractice claims.

On top of these challenges, the structure of N-of-1 precision medicine creates a further complication. Each N-of-1 precision treatment uses shared modalities to deliver individualized treatments; this means that information created in one treatment's development can benefit the development of another treatment. This unique feature both creates the potential for information-sharing that can reduce development costs and simultaneously undermines incentives to do so. Addressing this shared modality feature holds the key to regulating N-of-1 precision medicine.

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[2] Grace Yang, et al., *The National Economic Burden of Rare Disease in the United States in 2019*, ORPHANET J. OF RARE DISEASES 163, 163, 167 (2022).

Given the promise of N-of-1 precision medicine treatments and their uneasy fit within the existing framework for population-based drugs, this Article proposes a new paradigm. Drawing from the platform economics literature, the Article reframes the interconnected nature of N-of-1 precision therapies as a positive network externality, which can be well-managed in a multi-sided platform system. Onerous ex-ante premarket approval would be replaced by standards-based good practice review of pre-registration designs, similar to the regulatory structure currently governing laboratories. Rather than relying on the patent system to create incentives to create, laboratories would be paid for sharing data from pre-registered studies. Data sharing potentially reduces costs of development and helps insurance markets price the risk of covering such treatments. Finally, the gaps left by products liability and medical malpractice claims would be filled by monitoring the pre-registered designs. N-of-1 precision medicine can cure illnesses that previously constituted death sentences, extending lifespans and improving quality of life. This potentiality, however, will never scale without the legal infrastructure to facilitate development and ensure quality care.

Table of Contents

INTRODUCTION

Batten's Disease is a fatal genetic disorder. The gene mutation causes waste to build up in brain cells; patients with Batten's Disease lose their vision and experience muscle weakness, seizures, loss of coordination, cognitive impairment, and eventually death.[3] Mila Makovec experienced symptoms starting at age 3; it was only by age 6 that she was diagnosed with Batten's Disease.[4] Her condition puzzled doctors: Batten's disease requires both parents to pass on mutated genes,[5] but Mila's testing had revealed only one mutated gene.

Upon closer examination, Dr. Timothy Yu, a physician-scientist at Boston Children's Hospital, solved the mystery—a segment of extra DNA had inserted itself into the second copy of her gene and interrupted its production of a protein that brain cells depend upon to recycle waste.

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[3] CLEVELAND CLINIC, Batten Disease, *available at* https://my.clevelandclinic.org/health/diseases/6018-batten-disease, last access (July 25, 2025).

[4] Gina Kolata, *Scientists Designed a Drug for Just One Patient. Her Name is Mila*, NEW YORK TIMES, *available at* https://www.nytimes.com/2019/10/09/health/mila-makovec-drug.html (last accessed July 25, 2025).

[5] *Id*.

Without this protein, brain cells gradually sicken and die.[6] This type of mutation is challenging to find and had been missed by her previous testing. Such DNA insertion is not uncommon in human genomes and are often associated with beneficial evolution; however, this "transposon" created an otherwise fatal disorder.[7] While Batten's disease has no known treatment, because Mila's presentation was caused by this transposon, Dr. Yu created a treatment to "mask" it.

Dr. Yu created an oligonucleotide that would effectively correct this critical mutation, restoring production of the requisite protein and rescuing her brain cells from death.[8] Yu's team was able to show that upon interaction of her cell and three candidate oligonucleotides Mila's cells reacted by retaining less waste. The preferred treatment was named after Mila: "milasen." Milasen seemed to slow Mila's decline and reduced her seizures significantly.[9] Mila's intervention took time, however, and Mila eventually passed away in 2021.[10] Her doctors hope that her story may provide a path for treating other genetic illnesses.[11]

While Mila's treatment was an exceptional medical advance born of serendipitous access to a physician-scientist, external funding, and public attention, Mila's *plight* was not uncommon. Genetic diseases account for a significant burden of human illness, predominantly in children. To date these conditions have been linked to genetic mutations in over 5,000 different genes.[12] As in Mila's case, the consequences of such genetic illnesses are grave: 30% of children with genetic illness do not survive to see their fifth birthday, and many who do survive suffer from serious and debilitating impairments.[13] While individually rare, genetic diseases are collectively common, affecting 30 million individuals in the US alone, with

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[6] Nancy Fliesler, S*hooting for the Moon: From Diagnosis to Custom Drug, in One Year,* ANSWERS: CHILDRENS HOSPITAL, https://answers.childrenshospital.org/milasen-batten-disease/ (last accessed January 21, 2026).
[7] CLEVELAND CLINIC, *supra* note _.
[8] Kolata, *supra* note _.
[9] Kolata, *supra* note _.
[10] https://answers.childrenshospital.org/milasen-batten-disease/
[11] Fliesler, *supra* note _.
[12] Kolata, *supra* note _.
[13] Christian M. Hedrich *Importance and Potential of Rare Disease Research in Pediatric Rheumatology and Beyond: Pushing Frontiers*, 7 ACR OPEN RHEUMATOL, e70138, e70138 (2025).

an estimated economic cost of $1T.[14] More than 95% of these conditions do not yet have treatments.[15]

Treatments such as milasen present an exciting opportunity to treat such illnesses *at their source*—precisely targeting the underlying genetic mutation itself. These technologies are capable of reversing the effects of the genetic mutations underlying the ailments of the hundreds of millions of individuals globally. In practice, however, under current societal paradigms for incentivizing and regulating drug development, this will never occur.

N-of-1 precision medicine confounds traditional methods of 1) regulating ex-ante safety and efficacy, 2) providing manufacturer incentives to innovate, and 3) compensating patients for injuries caused by negligence.

In terms of regulation, the goals of N-of-1 precision medicine (treating one individual) deviate from population-based drug development, creating legitimate concerns over whether precision medicine constitutes drug development—which the FDA can regulate—or the "practice of medicine"—over which the FDA has no authority. Even if N-of-1 precision medicine counts as drug development, the current onerous ex-ante approval process creates significant delays in accessing such treatment. While the FDA acknowledges the interconnected nature of N-of-1 precision medicine through the shared modalities, the FDA still essentially regulates each precision medicine as its own drug—a system that did not anticipate the possibility that each individual might require their own precision medicine to be made, tested, and approved.

The patent-based system of incentivizing drug production relies on potential market size to ensure that a drug is profitable;[16] N-of-1 precision medicine treatments target as few as one individual, too few to justify the cost of drug development.

Finally, injuries caused by defective design or inappropriate implementation of a treatment traditionally have been compensated through products liability or medical malpractice suits, respectively. Both theories face

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[14] OMIM Pace of Gene Discovery Graph, *available at* https://omim.org/statistics/paceGraph, last visited April 16, 2025; Grace Yang, et al., *The National Economic Burden of Rare Disease in the United States in 2019*, ORPHANET J. OF RARE DISEASES 163, 163, 167 (2022).

[15] Global Genes: Allies in Rare Disease, https://globalgenes.org/rare-disease-facts/, last visited (January 21, 2026).

[16] Pierre Dubois, et al., *Market Size and Pharmaceutical Innovation*, 46 RAND J. OF ECONOMICS 844, 844 (2015).

obstacles in the context of N-of-1 precision medicine. For products liability, the implementation of N-of-1 precision medicine may not qualify as a "product," resembling more of a service. Even if courts consider N-of-1 precision medicine a product, the requirement of a reasonable alternative design blocks plaintiffs' cases. For medical malpractice, establishing a standard of care in individualized treatment (along with causation difficulties for patients with terminal illnesses) poses difficulties for the plaintiff's prima facie case.

On top of these tensions, the inherently interconnected nature of N-of-1 precision medicine treatments creates a further complication. Information created by one lab will be probative for labs working on related treatments. While this overlap sounds promising, as it creates the potential for information-sharing that could reduce the cost of treatment development, the same feature ensures that incentives for information production necessary for development are insufficient.

In light of these hurdles to extending the existing approach for population-based drugs to N-of-1 precision medicine, this Article proposes a new paradigm. Drawing from the platform economics literature, the Article reframes the interconnected nature of N-of-1 precision therapies as creating positive network externalities, benefits that increase as more laboratories join the network but that are not internalized by the laboratory producing the information. These positive externalities can be well-managed in a multi-sided "platform system," in which laboratories pre-register studies and share data. This platform system provides an alternate path for addressing the concerns poorly targeted by traditional regulation. The plodding premarket approval process is substituted for standards-based good practice review of pre-registered designs, similar to the regulatory structure currently governing laboratories. Replacing the patent system, laboratories are paid for sharing data from pre-registered studies. Finally, the gaps left by products liability and medical malpractice are addressed by the ex-ante standards-based review of treatment design. Precision medicine will never scale under a "one patent, one blockbuster" paradigm; this Article proposes a platform-based regulatory approach under which it can.

Part I introduces the concept of N-of-1 precision medicine and defines the differences between previous iterations of precision medicine and the ultra-individualized "N-of-1" version practiced with Mila. Part II provides an overview of the process for approving traditional population-based medicine as well as the levers for recourse for patient-related harms. Part III

enumerates the challenges that N-of-1 precision medicine creates for the traditional population-based drug approval and regulation process. Part IV applies the framework of platform economics to these challenges and proposes a platform-based solution, in which laboratories are mandated to participate and share data in order to lower development costs. Part V discusses why such a revolutionary change in regulation provides the only viable path forward for such powerful and important therapies. The promise of precision medicine is substantial but cannot be actualized without the legal infrastructure to facilitate and incentivize development and ensure quality care.

I. N-OF-1 PRECISION MEDICINE

Precision medicine has been used to define a range of medical strategies over time. The evolution of this general term culminates in treatment so individual that the treatment is developed for as few as one patient. This Article differentiates this ultra-individualized treatment from prior versions of precision medicine by denoting it "N-of-1 precision medicine." The legal infrastructure for this nascent wave of precision medicine is underdeveloped and—currently—misguided.

Early acknowledgements of personalized medicine essentially emphasized the importance of a patient's genetic profile to the success of the treatment. For example, pharmacokinetics—the process by which drugs are absorbed into the body, distributed and metabolized by enzymes, and eventually excreted—is sometimes very sensitive to a person's genetics.[17] Similarly, pharmacodynamics—the process by which a drug interacts with its target—is also genetic-specific.[18] Warfarin, a popular blood thinner, targets the VKORC1 gene and is metabolized by the CYP2C9 gene.[19] Genetic variation in both VKORC1 and CYP2C9 leads to differences in the way warfarin is absorbed and affects the target gene.[20] For this reason, the FDA recommended that an individual's phenotype be assessed before warfarin prescription in order to avoid decreased efficacy or side effects. Other similar drugs include imatinib (a tyrosine kinase inhibitor) or primaquine, an antimalarial.[21]

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[17] Laura H. Goetz and Nicholas J. Schork, *Personalized Medicine: Motivation, Challenges, and Progress*, 109 FERTILITY AND STERILITY 952, 952 (2018) ("[p]harmacokinetic activity is often under the control of a unique set of genes (drug metabolizing enzymes) that could harbor naturally-occurring genetic variants").
[18] Goetz and Schork, *supra* note _ at 954.
[19] *Id*. at 954–55.
[20] *Id*. at 954–55.
[21] *Id*. at 952.

Another example of early precision medicine is the field of immunotherapy used in cancer treatments. These immunotherapies generally work with an individual's immune system "to prime or trigger [it] to attack a cancer."[22] CAR T-cell therapy is a specialized form of immunotherapy which genetically engineer a patient's T-cells to produce proteins called chimeric antigen receptors (CARs) that latch onto cancer cells.[23] Like N-of-1 precision medicine, however, CAR-T-cell therapy was feared to be a niche treatment for a small number of patients; currently, however, CAR-T-cell therapy is standard cancer treatment.[24]

The modern wave of precision medicine goes further still. Rather than using individuals' genetic profiles to guide the use of general purpose drugs, "N-of-1 precision medicine" actually *develops* drugs tailored to the genetic profiles of individuals or for small groups of people. For instance, in cases like Mila's, interventions target a specific section of DNA to silence the effects of a particular mutation. In other cases, a precise intervention can target and actually edit the DNA code (for instance, converting an A to a G) to reverse a disease causing mutation in the cell that is suffering from its effects. The ability to directly target the source of a dysregulating process is powerful precisely because of its individualized target.

The implementation of personalized therapies involved a few modalities: antisense oligonucleotides (ASOs), short interfering RNAs (siRNAs), and CRISPR RNA and/or DNA editing.[25] ASOs are short single stranded synthetic RNA or DNA molecules, and siRNA is a double-stranded RNA nucleotide sequence, whereas CRISPR is the combination of a RNA or DNA editing enzyme with a synthetic "guide" RNA.[26] Because these modalities provide the building blocks of numerous personalized treatments, this essentially means that there are a few foundational molecules that are necessary to proceed with personalized treatments.

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[22] *Id*. at 952.

[23] *CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers*, NATIONAL CANCER INSTITUTE, (February 26, 2025), https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

[24] *Id*.

[25] Olivia Kim-McManus, et al., *A Framework for N-of-1 Trials of Individualized Gene-Targeted Therapies for Genetic Diseases*, 15 NATURE COMMUNICATIONS 9802, 9803 (2024).

[26] D. Collotta, I., Bertocchi, E. Chiapello, and M. Collino, *Antisense Oligonucleotides: A Novel Frontier in Pharmacological Strategy*, FRONTIERS IN PHARMACOLOGY (2023).

A key feature of these therapeutic modalities is that they are fundamentally *modular* in nature, constructed from a core set of nucleotide building blocks that can be flexibly rearranged to target different genes or genetic mutations.[27] This allows a therapeutic strategy to be applied to many different genetic targets for therapeutic purposes, not unlike delivering a package to different households by changing the shipping address. The shared modalities means that each developed treatment potentially provides information that can aid in development of another treatment. Despite this, even with access to these foundational modalities, a significant amount of money is needed to develop the personalized treatment.

While N-of-1 precision medicine treatment is in a nascent stage, professional organizations have sought to bring together stakeholders to discuss best practices. One such group is the N=1 Collaborative (N1C), which is an "umbrella organization to align and facilitate individualized treatment development efforts by sharing best practices and learning from successes and failures."[28] The N1C's guidelines for a general best practice for developing N-of-1 treatments provides insight into the process.

N1C separates development into three steps: 1) identifying patient illnesses amenable to the specific N-of-1 treatment,[29] 2) designing candidate modalities (such as ASOs) to impact the target,[30] 3) and manufacturing the treatment/safety testing/treatment.[31] The first step requires a physician to decide that an illness can be addressed by a specific modality (that the disease is caused by "mutations that impact splicing of an mRNA and result in aberrant or insufficient protein").[32] The specifics of this decision will depend on the genetic mutation and the modality chosen.

The second step requires a physician to then decide what of the thousands of versions of the modality are best to treat the condition. For example, there are many versions of ASOs that can intervene on a genetic mutation. Some candidates are more likely to create effects outside of the target effect

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[27] Collotta et al., *supra* note _, at 2.

[28] Annemieke Aartsma-Rus, et. al, *Consensus Guidelines for the Design and In Vitro Preclinical Efficacy Testing N-of-1 Exon Skipping Antisense Oligonucleotides*, 33 NUCLEIC ACID THERAPEUTICS 17, 18 (2023).

[29] Annemieke Aartsma-Rus, et cl. *OTS Rare Disease N-of-1+ Workshop Briefing Document* (2020), *available at* https://www.oligotherapeutics.org/wp-content/uploads/2021/07/OTS-N-of-1-Briefing-Doc_17-November-2020-FN.pdf 7

[30] *Id*. at 9.

[31] *Id*. at 13.

[32] *Id*. at 7.

(and should be accordingly eliminated) and really small chemical changes for specific ASO candidates can create big, unpredictable differences in safety and efficacy. Some of these determinations can be done with *in silico* screens (such as computer simulations), but others cannot.[33] For certain contexts, these screenings must consider more than one thousand candidate ASOs.[34] As part of the screening, safety (or inherent tolerability) of the treatment must be assessed in vitro (outside the human body). In vivo approaches in mice can also help to provide this information.

In the third step, good manufacturing practices are used to prepare the materials.[35] The guidance notes that currently, further safety studies are necessary for FDA approval of the investigational new drug (IND), though the necessary materials vary based on context. For example, treatment of very severe progressive diseases may require only "single dose escalation" rodent studies. The guidance also warns that even after treatment is started, safety should be repeatedly monitored, and the treatment may be modified.[36] These guidelines show that a lot of trial and error, medical judgment, and health care monitoring is involved in both developing and implementing N-of-1 precision medicine.

While this field is still in its nascent stage, two things become clear. First, its practice relies on a lot of choices. Even choosing the specific ASO to intervene involves up to one thousand options, each of which can have significant effects on treatment safety and efficacy. The more information a lab has on prior experience with each can increase the accuracy of treatment and reduce cost of experimentation. Second, even after treatment, N-of-1 precision medicine requires active monitoring and adjustment. These features, combined with the small number of patients targeted by each treatment, make traditional approaches to drug policy a poor fit for N-of-1 precision medicine.

II. TRADITIONAL APPROACH TO POPULATION-BASED DRUGS

Most drugs have been approved by the FDA through the traditional premarket approval process. This approval process provides evidence of generalized clinical safety and efficacy by using control groups. After the drug receives FDA approval for at least one use, it becomes commercially available for medical providers to prescribe. FDA approval grants market

[33] *Id*. at 9.
[34] *Id*. at 9.
[35] *Id*. at 13.
[36] *Id*. at 13–15.

exclusivity to the drug for a period of time before generic manufacturers are able to produce the drug at a lower price.[37] Patients who are injured by the drug—due to the defective design, warning, or manufacture—can recover from drug manufacturers through products liability suits. Patients who were improperly prescribed the drug may recover from the provider through medical malpractice. It is not a perfect system, but it is familiar.

N-of-1 precision medicine fits uneasily within this system. N-of-1 precision medicine currently does not consider generalized efficacy, and the patent system creates small economic benefits due to the small patient population. Moreover, the legal framework for products liability and medical malpractice limit the protection to patients and incentives to manufacturers that would otherwise exist for population-based medicine. This Part provides an overview of each policy lever, and Part III discusses the difficulties applying each to precision medicine.

A. Regulatory Background

In the early 1900s, federal laws did not require drug manufacturers to demonstrate evidence of either safety or efficacy. While common law doctrines regarding the liability of manufacturers of inherently dangerous products allowed consumers to recover for injuries caused by such products existed, there was no premarket approval required before drugs reached the market.

The Food, Drug, and Cosmetic Act of 1938 first required manufacturers to show the FDA evidence of safety, though not efficacy. It was not until after the thalidomide scandal that Congress required evidence of efficacy.[38] Thalidomide, a drug marketed as a sleeping pill, began to be connected to birth defects characterized by limb and bone abnormalities.[39] The scrutiny around this discovery led to Senator Estes Kefauver holding hearings regarding the "sorry state of science supporting drug effectiveness," and testimony about the "difference between well-controlled studies and the

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[37] Patent protection also provides a right to exclude other manufacturers from producing the patented elements.

[38] Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA, *available at* https://www.fda.gov/files/Promoting-Safe-and-Effective-Drugs-for-100-Years-%28download%29.pdf (last accessed June 27, 2025).

[39] Wagas Rehman, et al., *The Rise, Fall and Subsequent Triumph of Thalidomide: Lessons Learned in Drug Development.* 2 THER ADV HEMATOL. 291, 291–308 (2011).

typical drug study."[40] Based on this information, Congress passed the Kefauver-Harris Drug Amendments in 1962, which introduced the requirement to show evidence of systematic efficacy in addition to safety.[41]

Population-based drugs generally go through four phases of testing in clinical populations.[42] Phase I tests for safety in small samples and Phase II tests for efficacy in small samples. Phase III tests for both safety and efficacy over larger samples.[43] Phase IV theoretically is done after the drug is commercially introduced but is rarely used.[44]

For each of these phases, testing relies on a control group. This is true for safety but arguably even more important for proving efficacy. In an ideal drug study, patients will be randomly assigned into control and treatment groups: patients in the treatment group receive the medicine, while patients in the control group receive a placebo. The study should be "double-blind," meaning that neither the patients nor the experimenters observing the patients should know whether a patient is in the control or treatment group. The function of the control group is essential to identifying the improvement of symptoms, or the side effects, attributable to the drug.

While each phase corresponds to either safety, efficacy, or both, this Article focuses on efficacy for two reasons. First, generalizable efficacy is difficult to measure. Efficacy generally refers to an improvement in disease symptoms. The average efficacy effect is particularly difficult to identify systematically without a control group due to random fluctuations in disease symptoms over time. Indeed, individual patients can experience improvement in symptoms after receiving drugs without systematic efficacy. Such improvements may be caused by the placebo effect, in which the act of receiving the substance creates positive feelings that themselves create physical benefits.[45] A patient may also have an idiosyncratic biochemical makeup which incidentally interacts with the substance to improve health. Because of the rarity of these biochemical attributes, however, the same improvement could not be expected for another patient

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[40] Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA, *available at* https://www.fda.gov/files/Promoting-Safe-and-Effective-Drugs-for-100-Years-%28download%29.pdf (last accessed June 27, 2025).

[41] *Id*.

[42] https://www.fda.gov/media/82381/download

[43] *Id*.

[44] *Id*.

[45] Swapna Munnangi, et al. *Placebo Effect*, STATPEARLS (2025), *available at* https://www.ncbi.nlm.nih.gov/books/NBK513296/.

taking the substance. The second reason for focusing on efficacy is that non-efficacious drugs pose a more subtle danger to patients than unsafe drugs. Allowing a non-efficacious but safe drug may not seem dangerous, but it denies the patient the opportunity to be treated by a better substance. Even if no other alternative exists, since these substances are generally more costly than a placebo or sugar pill, the opportunity cost is accompanied by wasteful spending as well.

General efficacy is usually identified using rigorous research design. While the efficacy of drugs may vary by patient characteristic (such as weight, comorbidities, age, and genetics), randomly assigning patients to each group provides the average effect of the treatment. Without a control group, the efficacy of the drug can be either over- or underestimated. For example, consider a population with a rapidly degenerating condition and the use of a drug intended to slow the progression of the disease. Without a control group who receives the placebo, the drug would appear to be ineffective, as the patients in the treatment group do not appear to improve. Relative to the patients in the control group whose symptoms degenerate more rapidly, however, it becomes clear that the drug is effective. Conversely, consider a population with a condition affected by stress. The perception of being treated might itself improve a patient's condition. Without a control group to control for such a placebo effect, the efficacy of the drug would be overestimated. Randomly assigning patients to treatment-control groups means that their characteristics (which may affect the efficacy of the treatment) are unrelated to treatment status. This provides an unbiased estimate of the efficacy of a drug.

While the FDA's approach to premarket approval is necessary to identify the average population safety and efficacy effects, the process is onerous and often lasts years. Patients' access to drugs that have no FDA approval is limited, resulting in a reciprocal risk of being injured by the lack of a treatment.[46] The FDA has crafted a number of accelerated or priority approval pathways to address this issue, but the general concern about delay remains. The practice of off-label prescription—the prescription of drugs for indications, populations, or dosages for which the drug has not be approved—helps to soften the edges of this delay when a drug has already been approved for one use. Outside of that, very sick patients can apply for receive a drug while it is going through the approval process; however, the

[46] Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 700 (D.C. Cir. 2007). W. Kip Viscusi and Richard J. Zeckhauser. *Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals*, 44 THE J. OF LEGAL STUDIES S387–S422 (2015).

FDA "reserves the right, however, to deny any treatment IND request if (1) the agency believes there is no "reasonable basis" to conclude that the drug is effective; or (2) granting the request "[w]ould ... expose the patient [ ] ... to an unreasonable and significant additional risk of illness or injury."[47] Indeed, a group of patients, the "Abigail Alliance" brought suit arguing that they have a constitutional right of access to experimental drugs. The D.C. Circuit rejected this claim.[48] Accordingly, FDA delay can result in significant harm to patients through lack of access to care.

B. Pharmaceutical Manufacturer Incentives

While the FDA is tasked with ensuring that drugs that are developed meet the requisite safety and efficacy thresholds, the development of such drugs rely on pharmaceutical manufacturers undertaking these projects. While pharmaceutical manufacturers do not always initiate drug development, they often buy drug projects from smaller laboratories/companies and finish development.

In order for pharmaceutical manufacturers to pursue such projects, they must expect that the project will be profitable. The costs associated with drug development are extensive. Nine out of ten drug projects that have reached Phase I will fail in Phase I, II, or III.[49] The cost of clinical trials for each drug is also quite large. A researcher has to recruit a large enough sample in order to be able to identify the effect of a treatment, if it exists. Without a large enough sample, the study may erroneously fail to find a statistically significant effect despite the fact that it actually exists.[50] Accordingly, indications with small anticipated effect sizes will require a larger participant sample to have sufficient power to detect such small effects.[51] Moreover, studies that are anticipated to have higher variance in outcomes also need larger samples in order to properly test whether the

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[47] Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 699 (D.C. Cir. 2007)(citing 21 C.F.R. 312.34).

[48] *Id.* at 713–14.

[49] Duxin Sun, et al. *Why 90% Of Clinical Drug Development Fails And How To Improve It?* 12.7 ACTA PHARMACEUTICA SINICA B 3049, 3050 (2022).

[50] Statistical significance means that the estimated effect from an analysis is distinguishable from zero. This is a function of the effect size and the standard error associated with the estimate. Estimate error declines with sample size, so a small sample study of a drug that does work may not have a statistically significant result because the sample is too small. There are many other statistical issues (like bias) that affect the estimation of such an effect differently as well.

[51] Philip Cross, *Statistical Power: What It Is and How to Calculate it in A/B Testing*, CXL, (last visited Feb. 4, 2026), *available at* https://cxl.com/blog/statistical-power/.

estimated effect size is statistically distinguishable from zero.[52] Finally, for indications requiring long-term observation, costs increase as well. In short, the cost of clinical trials scales in the necessary number of participants and duration of observation.

Products like pharmaceuticals which represent the outcome of significant research and development are difficult to price in a "free" market. Ideally, the regulatory policy would provide both the correct 1) incentive to create such a product and 2) incentive to use such a product. The first incentive refers to the incentive of a company to create a product in light of the high fixed cost of entering the market. The second refers to the incentive to price the product in a socially optimal way. Policy that accomplishes both aims is rare.

As an example, consider the current patent system. The patent system essentially assigns an exclusive property right to a company to produce a good for a period of time. This monopoly power allows the company to charge monopoly prices,[53] which are higher than the marginal cost of producing the good. This above-cost price allows companies to have the incentive to produce the good even in the presence of large R&D costs. Unfortunately, the monopoly prices mean that too little of the good is sold in the market. People who would be willing to pay above the cost of producing the drug will not be able to buy the drug.[54] In short, patents

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[52] *Id*.

[53] Specifically, because a monopolist is a price-setter, not a price-taker, any increase in output sold negatively affects the price that it can charge. Consider 3 individuals: Amy, Billy, and Caitlin who each value the good at the following amounts: $10, $9, and $6, respectively. Assume the cost of producing the good is $3. Because the monopolist has the ability to choose price, it can price the good at $10 and sell one unit (to Amy, who is the only consumer who values the good enough to purchase it at $10), price the good at $9 and sell two units (to Amy and Billy), or price the good at $6 and sell three units (to Amy, Billy, and Caitlin). The monopolist makes a profit of $7 by setting the price at $10, a profit of $18 by setting the price at $9, and a profit of $9 by setting the price at $6. Even though selling the third unit at $6 produces nonnegative surplus to both the firm ($6–$3) and to the consumer ($6–$6), the monopolist would have to charge the same price for all three units. Because of this, the monopolist would no longer get the $18 profit from the first two units' profit, resulting in lower profits from increasing output from two to three. Because of this, the monopolist chooses to price at above-marginal cost, creating a deadweight loss.

[54] More technically, the amount of potential value created by a market is termed surplus. A transaction creates surplus when both the buyer and seller gain something from the transaction. For the consumer, this means that the price paid is less than the amount that a consumer values the good. For the producer, this means that the price paid is greater than the cost of producing the additional unit. The "optimal" level of goods sold is such that no additional units create positive surplus, the optimal quantity. Relative to this optimal

provide the correct incentive to create a good but too small of an incentive to use it.

As another example, suppose that the government decided to stop granting patents for pharmaceutical innovations; instead, the pharmaceutical market would face no governmental intervention. In cases like that, a pharmaceutical firm knows that they do not have any market power in selling their drug. Reduced to a purely competitive market, the firm would be forced to charge their marginal cost for each product. In order to have a product to sell, however, the firm would have needed to spend a lot of money in order to develop it. With costly R&D and a price equal to marginal cost, a firm would be unable to break even and would never undertake to develop such products. This intervention creates the correct incentives to use the good but not to create it.

Prominent alternatives have been suggested by legal scholars. Steve Shavell has proposed that the government provide a reward to innovators in order to incentivize costly investment in research and development.[55] Innovators would present their inventions to the government, who would offer a lump-sum reward in exchange for public ownership of the invention.[56] This intervention would address both the incentive to create (because the lump-sum reward would track the profits that could have been earned in the monopolist market) and the incentive to use (because there would be no monopoly over the invention, the product would be sold in a competitive market). The difficulty with this policy is identifying the necessary magnitude of the reward.

The United States' approach to pharmaceutical development has relied on awarding monopoly power, through the assignment of patents, to private companies who develop medical innovations. The benefit of this property-based system is that the government never has to evaluate the value of an innovation—the market determines the value through consumer demand.[57] This has also resulted in patent protection and exclusivity

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quantity, the lower quantity of goods sold in a monopolistic market is termed the "deadweight loss."

[55]Steven Shavell and Tanguy Van Ypersele, *Rewards versus Intellectual Property Rights,* 44 J. L. & ECON. 525*, 525* (2001).

[56] *Id.* at 529–30.

[57] Theoretically, insofar as precision medicine research laboratories have access to less capital and accordingly have a lower willingness to pay for studies, monopolists may be able to cater to these needs without reducing their prices for laboratories that are willing to pay (for example, pharmaceutical companies' laboratories). This "price discrimination" can naturally evolve where feasible or legal. If such differences in prices are not based on

dictating decisions about pharmaceutical development, including collusive behavior to prevent generic drug manufacturers from entering the market.[58]

Importantly, basing the decision on monopoly profits means that the size of the market is important. Exclusivity only matters if the market it large enough that monopoly profits outweigh R&D costs. This dynamic has led to Congress acknowledging the need for subsidies for firms developing drugs for rare diseases, by passing the Orphan Drug Act (ODA) in 1983, which provides pharmaceutical companies tax credits for certain clinical trials, among other things.[59]

C. Patient Recourse

While FDA premarket approval creates an ex-ante threshold of safety and efficacy for drugs, patients generally have ex-post remedies if they are injured in the course of treatment with said drugs. In many cases, patients can recover from pharmaceutical manufacturers under a products liability theory and/or medical providers under a theory of medical malpractice. This Section covers each theory of recovery in turn.

1. Products Liability

Under a theory of products liability, a consumer can sue a commercial seller or distributor for an injury occurring from a defective product. The commercial seller is defined as anyone "engaged in the business of selling or otherwise distributing products," and the consumer can recover for defects in product design, product manufacturing, or failure to warn.[60]

In the context of pharmaceuticals, products liability claims are not without difficulties. Courts have sometimes exempted from strict liability products considered "unavoidably unsafe."[61] Drugs are often lumped into this

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suspect categorizations (e.g., race, religion, sex, national origin), such price discrimination might be legal. However, in terms of feasibility, the firm must be able to prevent spillage across these markets. In this example, this means that pharmaceutical company laboratories should not be able to partner with research laboratories in order to take advantage of the lower processing fees.

[58] Eric Helland and Seth A. Seabury, *Are settlements in patent litigation collusive? Evidence from Paragraph IV challenges*. No. w22194. NATIONAL BUREAU OF ECONOMIC RESEARCH (2016).

[59] https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products

[60] Restatement (Third) of Torts: Prod. Liab. § 8 (1998).

[61] Restatement (Second) of Torts § 402A (1965).

category, particularly when they have social value but entail a "known but apparently reasonable risk."[62] Products liability can also be blunted by the learned intermediary doctrine, in which pharmaceutical companies' duty to warn consumers is limited because a learned intermediary (such as a physician) is generally prescribing the medicine.[63] The learned intermediary instead has the duty to warn, so long as the manufacturer provided sufficient information to the learned intermediary.[64]

Outside of these doctrines, suit for pharmaceutical products is viable—even for pharmaceutical products that have already obtained FDA approval. While many state suits over the negligent design of medical devices are preempted by FDA premarket approval,[65] the Food, Drug, and Cosmetic Act does not provide express preemption of products liability claims for drugs.[66]

Most design defect cases are assessed using either the risk-utility test or the consumer expectations test. The risk-utility test provides relief to consumers when "if the design defect were known at the time of manufacture, a reasonable person would conclude that the utility of the product did not outweigh the risk inherent in marketing a product designed in that manner."[67] In determining whether the risk outweighs the utility, courts use the following factors:

> (1) the product's utility to the public as a whole, (2) its utility to the individual user, (3) the likelihood that the product will cause injury, (4) the availability of a safer design, (5) the possibility of designing and manufacturing the product so that it is safer but remains functional and reasonably priced, (6) the degree of awareness of the product's potential danger that can reasonably be attributed

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[62] *Id*.

[63] *See* Restatement (Third) of Torts: Prod. Liab. § 6 (1998) cmt e (discussing the learned intermediary doctrine.")

[64] *Id*.

[65] In Reigel v. Medtronic, the Supreme Court held that the Medical Devices Act expressly preempted state law claims that would impose a requirement that are "'different from, or in addition to" the requirements imposed by federal law. § 360k(a)(1).'" Riegel v. Medtronic, Inc., 552 U.S. 312, 330 (2008).

[66] *See* Wyeth v. Levine, 555 U.S. 555 (2009).

[67] Denny v. Ford Motor Co., 87 N.Y.2d 248, 257, 662 N.E.2d 730, 735 (1995).

> to the injured user, and (7) the manufacturer's ability to spread the cost of any safety-related design changes.[68]

While products liability is considered a strict liability tort, the above test demonstrates that the standard resembles negligence. A "reasonable" design is one for which the utility outweighs the risk. Courts differ on whether a reasonable alternative design (RAD) is necessary or just helpful for the plaintiff's prima facie claim, with the Third Restatement recommending that it be required.[69]

The alternative test for design defect products liability is the consumer expectations test, which considers a design defective if "it is more dangerous than an ordinary consumer would expect when used in an intended or reasonably foreseeable manner."[70] The California Supreme Court has struck a balance between the risk-utility test and the consumer expectations test: in cases which "involve[] technical issues of feasibility, cost, practicality, risk, and benefit which are 'impossible' to avoid," the jury must use the risk-utility test instead of the consumer expectations test.[71]

2. Medical Malpractice

Another theory for patient recovery is through medical malpractice, asserting that the medical provider prescribing the drug breached their duty of care to the patient. The source of this claim is rooted in the patient-provider relationship and follows the structure of a negligence claim: duty, breach, actual causation and proximate causation.[72] As part of the fiduciary duty owed to the patient, the provider is supposed to "use minimally sound medical judgment and render minimally competent care in the course of the services he provides."[73] If within the course of treatment, a provider prescribes an inappropriate drug for their patient's treatment, they can be liable for medical malpractice. In order to bring a claim of medical malpractice, however, patients must establish that the provider breached the standard of care, the "minimally sound . . . judgment."[74]

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[68] *Id.*

[69] Restatement (Third) of Torts: Prod. Liab. § 2 cmt f (1998)("[A] plaintiff must prove that a reasonable alternative design would have reduced the foreseeable risks of harm. . . .").

[70] Huffman v. Electrolux Home Prods., Inc., 129 F. Supp. 3d 529, 542 (N.D. Ohio 2015) (citing *Hisrich v. Volvo Cars of N. Am., Inc.,* 226 F.3d 445, 449 (6th Cir.2000)).

[71] Soule v. Gen. Motors Corp., 882 P.2d 298, 308 (1994).

[72] Restatement (Third) of Torts: Medical Malpractice § 4 TD No 2 (2024) & cmt a-d.

[73] Hall v. Hilbun, 466 So. 2d 856, 866 (Miss. 1985).

[74] *Id*.

While scholars have proposed establishing the standard of care by scientific studies,[75] physician surveys,[76] or clinical practice guidelines,[77] courts have relied on expert testimony[78] and jury judgments. Moreover, in professional negligence—such as medical malpractice—custom is dispositive, in contrast to ordinary negligence where it is merely probative.[79] Because of this, a jury is asked to decide whether the type of treatment provided complied with the type of care a minimally competent provider would have provided. Failure to establish a custom creates difficulty for the plaintiff's prima facie case.

Similarly, causation can become difficult in the context of deadly illnesses. In order to establish the prima facie case, a plaintiff must prove that but for the inappropriate prescription, the patient would not have suffered harm by the preponderance of the evidence.[80] Imposing a probabilistic overlay to this burden of proof, some courts have barred plaintiffs from submitting this evidence to the jury without evidence that the plaintiff could have survived (or been unharmed) with a probability higher than 50%.[81] This is very difficult to do for plaintiffs who already have a low probability of survival.

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[75] William Meadow, *Operationalizing the Standard of Medical Care: Uses and Limitations of Epidemiology to Guide Expert Testimony in Medical Negligence Allegations*, 37 WAKE FOREST L. REV. 675, 675 (2002).

[76] Tim Cramm, Arthur J. Hartz & Michael D. Green, *Ascertaining Customary Care in Malpractice Cases: Asking Those Who Know*, 37 WAKE FOREST L. REV. 699, 726 (2002).

[77] Michelle M. Mello, *Of Swords and Shields: The Role of Clinical Practice Guidelines in Medical Malpractice Litigation*, 149 U. PA. L. REV. 645, 647(2000).

[78] Courts differ on the types of experts allowed to provide such testimony. Historically, the locality rule limited expert witnesses to physicians practicing in the same locality, under the theory that practice differed regionally and that an out-of-state expert could not accurately opine on how physicians practice in another location. States have moved away from the locality rule, instead allowing experts from other regions, often with the requirement to familiarize themselves with the resources of the particular physician. *See* e.g., Hall v. Hilbun, 466 So. 2d at 874–75 ("In view of the refinements in the physician's duty of care articulated . . . above, we hold that a qualified medical expert witness may without more express an opinion regarding the meaning and import of the duty of care . . . . Before the witness may go further, he must be familiarized with the facilities, resources, services and options available.")

[79] *See* T.J. Hooper, 60 F.2d 737, 740 (2d Cir. 1932); Johnson v. Riverdale Anesthesia Assocs., P.C., 563 S.E.2d 431, 433 (2002), *overruled by* Condra v. Atlanta Orthopaedic Grp., P.C., 681 S.E.2d 152 (2009) ("it is axiomatic that in order to establish medical malpractice, 'the evidence presented by the patient must show a violation of the degree of care and skill required of a physician. Such standard of care is that which, under similar conditions and like circumstances, is ordinarily employed by the medical profession generally.'")

[80] Elissa Philip Gentry, *Damned Causation*, 54 ARIZ. ST. L. J. 419, 426 (2022).

[81] *Id*. at 426–27.

To avoid barring these plaintiffs from suit, some courts have allowed such suits to go forward under a loss of a chance theory of recovery.[82] This theory allows the plaintiffs to recover not for the injury (indeed, its application has been largely limited to risk of death) but for the loss of the chance to survive.[83] The causation analysis is simplified, but the patient's estate recovers a proportion of wrongful death damages. In the absence of such doctrines,[84] high-risk patients have significant difficulty establishing a medical malpractice claim.

This traditional approach to premarket approval, pharmaceutical incentives, and tort compensation for population-based drugs is not without its flaws; each lever has areas where enforcement is difficult or contexts in which incentives are insufficient. The application of this traditional structure to N-of-1 precision medicine, however, is a particularly poor fit. The following section demonstrates the incompatibility of these traditional levers to N-of-1 precision medicine.

III. N-OF-1 PRECISION MEDICINE'S CHALLENGES

The small number of patients targeted by N-of-1 precision medicine creates potential issues for the traditional regulatory toolbox. In terms of premarket approval, one of the prime functions of FDA regulation—establishing population-based safety and efficacy—is not a priority for N-of-1 precision medicine. The difference in these goals creates difficulties for the FDA's current authority to regulate N-of-1 precision medicine. For pharmaceutical manufacturer incentives to develop treatments, the small market size (potentially as few as one patient) creates insufficient profits under the patent model. Finally, the individualized nature of the treatment creates difficulties for products liability and medical malpractice claims. Despite the incompatibility between individualized precision medicine and traditional levers of regulation, this Part outlines the type of oversight necessary to ensure patient safety and best practices.

A. Government Regulation and the Practice of Medicine

1. Control Groups and General Efficacy

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[82] *Id*. at 427–29.

[83] *Id*.

[84] Courts have responded a number of ways, either by adopting the loss of a chance doctrine, prohibiting suit without evidence of 51% survival, or by allowing evidence to go to the jury regardless. *Id*. at 428–29.

As noted above, the federal government establishes ex-ante standards to prove systematic safety and efficacy for population-based drugs. The reason for the need for this is that it is difficult to ascertain such systematic effects without randomized assignment (which does not happen in the free market or in medical practice). In order to collect rigorous evidence of such a systematic effect, premarket approval is necessary.

N-of-1 precision medicine complicates the identification of a causal effect. While preclinical studies provide information about the efficacy of the mechanism of action, clinical studies face a limit in the number of patients. A cross-sectional clinical trial cannot work if there is no other identically situated patient to assign to the control group. To address this lacuna, researchers can use a "crossover" design, (confusingly, also known as an N-of-1 study). Crossover studies alternate drugs with placebos for a single individual over periods of time.[85] For example, a patient may take an active drug for 2 months, have a washout period of 1 week, and receive a placebo for 2 months. These active-withdrawal periods would continue, allowing the individual patient to essentially serve as its own control group. So long as the on-off periods are randomized and double blinded,[86] this provides some confidence that the study isolates the causal effect of the drug. On the other hand, delayed effects of the treatment might complicate identifying the magnitude of the effect.[87]

While crossover designs cannot identify an average causal effect, this is a feature and not a bug of the design. In certain contexts, providers do not want to know the average treatment effect: they really want to know how an individual will experience the treatment. In such contexts—in which the average effect of a treatment is less important than the effect on a particular individual—crossover designs can be preferable alternative to such large group controlled studies.[88]

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[85] Anneliene H. Jonker, et al., *The State-Of-The-Art Of N-Of-1 Therapies And The Irdirc N-Of-1 Development Roadmap*, 24 NATURE REVIEWS DRUG DISCOVERY 40, 41 (2025). Similarly, for cost-effectiveness or comparative effectiveness research, two drugs can be alternated.

[86] RL Kravitz, et al., *Design and Implementation of N-of-1 Trials: A User's Guide*, AGENCY FOR HEALTHCARE RESEARCH AND QUALITY Publication No. 13(14)-EHC122-EF 1 (2014).

[87] Kravitz et al., *supra* note _, at 3 ("For practical reasons, treatments to be assessed in n-of-1 trials should have relatively rapid onset and washout").

[88] RD Mirza, S Punja, S. Vohra, and G Guyatt, *The History and Development of N-of-1 Trials*, 110 J. ROYAL SOCIETY OF MEDICINE 330, 331 (2017).

Currently, N-of-1 precision medicine does not use a crossover design.[89] Rather than leverage the activation and withdrawal periods to uncover a causal relationship between the treatment and patient improvements, the method merely compares the "before" period outcomes to those associated with the "after" period.[90] While this is appropriate to document the patient's health status, it is impossible to identify whether the treatment is the *cause* of the symptom improvement.

This is not to suggest that N-of-1 precision medicine treatments have no evidence of safety and effectiveness. Drawing on information about the mechanism of the disease, researchers expect that the treatment design would take roughly 6 months, followed by 6 months of proof-of-concept efficacy studies.[91] These studies are not for clinical outcomes, but for the mechanism of action. For example, in Mila's case, proof-of-concept studies established that when inserted into the cell, the drug reduced the number of lysosomes and waste spilling into the cell.[92] After the product is manufactured, researchers anticipate six months for safety studies.[93] However, these safety and efficacy studies are a far cry from the type of clinical trials performed for population-based drugs.

The reason for this change in study is in part practical and in part theoretical. Practically, most clinical trials require some threshold of "clinically meaningful change" that can classify patients into "responders" and "non-responders."[94] For individualized precision medicine, there are too few patients to establish such threshold (and individual observations will likely deviate from any average).

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[89] Anneliene H. Jonker, et al., *The State-Of-The-Art Of N-Of-1 Therapies And The Irdirc N-Of-1 Development Roadmap*, 24 NATURE REVIEWS DRUG DISCOVERY 40, 42 (2025). Indeed, similar obstacles exist for surgical procedures, which do not require premarket authorization. While the efficacy of these procedures is of the utmost importance, the individualized nature of each procedure makes controlled study difficult. The quality of such procedures is instead governed by medical malpractice. *See* Jonathan J. Darrow, *Explaining the Absence of Surgical Procedure Regulation*, 27 CORNELL J. OF L. & PUB. POL'Y 189 (2017).

[90] *Id*.

[91] Anneliene H. Jonker, et al., *The State-Of-The-Art Of N-Of-1 Therapies And The Irdirc N-Of-1 Development Roadmap*, 24 NATURE REVIEWS DRUG DISCOVERY 40, 42 (2025).

[92] Nancy Fliesler, *Shooting for the Moon: From Diagnosis to Custom Drug, in One Year*, BOSTON CHILDREN'S HOSPITAL, (2019).

[93] Jonker, *supra* note_

[94] Olivia Kim-McManus, et al., *A Framework for N-of-1 Trials of Individualized Gene-Targeted Therapies for Genetic Diseases*, 15 NATURE COMMUNICATIONS 9802, 9803 (2024).

Researchers have also noted that the purpose of the goal of N-of-1 precision medicine is not to create generalizable information but instead to treat an individual: "individualized treatment development is being done specifically for treatment. . . the primary goal [is] the well-being of the patient."[95] The goal of controlling symptoms makes the process resemble practice of medicine rather than drug regulation.

This theoretical distinction between the goals of crossover studies and individualized precision medicine studies is pivotal. Not only does individualized personalized medicine change the ability of scientists to assure themselves of rigorous efficacy and safety, but it determines the type of regulation that the FDA can exert.

2. FDA Authority to Regulate

As currently conceived, the differences between cross-sectional clinical trials, crossover designs, and N-of-1 precision medicine trials suggests that the goal of the N-of-1 precision medicine trials is to treat the patient rather than elicit a causal treatment effect. This goal is much more akin to the practice of medicine than the development of drugs.

While the FDA looms as a salient entity in the context of healthcare provision—particularly involving the use of pharmaceuticals and devices—there are important exceptions to its authority. Namely, the FDA does not have authority to regulate the practice of medicine.[96] Other entities have filled gaps in which the FDA has not exercised authority, including common law malpractice claims (and state law) and regulation under CLIA by CMS.

The FDA itself believes that it has the authority to regulate precision medicine and has done so through a "platform" framework.[97] In 2024, the FDA issued guidance which defines "platform technology" as

> a well-understood and reproducible technology, which can include a nucleic acid sequence, molecular structure, mechanism of action, delivery method, vector, or a combination of any such technologies that the Secretary determines to be appropriate, that the sponsor

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[95] Jonker, et al., *supra* note _ at 41.
[96] FOOD AND DRUG ADMINISTRATION, *About FDA: Patient Q&A?,* November 2024, *available at* https://www.fda.gov/media/151975/download.
[97] This is not to be confused with the economic use of the term "platform," which will be proposed in Part IV.

> demonstrates (1) is incorporated in or used by a drug and is essential to the structure or function of such drug; (2) can be adapted for, incorporated into, or used by, more than one drug sharing common structural elements; and (3) facilitates the manufacture or development of more than one drug through a standardized production or manufacturing process or processes.[98]

While no suit has yet been filed to contest the FDA's authority to regulate precision medicine, the real-world examples suggest that their authority to do so might be on shaky legal ground. Even if the legal authority is possible, it is not clear that the current premarket approach to N-of-1 precision medicine is optimal.

The following sections discuss two contexts comparable to individualized precision medicine—off-label prescription and laboratory developed tests (LDTs)—in which the FDA's authority to regulate has been challenged.

a. Off-label Prescription

Off-label use refers to the prescription of a drug for populations, indications, or dosages for which the drug has not been approved. Physicians are free to prescribe off label; indeed, several standard prescriptions are not formally approved.[99] Generally, the only limitation of physician prescription is the threat of medical malpractice.[100]

The FDA has involved itself in activities related to off-label use, historically prohibiting the promotion of off-label uses of drugs by pharmaceutical companies as per se illegal misbranding.[101] This stance has faced significant legal challenges,[102] as courts have found this restriction infringe on pharmaceutical companies' commercial free speech rights. Throughout this battle, however, the FDA has continually rejected the authority to regulate

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[98] *See also* 21 U.S.C. 356k(b).

[99] Christopher M. Wittich, Christopher M. Burkle, & William L. Lanier, *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 87 MAYO CLINIC PROCEEDINGS 982, 983 (2012).

[100] Wittich et al., at 987 ("When a patient believes that he or she was harmed by an off-label use of a medication, it must be established that the prescribing physician deviated from the standard of practice.")

[101] *See* Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 BUL REV. 545 (2014); Elissa Philip, United States v. Caronia: *How True Does Truthful Have to Be*, 67 VAND. L. REV. EN BANC 157 (2014).

[102] *Id*.

the prescription of drugs for off-label purpose, classifying this as the practice of medicine.[103]

Because the drugs used for off-label purposes are FDA-approved for other purposes, the FDA does not explicitly certify either safety or efficacy of these off-label uses, having only certified the formally approved indications. Instead, the FDA sees the discretionary prescription of drugs by physicians for purposes within the scope of their expertise to be the domain of the practice of medicine rather than pharmaceutical regulation.

The FDA's experience with off-label prescription has implications for its stance on N-of-1 precision medicine. Off-label *prescription* is correctly classified as the practice of medicine because the purpose is not to create a generalizable treatment but to alleviate a patient's symptoms. The same is true for N-of-1 precision medicine, should the study design described in Section III.A.1 continue. Rather than use a crossover design, aimed at eliciting a treatment effect from an individual by using variation in treatment timing as a control group, the use of a pre/post treatment is aimed at best controlling a patient's symptoms. The goal is to alleviate one patient's illness, not create a generalizable treatment.

The fact that N-of-1 precision medicine creates information that may reduce the development cost of related N-of-1 precision medicine treatment does not distinguish it from off-label use. Off-label use often spurs similar treatment for patients found in the same position (and is spurred by other off-label use). If a physician reports that a side effect of an approved treatment may alleviate their patient's symptoms, another physician may try the same treatment with their patient. As this mimicry itself does not transform off-label prescription from the practice of medicine, neither does it for N-of-1 precision medicine.

One difference between N-of-1 precision medicine and off-label prescription is that the former may incorporate elements that have never been approved. The primary modalities used for individualized precision medicine—oligonucleotides such as antisense oligonucleotides or small interfering RNA (siRNA)—are generally previously FDA-approved.[104] The

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[103] 21 U.S.C. 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."

[104] Nucleic Acid Therapeutics: Approvals and Potential Blockbusters, *available at* https://www.biochempeg.com/article/410.html, last accessed (August 1, 2025).

customized implementation, involving additional elements to the modalities, however, often have not previously received FDA approval. Insofar as all the elements in the combination have been previously FDA-approved, this looks very similar to a treatment plan, which is governed by medical malpractice. Insofar as some of the elements have never received FDA approval for any use, however, this may warrant more oversight. As the next Section notes, however, this does not necessarily mean FDA premarket approval.

b. Laboratory Developed Tests

The FDA's authority to regulate laboratory developed tests (LDTs) has been successfully challenged. LDTs are "in vitro diagnostic products (IVDs) that are intended for clinical use and are designed, manufactured, and used within a single laboratory."[105] IVDs are devices that conduct tests outside the body, often used to test samples of blood, saliva, or tissue.

The FDA has the authority to regulate medical devices under the Medical Device Amendments of 1976 (MDA). While IVDs are considered medical devices within the context of the MDA, the FDA has historically excluded LDTs from enforcement.[106] This regulatory approach developed "as a matter of practice," due to the fact that, *inter alia*, LDTs were "intended . . .to meet the needs of a local patient population . . . . and were performed by laboratory personnel with specialized expertise; to be used and interpreted by physicians or pathologists in a single institution responsible for the patient (and who were actively involved in patient care)."[107] Over time, however, the FDA has attempted to exert more authority over LDTs.

In 2018, FDA provided guidance about the regulation of such IVDs in the context of next generation sequencing (NGS),[108] a powerful tool for precision medicine. Scholars pushed back on the notion that FDA regulation was necessary, particularly given the extant regulation of other entities like the Centers for Medicare and Medicaid Services (CMS) through the

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[105] https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests

[106] The FDA itself admits that it has "generally exercised enforcement discretion for most LDTs, meaning that the agency generally has not enforced applicable requirements with respect to most LDTs." https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests

[107] Medical Devices; Laboratory Developed Tests, 89 FR 37286-01, 37286.

[108] FDA, *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based on In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases*, (April 13, 208), *available at* https://www.fda.gov/media/99208/download.

Clinical Laboratory Improvement Amendments (CLIA).[109] Frank Luh and Yun Yen note that the FDA had previously took the position that laboratory-developed tests were not subject to the same level of FDA oversight because they were "relatively simple lab tests and generally available on limited basis."[110]

In May 2024, the FDA issued a final rule clarifying that, despite the previous enforcement discretion, LDTs were subject to the same type of regulation as other IVDs. Citing the increased risk associated with the "high-tech instrumentation and software" on which current LDTs rely and the larger reach of such devices and the fact that the tests are "often used in laboratories outside of the patient's healthcare setting and are often run in high volume," the FDA argued that regulation was necessary.[111]

This change in course was immediately subject to legal scrutiny. After the Final Rule was published in May 2024, a number of trade associations, professional societies, laboratories, and physicians filed suit contesting the validity of the rule. The plaintiffs alleged that the Final Rule violated the Administrative Procedure Act (APA) because "it is 'in excess of [FDA's] statutory jurisdiction, authority, or limitations' and is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.' "[112] The U.S. Eastern District of Texas held that the FDA's final rule did exceed its statutory authority and set aside and vacated the rule. The FDA had 60 days to file an appeal but declined to do so.[113]

While the court's determination that the FDA had exceeded its statutory authority in attempting to regulate LDTs likely had much to do with developments in administrative law, [114] the need for FDA premarket

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[109] Frank Luh and Yun Yen, *FDA Guidance For Next Generation Sequencing-Based Testing: Balancing Regulation And Innovation In Precision Medicine*, NATURE GENOMIC MEDICINE 28 (2018).

[110] *Id*.

[111] 89 at 37289.

[112] American Clinical Laboratory Association et al. v. U.S. Food and Drug Administration, Case 4:24-cv-00479-SDJ, https://www.acla.com/wp-content/uploads/2025/03/Memorandum-Opinion-and-Order.pdf (internal quotation marks and footnotes omitted).

[113] Susan Kelly, *FDA Declines to Appeal Court Order that Stopped LDT Final Rule,* MEDTECHDIVE, https://www.medtechdive.com/news/FDA-declines-appeal-lab-developed-tests-LDTs-ruling/749667/

[114] The *Chevron* doctrine, established by Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., instructed courts to defer to agency interpretation of a statute when Congress's intent is unclear or ambiguous and when the agency interpretation is reasonable, Lisa Schultz

regulation is less for N-of-1 precision medicine than LDTs even by the FDA's reasoning. Indeed, the grounds on which FDA justified its historical inaction on LDTs weigh against its premarket control of N-of-1 precision medicine: LDTs were previously in-house to a patient's healthcare setting and implemented by "laboratory personnel with specialized expertise; to be used and interpreted by physicians or pathologists in a single institution responsible for the patient (and who were actively involved in patient care)."[115]

First, as currently conceived, N-of-1 precision medicine is only practiced in the context of a patient-provider relationship. Patients taking N-of-1 treatments may have the treatments administered in-office with their physician. Patients also have consistent check-ins to monitor safety and efficacy with the treating physician. This is a far cry from even the LDT context, in which the FDA claimed the tests were used "in laboratories outside of the patient's healthcare setting devices."[116]

Second, the volume-based concerns the FDA raised with LDTs are not present with N-of-1 precision medicine. The treatments are not marketed en masse; even if a treatment is created for more than one patient, the determinations in selecting the treatment are ultra-individualized and made by an expert practitioner.

Absent FDA premarket approval, LDTs are not without oversight. Instead, the Center for Medicare and Medicaid Services (CMS) exercises oversight of LDTs through the Clinical Laboratory Improvement Amendments (CLIA). CLIA requires laboratories to meet certain standards in order to perform testing on human samples.[117] The extent of the requirements vary by the type of function the laboratory performs. If a laboratory only performs "waived tests," "simple tests with a low risk of an incorrect result," it is exempt from some CLIA requirements. If the laboratory performs more complex tests ("nonwaived"), requirements include an

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Bressman & Kevin M. Stack, *Chevron Is a Phoenix*, 74 VAND. L. REV. 465 (March 2021). Over the subsequent decades, the *Chevron* doctrine was amended by a complicated set of intermediate doctrines, until it was recently overruled by Loper Bright Enters v. Raimondo, 603 U.S. 369 (2024). In rejecting the *Chevron* doctrine, the Supreme Court held that "[c]ourts must exercise their independent judgment in deciding whether an agency has acted within its statutory authority, as the APA requires." 603 U.S. at 412

[115] 89 FR at 37286.

[116] 89 FR at 37289.

[117] https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/howobtainclicertificate.pdf

inspection along with other quality standards. CMS classifies LDTs as nonwaived tests, subjecting laboratories producing such to the full range of requirements.[118]

These legal challenges highlight not only the weaknesses in the FDA's authority to regulate N-of-1 precision medicine but the prudential concerns with such premarket approval even if legally authorized. Absent FDA premarket regulation, alternative structures such as CLIA oversight can provide a check on development of treatment without unduly obstructing access to the treatment. In light of the goals of patient treatment, rather than causal inference, the monitoring of best practices and standards balances the need for accountability with patient access.

B. Pharmaceutical Manufacturer Incentives

The incentives for pharmaceutical manufacturers to develop N-of-1 precision medicine treatments differs from those for developing population-based drugs. As noted in Section III.B, the current patent-based incentive scheme relies on pharmaceutical manufacturers anticipating sufficient monopoly profits to cover R&D costs. In the context of N-of-1 precision medicine, potential monopolist profits over as few as one individual provides a poor incentive.

On the other hand, the development costs (R&D) differ for N-of-1 treatments. Given the lack of control group or general evidence of clinical causation, clinical trials costs may be lower than those of population-based drugs. Other costs, such as licensing existing patented drugs,[119] laboratory services manipulating treatment modalities, and testing different alternatives for treatment, can still result in considerable development costs.

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https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf

119 While N-of-1 precision medicine is affected by patent protection, it does not seem to be as large of an obstacle in this field. For precision medicine, the principal modalities (such as ASOs, siRNAs, and CRISPR RNA and/or DNA editing) are no longer covered by patent protection. Laboratories, however, may patent particular uses of the modality (i.e., specific treatments) in order to preserve their intellectual property. These use protections are more incremental than the original patent protections, but each would contribute to the patent thicket. In some instances, precision medicine treatments may need to incorporate existing patented treatments. In several anecdotal cases, pharmaceutical companies may develop drugs and seek patent protection but not actually market the drug. This patent squatting is not necessarily done for malicious purposes. The drug may not be viable or cost-effective to market (or it may compete with another of the company's products). In contexts like this, both the pharmaceutical company and laboratory may benefit from a licensing agreement allowing the laboratory to use the patented medicine.

Importantly, as noted in Part I, a lot of the preclinical costs of designing N-of-1 treatment come from collecting information on the best combinations of designs, information that can be probative to the development of similar N-of-1 treatments.

One option for dealing with this mismatch between development cost and potential market to for the government to explicitly subsidize research costs for precision medicine uses. There is precedent for this even in the traditional drug context: the drug development process does not operate independently from governmental intervention. As of 2022, 40% of basic research was funded by the federal government, the lowest point it had been in the prior 69 years.[120]

The federal government has also provided additional incentives to pharmaceutical companies to supplement the incentives to create provided by the private market. The Orphan Drug Act (ODA) was passed in 1983 to provide pharmaceutical companies with financial incentives to develop drugs for small populations. Once a drug receives an orphan drug designation for an indication, a pharmaceutical company can receive tax credits for certain clinical trials, exemption from user fees, and potential market exclusivity after approval.[121] This type of intervention explicitly subsidizes the cost of clinical trials and promises increased profits through market exclusivity. Such interventions are not without their own issues. For example, Wesley Yin studied ODA filings and found that firms began to develop drugs for rare subdivisions of non-rare diseases.[122] This perverse parsing of the legislative text is not in line with policy goals and demonstrates how firms respond to incentives—though not always in intended ways. Indeed, Yin also estimates that roughly ten percent of the innovative drugs in the rare subdivisions would have been pursued even without the ODA.[123] This crowding out of private incentives is always a concern for such interventions. Relative to the rare diseases targeted by the Orphan Drug Act, defined as diseases affecting fewer than 200,000 people in the US,[124] current precision medicine can target as few as one individual patient. The government subsidy necessary to target such individuals would need to be sizable.

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[120] https://ncses.nsf.gov/pubs/nsf24332

[121] https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products

[122] Wesley Yin, *R&D Policy, Agency Costs and Innovation in Personalized Medicine*, 28 J. OF HEALTH ECON. 950, 950 (2009).

[123] *Id*.

[124] *Id*.

C. Consumer Recourse through Liability

Given the potential of mismatch between FDA authority and N-of-1 precision medicine, the ability of patients to recover for injuries sustained by ill-designed or negligently implemented treatments increases in importance. Unfortunately, current interpretations of both products liability and medical malpractice theories of recovery cast doubt on the ability of affected patients to recover under either.

1. Products Liability

As Section II.C.1 illustrates, patients can often recover for drug defects insofar as their injuries are caused by the defect. While the learned intermediary and the unavoidably dangerous product doctrines limit the ability to recover, products liability remains an important lever for patients.

Despite this, products liability is unlikely to be a major component of high N-of-1 precision medicine prices for the following reasons. First, patients will often have difficulty proving causation. Unless the injuries caused by the precision medicine treatment are distinct from the disease progression, it might be difficult to attribute injury to a products liability claim. Second, even with the "strict liability" practiced by most courts, products liability for design defect has morphed into a pseudo-negligence inquiry.[125] Accordingly, in some jurisdictions, pharmaceutical companies are only liable for "foreseeable" harms, and a "reasonable alternative design" (RAD) is required to bring suit.[126] For precision medicine, the RAD will likely be a limiting factor for most plaintiffs.

More importantly, individualized precision medicine may not qualify for products liability, depending on the scalability. Individual treatment may appear more like service than a good, and products liability excludes from its scope services. The Third Restatement of Torts Services notes that "[s]ervices, even when provided commercially, are not products . . .. Moreover, it is irrelevant that the service provided relates directly to products commercially distributed."[127] Contexts in which products and services are combined are only considered products when "either the transaction taken as a whole, or the product component thereof," satisfies

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[125] George W. Conk, Is There a Design Defect in the Restatement (Third) of Torts: Products Liability?, 109 *The Yale Law Journal* 1087, 1087 (2000).

[126] *Id*.

[127] Restatement (Third) of Torts: Prod. Liab. § 19 (1998).

the definition of product.[128] A physician implementing treatment using a genetics-based intervention may not look like "transfer[ring] ownership for use or consumption or for resale" or "provid[ing] the product to another either for use or consumption or as a preliminary step leading to ultimate use or consumption."[129]

In part, the question of whether N-of-1 precision medicine retains liability under products liability depends on how the technology will scale. If a separate commercial seller develops drugs for small groups of patients based on genetic features and sells them in the stream of commerce, courts may be more likely to consider the treatment as a product. If instead the individual physicians develop treatment in-house as a part of their relationship with the patient or if considerable customization to the modality is present in the course of treatment, products liability is a more uneasy fit.

2. Medical Malpractice

Insofar as the expected liability is based on the physician's choice to use N-of-1 precision medicine, rather than the nature of the drug, physicians' liability might be more relevant.[130] Gary Marchant and coauthors wrote about the potential for physician liability for precision medicine over a decade ago.[131] Writing in the context of a broader definition of precision medicine, Marchant notes that genetic testing may become the standard of care without physicians having received sufficient training in it. Noting that many treatments now have a genetic testing component which identifies the

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[128] *Id.* at § 20. The Restatement provides the following definition:

> (a) One sells a product when, in a commercial context, one transfers ownership thereto either for use or consumption or for resale leading to ultimate use or consumption. Commercial product sellers include, but are not limited to, manufacturers, wholesalers, and retailers.
>
> (b) One otherwise distributes a product when, in a commercial transaction other than a sale, one provides the product to another either for use or consumption or as a preliminary step leading to ultimate use or consumption. Commercial nonsale product distributors include, but are not limited to, lessors, bailors, and those who provide products to others as a means of promoting either the use or consumption of such products or some other commercial activity.

Restatement (Third) of Torts: Prod. Liab. § 20 (1998)

[129] *Id*.

[130] It is not obvious how physician liability will impact the price of precision medicine, in part due to the third-party financing of medical services.

[131] Gary E. Marchant, Doug E Campos-Outcalt, & Rachel A Lindor, *Physician Liability: The Next Big Thing for Personalized Medicine?* 8 PERSONALIZED MEDICINE 457, 457 (2011); Gary E. Marchant & Rachel A. Lindor, *Personalized Medicine and Genetic Malpractice*,15 GENETICS IN MEDICINE 921, 921 (2013).

best course of treatment (particularly cancer treatment or prenatal testing), Marchant predicts that the uncertainty over standard may create liability pressure for physicians.

Marchant correctly notes that in bringing such cases the loss of a chance doctrine will likely play a large role. The loss of a chance doctrine allows patients to bring suit not for physical injury (in particular, death from medical malpractice) but for the reduction in the chance of survival that the breach of the standard of care caused. The importance of such a doctrine to precision medicine is that plaintiffs filing under a genetic malpractice theory may indeed find it difficult to prove causation by the preponderance of the evidence because their baseline chance of survival is so low.[132]

For physician liability, Marchant is correct to note that the uncertainties regarding the standard of care can be a source of liability. However, these uncertainties seem more applicable to the traditional version of precision medicine than the N-of-1 version. While physicians may wrestle with the correct context in which to use genetic testing to customize treatment, the choice to engage in it is more straightforward for N-of-1 precision medicine. By the time individualized precision medicine is considered, a patient has either been classified as having a disorder that can benefit from direct gene intervention or all other treatment has failed.

Insofar as medical malpractice is brought for the inappropriate implementation of N-of-1 precision medicine treatment, there are several reasons to believe that medical malpractice would be particularly ineffective in this context.

First is an issue of causation. The patients receiving N-of-1 precision medicine generally have had other treatments fail or have been told that there is no possible other treatment. The standard for establishing causation is the preponderance of the evidence standard, requiring that it be more likely than not that but for the breach, the patient would not have experience the injury. Courts interpreting this standard in explicitly probabilistic cases have sometimes held that the sickest patients cannot establish the preponderance of the evidence because they cannot prove that it was more

[132] Some courts have interpreted the preponderance of the evidence standard in such "probabilistic causation" cases to require at least a 50% survival rate prior to the alleged negligent act. Elissa Philip Gentry, *Damned Causation*, 54 ARIZ. ST. LJ 419, 419 (2022). Gentry criticizes this interpretation of both the preponderance of the evidence standard and challenges the notion of "probabilistic causation" cases being distinct from other causation issues.

likely than not that they would survive without the breach. While this way of viewing causation is flawed, this can present a hurdle for patients.[133] Other courts have pivoted to the loss of a chance doctrine in order to evade this outcome, providing proportional recovery.

The bigger hurdle, however, is the standard of care. The fact that an injury occurred (either through the underlying indication failing to resolve or through a side effect from the treatment) is not sufficient to bring a medical malpractice suit. In order to establish breach, the plaintiff must prove by the preponderance of the evidence that the medical provider did not act with customary care.[134] In the context of N-of-1 precision medicine, establishing the customary care would be difficult for a plaintiff. By definition, the ailment is so individualized that a new treatment had to be developed for it. Because of this, it would be difficult for a plaintiff to present evidence on what a minimally competent physician would have done instead.

Despite the potential ineffectiveness of medical malpractice, some oversight is not only preferable but necessary. In contexts where the promulgation of knowledge is in tension with the treatment of patients, adoption of certain techniques can sacrifice patient welfare.[135] Even where there is no such tension, the absence of oversight/liability negatively affects patient safety.

D. Optimal Regulation of N-of-1 Precision Medicine

Despite the fact that premarket approval from the FDA is an uneasy fit with N-of-1 precision medicine, not only is regulation necessary but *federal* regulation is necessary. While the practice of medicine is generally left to the states to regulate through state boards and medical malpractice suits, aspects of medical practice are regularly overseen by the federal government. Courts have noted that "a notion of federalism which reserves

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[133] Gentry, *Damned Causation*, *supra* note_, at 426–27.

[134] Unlike in ordinary negligence cases (in which customary care is probative but not dispositive of the standard of care), *See* T.J. Hooper, 60 F.2d 737, 740 (2d Cir. 1932); Johnson v. Riverdale Anesthesia Assocs., P.C., 563 S.E.2d 431, 433 (2002), *overruled by* Condra v. Atlanta Orthopaedic Grp., P.C., 681 S.E.2d 152 (2009), the standard of care for professional negligence is generally defined as customary care..

[135] As an example, consider an oncologist treating a stage 4 cancer patient. The oncologist is also leading a clinical trial for an experimental drug, a trial that requires that a "control group" receive a placebo in order to accurately identify the benefit conferred by the experimental drug. The oncologist as a researcher has a duty to randomize patients into that placebo group in order to develop quality information. The oncologist as a provider has a duty to care for his patient and work toward their health. Assigning the patient to a placebo group is in tension with this provider duty.

all rights over such regulation to the states, . . . is without merit."[136] Indeed, "[t]he fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the Act which may at times impinge on some aspect of a doctor's practice."[137] For individualized precision medicine, the existence of certain centers for receiving such treatment—networks which may span academic centers, hospitals, and state lines—the consistent regulation of such activity implicates interstate commerce.

This would not be the first time interstate commerce would be used to impose federal regulation of medical services. The Clinical Laboratory Improvements Act (CLIA) is an excellent example of such federal authority. The Clinical Laboratory Improvements Act of 1967 originally exempted laboratories that did not receive Medicare payments and those that operated purely intrastate. The statute was revised in 1988 to apply to all laboratories, as "the Committee has concluded that all laboratory testing necessarily affects interstate commerce and the public health."[138] requires that laboratories performing human sample testing to meet specific standards for facilities and personnel.

In certain cases, however, premarket approval is not a viable intervention. An innovative field such as individualized precision medicine is an area in which regulators may not be able to keep pace with industry. For the same reason that standard of care becomes difficult to establish, invasive regulation runs the risk of being outpaced by scientific advancements. Based on the foregoing discussion, the preferable form of oversight should not be based on litigation, nor premarket approval required for population-based drugs. It would consist of principle-based best practices for developing individualized precision medicine treatments and track compliance with such principles.

IV. A NEW PARADIGM

A. A Platforms-Based Approach

A key characteristic of individualized precision medicine is the fact that each bespoke therapy simultaneously *creates* information that can slash the cost of the next therapy. To some extent, this is true of all drug development: data from R&D projects are generally informative for related

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[136] Pharm. Mfrs. Ass'n v. Food & Drug Admin., 484 F. Supp. 1179, 1187–88 (D. Del.), aff'd, 634 F.2d 106 (3d Cir. 1980).

[137] *Id*. at 1188.

[138] H.R. REP. 100-899, 22, 1988 U.S.C.C.A.N. 3828, 3843

drugs. Despite this potential for learning, much of the data created by pharmaceutical companies or labs are not publicized. While stories of malicious suppression of data are prevalent,[139] this censoring can occur as a function of neutral forces such as publication bias[140] and intellectual property protection.[141]

N-of-1 precision medicine is unique in how strongly each treatment relies on a shared set of modalities. As noted in the FDA's definition of framework technologies,[142] these shared modalities mean that information about the experience of one personalized treatment can be informative to developers of other personalized treatments. Because of this feature, each piece of information created is more probative for the development of other precision medicine treatments.

Specifically, choices attempted by prior projects and their relative success can reduce the number of permutations run by other laboratories. As noted in Section I, development of an N-of-1 treatment can begin with as many as one-thousand candidate designs. Experiments and effort used to winnow these candidates into best options take time and resources. Sharing prior results can reduce this and potentially cut development costs.

While this feature creates the potential for learning and cost-reduction through information sharing, it also predictably ensures that adequate sharing will not occur absent external intervention. Because the information benefits other individualized precision medicine developers, its social benefit is greater than the benefit it accrues to the researcher creating it. The researcher cannot "internalize" all the benefits the information confers, so the researcher creates too little of such information. This classic example of a positive externality results in insufficient creation (and, more importantly, insufficient sharing of) drug trial information, which cannot be addressed by conventional patent-and-price mechanisms.

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[139] For example, Warner-Lambert conducted a study of Neurontin for the treatment of bipolar disorder in 1998, which found that Neurontin was less effective than a placebo. Warner-Lambert did not publish the study until 2000. Jeanne Lenzer, *Pfizer Pleads Guilty, but Drug Sales Continue to Soar,* 328 BMJ 1217, 1217 (2004).

[140] Publication bias occurs when researchers do not submit, and journals do not publish, studies with null results. *See In re* Neurontin Mktg. **&** Sales Pracs. Litig., No. 04-cv-10739-PBS, 2011 WL 3852254, at *8 (D. Mass. Aug. 31, 2011), *aff'd,* 712 F.3d 21 (1st Cir. 2013) ("Another type of publication bias described by Dr. Dickersin is 'location bias' or 'gray literature bias' where a company publishes a negative trial in a journal that has a smaller circulation than more well-known medical journals.").

[141] In particular, companies with a proprietary interest in a substance may hesitate to share research findings with the public before legal protection is granted.

[142] *See supra* Part II.

A more promising blueprint comes from Nobel Prize laureate Jean Tirole's theory of multi-sided platforms. Platforms[143] refer to a coordinating entity between different interested parties. Jean Tirole notes that "many if not most markets with network externalities are characterized by the presence of two distinct sides whose ultimate benefit stems from interacting through a common platform."[144] While this dynamic generalizes to "multi-sided" markets, an example of a two-sided market is sufficient for the intuition. Suppose an artist is deciding between selling their creations on their own personal website or creating an account on Etsy, a "global marketplace for unique and creative goods" where buyers and sellers congregate to buy/sell.[145] While both options create opportunities to sell wares, a small seller would rationally prefer to join Etsy because they can easily attract multiple buyers because buyers are already on the platform to peruse other sellers. Rather than steer buyers to a separate personal website, the "network externality" of virtual location make sellers automatically more visible. Similarly, buyers wishing to buy creative works will gravitate toward Etsy because they know that they can easily browse through multiple sellers, reducing search costs for the buyer. In other words, the "network externalities" of virtual location and attention creates reciprocal benefits for locating in the same place. The more sellers join Etsy, the more buyers benefit. The more buyers join Etsy, the more each seller benefits.

The same dynamic is present in credit card networks, in which merchants want to accept the most popular credit cards, as this will increase their attractiveness to consumers. Consumers also want to choose the most accepted credit cards, as it increases their ability to access merchants. Both merchants and consumers benefit when more merchants/consumers coordinate on the same credit cards.

Platforms can be one-sided as well, meaning that while there is only one group of users, the value of the platform increases with the size of the group. A prime example of such a one-sided market is social media. People seeking connection want to join the most popular social media sites because it increases the likelihood that they connect with other people. If the number of potential connections increase with the number of users, individuals want to congregate on the same platform. This dynamic is well-demonstrated by

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[143] Confusingly, the framework that the FDA uses to govern precision medicine is also termed a "platform framework."

[144] Jean Charles Rochet & Jean Tirole, *Platform Competition in Two-Sided Markets*, 1 EUROPEAN ECONOMIC ASSOCIATION 990, 990 (2003).

[145] https://www.etsy.com/about

various exoduses from Twitter as a platform. In the wake of the Twitter boycott, former users struggled to coordinate on an alternative site to maintain the same level of connectedness.

For individualized precision medicine, the three relevant constituencies involve patients, laboratory manufacturers, and payers. Each group's participation generates cross-side externalities that standard bilateral contracts cannot capture.

Consider the laboratory side first. When a university core facility produces an antisense oligonucleotide for a single child with Batten disease, it also generates a trove of manufacturing validations—purity assays, off-target screens, stability data—that any subsequent lab could reuse. Yet under the status quo, the originating lab would bear the entire cost of those tests while future entrants freeride. Predictably, too few labs enter and those that do face incentives to skimp on data collection. If instead participating labs were able to access data from other participating labs, this would mimic the dynamics of a one-sided market. Labs would prefer to join a platform where other labs doing related work already exist, and the value each lab receives from the platform scales with size.

Patients and payers can peripherally reap the benefit of such consolidation. While patients and payers are technically separate entities, we consider them jointly for the following reason: patients rarely self-pay for medical service. Instead, agreements with third-party payers determine the amount that a patient is responsible for and how much the third-party payer will cover. Moreover, third-party payers generally negotiate prices with pharmaceutical companies, further distorting the relationship between a patient's willingness to pay and the fee paid.[146] Despite this, under certain conditions, a patient's value of a treatment is connected to the payer's value.

Both patients and payers benefit from more labs participating in the platform in two ways. First, insofar as increased participation actually reduces the costs of development by reducing the amount of duplicated work, patients/payers are able to receive treatment at lower prices. Even if the cost of individualized precision medicine does not significantly drop, the additional information may make costs more predictable. Similarly, the more labs that publish high-quality release data, the faster dosing protocols

[146] This process often occurs indirectly through the use of a pharmaceutical benefit manager (PBM).

converge. Either dynamic results in a more insurable risk[147] and accessible treatment.

The subsequent Section provides detail on how such a platform would operate to address both regulatory and financing challenges of this innovative treatment field.

B. Proposal: Accredited Center Model as A Platform-Economics Approach

In light of the unique challenges for individualized precision medicine, this Section proposes establishing an Accredited Center for Precision Therapeutics (ACPT) network, which would bring together patients/payers, laboratory manufacturers, and regulators. Participation in the platform would be mandatory for any laboratory producing N-of-1 precision medicine, and access to the platform would require user fees by participating laboratories. Conditions for participation in the platform would include specific disclosure requirements. In addition to penalties associated with non-disclosure, the platform would pay rewards for data disclosure. The platform would also allow third-party payers to access the platform for a modest user fee. The remainder of this section outlines the details of this platform-based approach to precision medicine.

Using the principles of a platform, this Section proposes that the ACPT offer subsidies for laboratory manufacturers for the data they disclose, financed by access fees by fellow laboratories and patients/payers. The amount of each subsidy will vary by quality of information provided through the disclosure requirements. Accordingly, a laboratory manufacturer working on an important gap in treatment will receive more in subsidy than a manufacturer working on an area with multiple extant projects. Similarly, laboratory manufacturers with poor histories of safety would receive less in subsidies. In doing so, laboratory manufacturers are exposed to the demand for quality care from patients/payers without onerous premarket approval demands. The conditions for participation would accomplish the same goals as FDA oversight and would correct some of the financing challenges associated with interconnected medicines.

1. Disclosure Design

[147] *See* discussion in Part V.B.

As noted in Section I, precision medicine requires a lot of judgment calls in designing the protocol. By the time a particular technique has been chosen, many alternative designs often had been tried and discarded. This sort of calibration is common in pharmaceutical development but exacerbated in N-of-1 precision medicine. The outcomes of such previous combinations are often undisclosed; however, this information would provide a significant starting point for laboratories starting new projects.

The platform would provide such information by requiring disclosure that satisfies 3 conditions. First, the disclosure would divulge the relevant genetic sequence that is being targeted. Because this is patient data, there is a privacy interest that must be protected, which could be addressed by removing any other identifying characteristics from the record.[148]

Second, the disclosure would pre-register design. The set-up of the procedure to be performed must be registered before the procedure is performed (or results collected). The design will be public to platform laboratories in order to decide whether the results are relevant to the lab's project. Pre-registration has been required for scientific experiments for some time. The International Committee of Medical Journal Editors (ICMJE) requires that any clinical trial with a starting enrollment after July 2, 2005, must be registered in order for their results to be published in an affiliated journal.[149] While this registration requirement is not always well-enforced,[150] the expectation of pre-registration and data disclosure is not new. This platform would enforce these requirements not just for ultimate drug designs, but for all the intermediate steps. The reason an enforcement policy like this works is that a laboratory does not know which adjustment will be the right one for them. If they manage to find a good outcome but have not registered it, they would be unable to publish it. Unlike the ICMJE mandate, the repercussions for failing to disclose such designs and outcomes affect the ability to operate. Not only does an N-of-1 precision medicine treatment require pre-registration in order to be implemented, but evidence of nondisclosure would come with penalties.
In addition, unlike with other contexts in which multiple designs may appear to be evidence of searching for non-representative results (for

[148] Notably, similar issues are faced by electronic medical records.
[149] New England Journal of Medicine, *The ICMJE and Clinical Trial Registration* (May 25, 2004), https://www.nejm.org/doi/full/10.1056/NEJMe048225; International Committee of Medical Journal Editors, *Clinical Trial Registration* (accessed Sept. 4, 2025), https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html.
[150] Jennifer Kao, Joseph S. Ross, and Jennifer E. Miller, *Transparency Of Results Reporting In Cancer Clinical Trials*, 6 JAMA NETWORK OPEN 1, 3 (2023).

example, p-hacking[151]), such design decisions do not undermine the credibility of drug development, so there is no reputational harm in disclosure.

Finally, disclosure mandates would include results. While laboratories can search based on experimental design, they would have to request access from the platform in order to access the results of a particular trial. Not only does this step provide an additional level of privacy protection for the results of such studies, but it creates a helpful record. The platform can use the number of these requests to track the number of fellow laboratories that found the design to be relevant to their projects and forms a basis for the market-based component of the reward. Finally, it ensures that laboratories are screening studies based on similarity of question and design, not cherry picking studies that yielded significant results.

2. Platform Subsidies

Recall from Section III.B. that a platform creates benefits from coordination due to the fact that the participating actors receive positive externalities from the presence of others.[152] As in the context of Facebook and other such one-sided markets, the presence of other actors may increase the value to all participating actors.

In the context of individualized precision medicine, peer laboratories benefit most from fellow laboratories' disclosures and data. Such data allows laboratories to reduce their research costs by not duplicating former work. Such information also reduces costs by allowing labs to create better informed treatments built off the work of others.

Given that participants both generate and receive positive externalities from sharing—and that these positive externalities are some of the strongest incentives—participating laboratories would pay an access fee. When a

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[151] For a discussion of p-hacking, *see* Stephan B. Bruns & John P.A. Ionnidis, *p-Curve and p-Hacking in Observational Research*, PLOS ONE (2016), *available at* https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149144

[152] The magnitude of these externalities need not be symmetric, however. Using the example of Etsy, suppose that sellers derive more benefit from the clustering of customers than customers do from the clustering of sellers. In cases like this, the side enjoying the largest network externality can be asked to shoulder more of the cost without deserting the platform. In this example, Etsy can provide a financial incentive for customers to join, financed by a fee charged to sellers. The sellers still find it preferable to join the platform with the fee because they receive a still larger benefit from locating amongst multiple customers.

laboratory provides data in a standardized format, it will receive a "premium," to internalize the positive information externality. Specifically, in order to receive the premium, a laboratory must share unprocessed results of a trial in a standardized format within thirty days of completion. While the unprocessed results would be subject to confidentiality (and disclosed through the platform itself to encourage such confidentiality), this requirement is key to generate information that benefits other individualized precision medicine developers.

The subsidy is not the only incentive to participate and share, as federal regulation and oversight would require both. This "carrot-and-stick" approach is necessary for two reasons. First, given that the number of laboratories engaging in individualized precision medicine is likely to be small, there is room for considerable strategic interaction between firms. A firm facing a standard bounty for sharing data may rationally believe that it is better off keeping its data secret and cornering the market on a subset of treatments. Second, even without the complications of a thin market, the positive externality has the potential to be larger than the premium; adding mandatory participation helps to guard against selective participation.

To ensure accuracy of reporting, the platform subsidy would be accompanied by a clawback provision. In the event that a laboratory fraudulently discloses or fails to disclose, either by falsifying records, suppressing records, failing to register, or other similar activity, the laboratory would be fined. In the event that the laboratory received a subsidy, the fine would be a multiple of the subsidy amount. In other contexts, such fines may follow the structure of CLIA violations, which can include suspension of certificate to operate and civil penalties.[153] The Office of Inspector General also has the authority to exclude entities from participating in federally funded health care programs,[154] a considerable financial blow to pharmaceutical companies.

One concern with assigning a premium for data disclosure is that it may not be clear how high the premium should be. Determining the value of the premium has similar weaknesses to assigning a reward for innovations: government information about the value of the innovation is unlikely to be more precise than the industry's. In order to avoid this issue, the amount of the subsidy is determined in a hybrid manner. Each lab disclosure would

[153]https://www.law.cornell.edu/cfr/text/42/493.1840#:~:text=CMS%20may%20also%20take%20adverse%20action%20based,hearing%20decision%20that%20upholds%20suspension%20or%20limitation.

[154] https://oig.hhs.gov/exclusions/

receive a flat reward and a market-based reward. The market-based reward would vary based on the number of requests for the data, as a pseudo-license fee.

In addition to the benefits that accrue to peer laboratories, patients/payers also peripherally benefit from this association.[155] Insofar as sharing information results in reduced costs, this should translate into lower prices for patients and payers. Only paying for treatments that avoid duplicating work also provides an incentive for precision medicine providers to join the ACPT platform.

Even if the platform does not decrease the price of individualized precision medicine, it may provide an incidental benefit to third-party payers by making costs more predictable. This is an important feature for insurance markets due to the way insurance companies account for profits. For insurance companies who expect to cover some individualized precision medicine cannot plan reserves or negotiate volume discounts. The inability to predict costs due to uncertainty itself is a cost.

Insurance companies must consider potential liabilities in order to plan reserves, negotiate volume discounts, and price premiums. One oddity of the insurance market is that each premium dollar is earned in real time, while liabilities are deducted immediately. This means that an insurance company's profits can fluctuate quickly based on expectations for the future.[156] If an insurance company realizes that one of their insureds has to be treated with a bespoke therapy, their expectations for their current liability can skyrocket. Any uncertainty in the cost of the bespoke treatment can make this expectation even less certain. Because insurance companies earn premiums day by day, they must increase current premiums to cover the new liabilities. This instability leads to wild swings in premiums that would be problematic to consumers. Indeed, the literature surrounding medical malpractice insurance premiums demonstrates how uncertainty in long-term liabilities (such as the magnitude of non-economic damages) can wreak havoc on the stability of premiums.[157]

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[155] For sake of simplicity, we have combined the interests of the patient with the payer. In the event of coverage, this assumption is valid, as the patient's interest in treatment is health-related and the payer internalizes the financial burden of such treatment. Potential deviations in interest between these two parties will be discussed in Section IV. B.

[156] Baker, *supra* note _, at 49–50.

[157] Tom Baker, THE MEDICAL MALPRACTICE MYTH, 46–56 (2005). Patricia Born, Evan M. Eastman, & W. Kip Viscusi, *Reducing Medical Malpractice Loss Reserve Volatility through Tort Reform*, 24 NORTH AMERICAN ACTUARIAL J., 626, 627 (2020).

If every N-of-1 precision medicine therapy emerges from ACPT and arrives packaged with standardized release and outcome data, actuaries can price coverage ex ante. If costs become more predictable, premiums are more likely to be stable. Faced with this value proposition, payers can be assessed a modest "precision-medicine fee," pooled nationally and distributed as per-case data bounties to accredited labs. The levy is not a hidden tax so much as a swap: it replaces today's volatile outlays with a predictable subscription that, in turn, lowers future claims.

The availability for subsidies for good quality data is a good avenue for incentivizing proper principles for approaching development of treatment. While researchers are pushing the frontiers of knowledge in developing individualized precision medicine treatments, that does not mean that there are not best practices for designing treatment. Rather than condition the subsidy on the actual outcomes created, the fact that requests for data (and, consequently, premiums) are made based on the trial design—that is, the *potential* for good quality data to be gleaned from the study—incentivizes the platform to follow best practices in the absence of premarket approval.
As noted in Section III.B., oversight of individualized precision medicine is important, given the low viability of medical malpractice and products liability suits. Patients with genetics-based disorders deserve the same level of care as patients with other disorders. The fact that medical malpractice and products liability do not provide robust guardrails creates a greater need for other types of oversight.

3. Safe Harbors

The structure of the platform pre-registration and premium also provides structure for liability design.

If N-of-1 precision medicine is determined to be subject to products liability, participation in the platform itself can be a defense to a design defect claim. For the risk-utility test, compliance with good practice review, reliance on previously disclosed data, and proper disclosure can create a rebuttable presumption that the product's risks were outweighed by its utility. For consumer expectations test, consumer expectations are often pretty low for individualized precision medicine, as these treatments are currently experimental. Insofar as this changes, consumer expectations may become more problematic. We agree with the California Supreme Court, however, that such technical products are an ill fit with the consumer expectations test.[158]

[158] Soule v. Gen. Motors Corp., 882 P.2d 298, 308 (1994).

For medical malpractice, as noted above, a provider can only be held liable if the care they provided fell below the standard of care. The standard of care is generally defined by custom, such that a provider must act at least as a minimally competent provider. Given this standard, rather than immunizing the liability of precision medicine providers directly, participation in the ACPT platform provides strong evidence of compliance with the standard of care. In particular, receipt of the premium provides evidence that the treatment design is consistent with the standard of care. Fraudulent submissions, highlighted by the clawback provision, to ACPT may undermine the presumption of compliance.

A Tirolean platform therefore supplies a limited, *earn-in* safe harbor: comply with ACPT protocols, upload follow-up data creates a presumption of conforming to the standard of care. Compliance is thus priced as an insurance premium paid in kind—data—rather than in dollars.

4. Implementation

In terms of implementation, a public entity would be best suited to oversee the platform. For much of Medicare/Medicaid requirements, however, CMS does not directly supervise regulated entities. Instead, private accreditation organizations often perform audits and screening, and CMS uses these approvals as evidence that Medicare/Medicaid standards have been satisfied.

Indeed, compliance with CLIA can be evinced through either a certificate of compliance (in which a State Agent or CMS surveyor certifies that the laboratory is in compliance with CLIA requirements) or a certificate of accreditation (which certifies the same through a CMS-approved accreditation organization).[159] CLIA similarly requires that accreditation organizations be approved at least every six years.[160] The periodic recertification helps to undermine the opportunity/pressure for regulatory capture.

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159 https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/howobtainclicertificate.pdf

160 JOINT COMMISSION, Renewed Deeming Authority for Laboratories, (Jun. 27, 2024) https://www.jointcommission.org/en-us/knowledge-library/news/2024-06-renewed-deeming-authority-for-laboratories

Understandably, self-regulation through accreditation has the potential for self-dealing and regulatory capture. The potential of such capture seems reduced in this context, however. The danger associated with accreditation is with its voluntary nature. Accreditation organizations gain influence by being well-known in the field. Because institutes are not compelled to seek accreditation with a particular organization, new accreditation organizations are essentially competing for subscribers in order to wield the influence necessary to become a certifying agent for a government program like Medicare. A classic example of such a dynamic is the Joint Commission, formerly known as the Joint Commission on Accreditation of Healthcare Organizations, a private accreditation organization that featured prominently in Medicare approvals. For years, accreditation by the Joint Commission was deemed sufficient to be found in compliance with CMS requirements for participation in Medicare.[161] The need for the Joint Commission was in fact due to the quick rollout of Medicare and the necessity of a credential that most hospitals could immediately satisfy.[162] Since the joint Commission had accredited most large hospitals in the nation, and had a good reputation, it was a prime candidate.[163] After pushback from consumers, Congress amended the Social Security Act in 1972 to allow the Department of Health, Education, and Welfare to require hospitals to comply with Medicare certification standards that were more stringent than the Joint Commission's and created more oversight over the Joint Commission's decisions.[164] An escalating level of control over the relationship between accreditation and CMS compliance continued until 2008, where legislation removed the "deemed" status of the Joint Commission accreditation and instead required that it apply for deemed status periodically.[165] These sort of institutional checks can prevent or mitigate regulatory capture while leveraging the manpower of private accreditation organizations.

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[161] Timothy Stoltzfus Jost, *Medicare and the Joint Commission on Accreditation of Healthcare Organizations: A Healthy Relationship*, 57 L. & CONTEMP. PROBS. 15 (Autumn 1994).

[162] *Id*. at 24.

[163] *Id*. at 24–25.

[164] *Id*. at 18–19.

[165] Medicare and Medicaid Programs; Conditional Approval of the Joint Commission's Continued Deeming Authority for Critical Access Hospitals, 73 FR 63480 (October 24, 2008) ("The regulations at § 488.8(d)(3) require accreditation organizations to reapply for continued approval of deeming authority every six years, or sooner as we determine.")

V. THE NECESSITY OF A PLATFORM APPROACH

While a subscription-based platform may seem like a revolutionary change, such a paradigmatic shift is necessary to deal with the unique nature of N-of-1 precision medicine. FDA pre-approval not only is potentially legally unsupported, but it is too slow and unsophisticated to keep pace with innovation. Despite this, systematic documentation and assessment are essential to both reducing costs of future treatments and protecting patients. The proposed disclosure allows laboratories to learn from one another and creates a process for ensuring good practice implementation.

Such a novel shift creates potential for perverse and unanticipated consequences. This section addresses potential weaknesses in turn and explains why the general structure is the best option for this burgeoning field to develop.

A. Excessive Entry

One concern might be that the provision of the data premium will just subsidize laboratories to enter this nascent field. However, because the premium is only provided to data reports that meet the standards of the ACPT board, this is less of a danger. Moreover, because the data premium is set in part based on requests for the study results, laboratories are incentivized to produce data that has potential to help other laboratories.

B. Financing

While platform information sharing has the potential to reduce development costs associated with N-of-1 precision medicine, concerns about accessibility may remain. If development costs remain high, patients who need the treatment may still be unable to access it. While the intricacies of pharmaceutical pricing are beyond the scope of this article, several insights are worthwhile here.

The fact that N-of-1 precision medicine is expensive is not an obstacle to coverage. Even traditional population-based drugs rely on insurance coverage for accessibility. As noted in Section II.B, patents and intellectual property monopoly power characterize pharmaceutical markets. Most patients do not pay a "market price" for population-based treatments. Instead, pharmacy benefit managers ("PBMs") negotiate drug prices with pharmaceutical managers for multiple insurance plans. These negotiated prices are more a function of the relative size of the bargaining actors (PBMs and pharmaceutical manufacturers). These deals result in drugs being placed on formulary tiers, which determine how much a patient pays

out of pocket. For example, if the negotiated deal results in the patented drug being placed on the lowest-tier of the formulary, patients have lower cost-sharing in selecting that drug than if they select a drug on a higher tier. The pharmaceutical manufacturer benefits from having their drug on a lower tier because more patients are likely to use it. Depending on the insurance plan, patients either have a higher out-of-pocket payment or receive no cost-sharing for drugs not listed on a formulary. Just as with population-based drugs, a robust insurance market is necessary in order for patients to have access to N-of-1 precision medicine treatments.

Medical necessity is generally the standard by which insurance companies determine coverage. While insurance contracts commonly exclude experimental treatment, the methodical development and oversight of N-of-1 precision medicine can provide a path to establishing medical necessity. Patients turning to N-of-1 precision medicine by definition should have exhausted other avenues of treatment. Moreover, the platform substitutes for premarket approval, meaning that registration and compliance with good practices is the only way to access treatments.

If traditional insurance companies are not required to add this coverage to existing policies, "precision medicine standalone policies" may evolve separately. A great example of such supplemental coverage is cancer insurance. Cancer treatment (like N-of-1 precision medicine) creates considerable costs to treat, with initial care ranging from $28,109 (prostate cancer) to $68,293 (lung cancer); continuing care from $2,603 (prostate cancer) to $56,246 (colorectal cancer); and end of life care from $74,227 (prostate cancer) to $169,588 (leukemia).[166] While some of these costs are covered by a general health insurance plan (depending on the plan), supplemental cancer policies are available to cover expenses not covered by general health insurance.

Regardless of whether precision medicine coverage is integrated into existing health insurance contracts or purchased as a supplemental policy, two features are necessary for the market be stable. First, such insurance must be mandatory. Allowing patients to opt into coverage once the need for precision medicine eventualizes is subject to the same adverse selection dynamics that plagued traditional health insurance and leads to the unraveling of the market.[167] Second, in order to insure risks, the

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[166] https://www.cancercenter.com/community/blog/2023/07/managing-cancer-treatment-cost#Q1.

[167] For an explanation of adverse selection in the context of choosing from a menu of

expenditures should be predictable. Work by Tom Baker, Patricia Born, and others discuss the volatility associated with different insurance markets, emphasizing the importance of not only the magnitudes of potential liabilities but the predictability.[168] Our proposed solution provides key data for this stability. Information gleaned by insurance companies from the ACPT help to increase predictability and stability premiums. This proposal not only makes the potential insurance liabilities potentially lower but also more predictable, which reduces some of the barriers to the development of a market for such risks.

While N-of-1 precision treatment may appear to be uncommon and expensive, this is true of many treatments. Currently, many patients use crowd funding or charity foundations to pay for individualized precision medicine. Not only does this accentuate equity concerns, but it is potentially a very regressive way to approach such costs. While the government must mandate coverage of such treatments, or the purchase of policies covering such treatments, our proposed platform solution creates the market circumstances to help the resulting insurance market thrive.

C. Strategic Behavior by Laboratories

Another concern may be that the premiums associated with disclosing data are not sufficient to keep laboratories from strategically suppressing data. This concern is understandable, given the close knit nature of the industry. The proposed platform ameliorates part of this concern by making participation in the platform mandatory rather than voluntary.

Insofar as N-of-1 precision medicine becomes implemented by large pharmaceutical companies rather than mere academic laboratories, a further concern may be that such large companies have the resources and incentives to behave more strategically. While this concern is indeed important, it is a common one for pharmaceutical regulation. The proposal allows for the fines associated with fraudulent submission or suppression to follow the framework associated with CLIA penalties. If these fraudulent submissions lead to submission of non-reimbursable claims to Medicaid or Medicare for payment, liability under the False Claims Act is also possible (currently a

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insurance plans, *see* David M. Cutler and Richard J. Zeckhauser, *Adverse Selection in Health Insurance, Frontiers in Health Policy Research* 2–3, MIT 1998 (Alab M. Garber ed). Similar dynamics occur in deciding whether to buy insurance. *Id.* at 2.

[168] Tom Baker, THE MEDICAL MALPRACTICE MYTH, 46–56 (2005). Patricia Born, Evan M. Eastman, & W. Kip Viscusi, *Reducing Medical Malpractice Loss Reserve Volatility through Tort Reform*, 24 NORTH AMERICAN ACTUARIAL J., 626, 627 (2020).

prime enforcement mechanism against pharmaceutical companies).[169] Finally, exclusion from federal health programs is a powerful tool to incentivize compliance.[170]

D. Equity Concerns

Finally, there are at least two equity concerns associated with N-of-1 precision medicine. First, access to such treatment is likely not particularly equitable. Very few people have access to a neurologist who could custom-create a treatment directed at their genes. Given that these treatments are currently financed by crowdfunding efforts, some patients might be more likely to garner the resources necessary to access treatment even if available. During Mila's treatment, news outlets noted the potential inequities in pursuing such bespoke treatments.[171] These features demonstrate the importance of scaling access in a systematic way.

The second, and thornier, equity concern questions whether society should be willing to invest in making treatment scalable. In its nascent stage, N-of-1 treatment is likely to be more expensive than other types of treatment. Insofar as an ailment could be treated with another therapy, this is likely the more cost-effective solution. Cases that are good candidates for N-of-1 treatment should not have other options that are more cost-effective. In the absence of the N-of-1 treatment, these patients will either die or continue to suffer the debilitating symptoms of the disease. Spending money on N-of-1 treatments potentially crowd out funding for targeting other, more cost-effective treatments. This is not unique to N-of-1 treatments and is an inescapable fact in light of scarce resources. Advances in health technology often leads to higher cost treatments (rather than lowering costs), and these questions should be tackled within the broader context of cost-effective care.

It does appear clear, however, that N-of-1 treatments are worthwhile in certain contexts, saving lives and drastically improving quality of life. As this field develops, this Article provides a path forward to allow access in a more equitable way.

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[169] Ralph F. Halland Robert J. Berlin. *When You Have A Hammer Everything Looks Like A Nail: Misapplication Of The False Claims Act To Off-Label Promotion*. 61 FOOD & DRUG L.J. 653, 653 (2006).
[170] Joan H. Krause, *Truth, Falsity, and Fraud: Off-Label Drug Settlements and the Future of the Civil False Claims Act*, 71 FOOD & DRUG L.J. 401, 417 (2016).
[171] Kolata, *supra* note _.

CONCLUSION

N-of-1 precision medicine represents a shift in the way illnesses are treated, eschewing general population-based approaches for truly individualized interventions. This methodological advance has the potential to transform fatal illnesses to treatable conditions and to save lives of millions of individuals (each suffering from different genetic mutations). Treating N-of-1 precision medicine the same as population-based medicine runs the risk of squelching the nascent field. Premarket regulation by the FDA is overly burdensome and slow, and potentially legally unsupported. Relying on patents to spur innovation fails in the face of the handful of patients affected by each mutation. Ex-post tort remedies fail to provide deterrence or compensation: For medical malpractice claims, patients face difficulties in establishing the standard of care or causation. For products liability, even if N-of-1 precision medicine qualifies as a product, plaintiffs will have difficulty establishing a reasonable alternative design.

Despite the difficulty in applying the traditional framework to N-of-1 precision medicine, some oversight is necessary. Given the gaps in tort recovery, regulation must find a way to ensure best practices. This Article provides a path forward that balances access to innovation and patient care.

By leveraging one of the challenges of N-of-1 precision medicine—its use of shared modalities to deliver treatment—this Article reframes this overlap as a positive network externality well-addressed by a multi-sided platform. Drawing from Nobel laureate Jean Tirole's work, the Article proposes that in lieu of premarket approval, laboratories be mandated to participated in a platform in which they preregister studies and share data. The preregistered studies would be monitored in much the same way laboratories are currently monitored through CLIA, ensuring best practices. The positive network externality—which would otherwise create insufficient incentives to create and share data that could help to cut development costs for other laboratories—would be addressed through premiums laboratories receive for sharing data. These premiums would be a hybrid of a flat fee and a volume-based fee determined by the number of laboratories requesting the data.

While a departure from FDA premarket approval of population-based drugs, this approach is necessary to allow this technology to advance without sacrificing patient safety. Importantly, the data sharing provided from the platform is also necessary for a robust insurance market to price the risk associated with such genetic illnesses.

Agile regulation requires us to determine when technology outpaces traditional frameworks. To achieve the promise of treatment approaches that can treat illnesses previously considered fatal, legal infrastructure must advance as well.