

# The Rise of the Bio-Citizen



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## **ACKNOWLEDGEMENTS**

The Citizen Health Innovators Project focuses on developing regulatory and governance mechanisms for the fast-growing ecosystem of health innovators, built around maker spaces and community biolabs, to support responsible innovation in distributed networks. The Project also aims to unveil the conditions, barriers, and opportunities for empowering citizens and patients who attempt to actively participate in the knowledge-production associated with biomedical research, in particular chronic and rare genetic diseases.

We would like to recognize Todd Kuiken's invaluable contributions to the development of this project as well as Walter Johnson, Garrett Dunlap, and Franco Bueno Mattera for their insights in the writing and editing phase and help with the project's website. This project aims to kick-start a long-term process of establishing a social license to operate, creating public trust and support for a democratized health research ecosystem. Support for the Citizen Health Innovators Project was provided in part by the Robert Wood Johnson Foundation. The views expressed here do not necessarily reflect the views of the Foundation.

**This is a preliminary analysis that may be subject to change upon the completion of the project workshops to be held in March 2018.**

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## EXECUTIVE SUMMARY

Under the designation “patient-led research” (PLR) or “citizen-driven biomedical research,” citizens, patients, and families have increasingly become the leading force in the initiation or conduct of health research projects, pursuing a range of activities from analyses of genomic data for diagnosing rare diseases, identification of potential therapeutic drugs, organization and crowdfunding of clinical trials’ cohorts, and even self-surveillance or self-experimentation. Many of the participants in citizen-driven biomedical research are patients and families confronted with a condition that is the subject of their research, therefore facing new epistemic and governance challenges, and often testing the ethical and regulatory limits within which health research has traditionally operated.

This new form of research where citizens and patients are the primary *producers* and *mobilizers* or *instigators* of knowledge promises to break new ground in underserved health domains, but also suffers from a lack of legitimacy when it comes to assessing the quality of patients’ experiential data. Moreover, this endeavor gradually transfers the responsibility to preserve safety and ethics to *lay experts*, probing new ethical matters of concerns – from blurring boundaries between treatments and self-experimentation, peer-pressure to participate in trial, exploitation of vulnerable individuals or third parties (children), to a lack of regulation concerning quality control and risk of harm. Very little research currently focuses on adequate ways to adapt or design responsible governance and ethical standards tailored to citizen-driven biomedical research.

The present report addresses important unresolved issues that could compromise the development and recognition of citizen and patient-driven biomedical research: by (1) analyzing the practices and methods enacted by citizens and patients to produce and mobilize experiential biomedical knowledge as *evidence*; by (2) identifying the specific ethical and governance challenges patients and citizens encountered when conducting research; by (3) evaluating and adapting oversight mechanisms tailored to prevent these controversial epistemic and governance issues. In the process, the report also unveils matters of concern that are of interest to both citizens and regulators, and which are zones of *undone science* and *unregulated science*, such as underserved condition-areas like rare genetic diseases. Another important merit of this report is to provide regulatory institutions with an analysis of the different practices enacted by citizens and patients to articulate “experiential knowledge” with “credentialed knowledge,” therefore contributing to the current development of real-world evidence-based medicine.

Notwithstanding ongoing challenges, we should not simply disregard medical research conducted outside of traditional institutions as de facto less safe, less reproducible, or unethical. Patients often have in-depth experiential knowledge of their conditions along with a vested interest to make sure that a treatment or device will be effective, safe, and beneficial. Yet, facing regulatory uncertainty, they might not overcome the “chill factor” – a phenomenon described by citizen scientists and DIY inventors as the fear to confront regulators by sharing the recipe for a new invention. The press has recently covered cases of biohackers who self-experimented with unregulated gene-therapies. But the stories encountered in community biolabs, such as Biocurious and Denver Biolabs, are different: mentors, amateurs, and students want their proof of concept to be safe and reproducible, achieving specific standards in the research processes and evidences they rely on.

The next step is to foster legitimacy for citizen-driven biomedical innovation by supporting citizens and patients to document and share their data, evidence, and ethical concerns in ongoing conversations with regulators and society. Because they respect biological safety levels and function as a peer-review culture, community biolabs constitute an ideal ecosystem for mentorship in the most current bioengineering techniques and their related risk-benefit trade-offs. These labs might be the perfect place to start a continuing dialogue about how to adapt our regulatory standards to a more democratized form of biomedical innovation. What we need is empowerment, but also more collective intelligence. If risks are properly managed without dampening the now more-democratized reality, then we might all gain in the process.

We need  
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intelligence.

## A Few Takeaways

### The New Bio-Citizen

The attributes of a new “bio-citizen” in a “citizen-driven biomedical research” scenario looks like this: scientists, patients, congressmen, employees — *everyone* — will be monitoring the DNA of their own bodies, including markers of health and disease, on shared cloud labs. Portable genome sequencers, the size of a USB stick and connected to our smartphones, would also be integrated to our most strategic technical systems, including agro-food facilities, airports, and hospitals. In their homes, individuals would have access to liquid biopsies – blood tests that could track their most vital biomarkers and identify the pieces of DNA shredded by a cancer tumor or a viral agent at an early stage. Devices in their homes and worn on their bodies passively collect vital signs, sleep, and manifold behavioral and environmental data. Algorithms are trained to analyze individual datasets against population-level data, and to trigger alerts when necessary, either to reinforce positive trends or intervene in negative ones. If millions of bio-citizens were streaming data to the cloud, they would build the most powerful data set for preventive and precision medicine the world has ever known.<sup>1</sup>

### Regulatory Perspective

The 21<sup>st</sup> Century Cures Act directs the US Food & Drug Administration (FDA) to create a trial framework for implementing the use of real-world evidence (RWE) by the end of 2018. In July 2016 the FDA published draft guidance on utilizing RWE in medical device oversight<sup>2</sup>, suggesting RWE could become applicable across FDA regulation and not just apply to drug regulations. RWE may help address issues with current clinical trial designs, which require large patient cohorts and high costs but still lack generalizability.<sup>3</sup> However, existing sources of RWE

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<sup>1</sup> Eleonore Pauwels, “The New Bio-Citizen: How the Democratization of Genomics will Transform Our Lives from Epidemics Management to the Internet of Living Things” *The Wilson Center, Policy Briefs*

<sup>2</sup> U.S. Food and Drug Administration, (2016), “Use of real world evidence to support decision-making for medical devices,” Retrieved on June 4, 2017 from: [<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>]; Hills, B. & Zegarelli, B. (2016), “21st Century Cures Act requires FDA to expand the role of real world evidence,” Retrieved on June 4, 2017 from: [<https://www.healthlawpolicymatters.com/2016/12/19/21st-century-cures-act-requires-fda-to-expand-the-role-of-rwe/>].

<sup>3</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), “Real world evidence — What is it and what can it tell us?” *The New England Journal of Medicine*,

were not designed to aid regulatory decision making and could present analytical challenges.<sup>4</sup> Patient experience data may be able to serve a similar role, but limited literature exists on the potential risks and benefits of using patient experience data in regulatory approval.

### **Knowledge, Legitimacy, and Patient Empowerment**

Historically, credible knowledge has been synonymous with scientific (or traditional) knowledge. Yet, citizen-driven biomedical research and innovation is beginning to change this paradigm by injecting patient experience, i.e., experiential knowledge, into health research.

Most of the time, patients who produce knowledge and innovate address crucial user-centered issues. Often, peers and doctors who have become their collaborators in a shared innovation journey vet their design. Nonetheless, we argue that it is important to think creatively about how to help citizens and patients share this data, evidences, tacit knowledge, value trade-offs, and ethical concerns in ongoing conversations with regulators and society at-large.

Bridging the gap between the perceived legitimacy of scientific, or credentialed, knowledge and experiential knowledge produced by patients and their families may increase the level of scientific innovation in the future. Yet, even with the increasing involvement of tech companies in the open and participatory health movement, new forms of research powered by citizens and patients keep conflicting with more credentialed knowledge and the traditional research community. Exclusionary practices on either side are a common cause for potentially valuable health research and innovation to fail.

Responsible health innovation does not just require participant understanding and access to their health data generated by medical devices and genetic sequencing companies. Open and participatory health also requires corporations like 23andMe to allow customers to easily share their genome sequencing data with others. The next step is to help build a biomedical research system that will depart from its legacy, from its status quo, to become truly inclusive and participatory in its structure, engagement, and governance.

### **Tensions Between Ethics, Privacy, and Empowerment**

Another hard truth is that the potential for citizens to take a proactive role in their own diagnosis and treatments, outside of medical practices, probes many unresolved ethical issues: blurred boundaries between treatments and self-experimentation, peer pressure to participate in trials, exploitation of vulnerable individuals, lack of oversight concerning quality control and risk of harm, privacy concerns, and more.

The amount of health and biomedical genomics data to be stored, curated, and protected in the digital bio-space will keep growing, requiring powerful and expensive computing platforms. It will create a complex architecture with new needs related to the protection of privacy and the governance of such an increasingly data-driven society. Yet, we must also remain lucid about who will primarily contribute and who will reap the rewards of streaming our DNA, biomedical data, and day-to-day behaviors to the cloud. The way forward is to make sure that this trove of data does not benefit only those who already reign over our medical and digital

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375(23): p. 2293; Pazdur, R. (2016), "Evaluating FDA's approach to cancer clinical trials," (September 16), Retrieved April 9, 2017, from: [<https://blogs.fda.gov/fdavoices/index.php/2016/09/evaluating-fdas-approach-to-cancer-clinical-trials/>].

<sup>4</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), "Real world evidence — What is it and what can it tell us?" *The New England Journal of Medicine*, 375(23): p. 2293.

infrastructures, but build “counter powers” –global common spaces where citizens can learn to turn the data from their own health challenges into innovations.

We, as a society, are at a tipping point. We could build a new innovation ecosystem that ensures safe and responsible citizen participation in health research by empowering participants with their own health data, or, enact strict regulations that prevent the collection and analysis of digital health data from becoming a high-profit business. We suggest the former will better serve the public at large.

### **Governance, Collective Intelligence, and Community Biolabs**

We must recognize the urgent need to build legitimacy, but also tailored regulatory support for new forms of democratized health research. The path forward is not to promote radical, unregulated science, but to develop engagement channels that force citizens, patients, ethicists, and regulators to rethink and design an adaptive oversight system—one that fosters empowerment and responsibility rather than adherence to the status quo.

Because they respect biological safety levels and function as a peer-review culture, community biolabs constitute an ideal ecosystem for mentorship in the most current bioengineering techniques and their related risk-benefit trade-offs. By the same token, these labs are the perfect place to start a continuing dialogue about how to adapt our regulatory standards to an increasingly democratized form of biomedical innovation.

### **A Few Needs**

- More adaptive legal and regulatory frameworks
- Deeper understanding of current practices in citizen-driven biomedical research and how participant-led research (PLR) activities may require different procedures
- The promotion of co-design and shared decision-making amongst bio-citizens, regulators, and crowdfunders
- Support for transparency and open communication about study design, results, and their meaning
- An online platform where citizen-driven biomedical research and innovations may be publically registered (which may serve as an alternative peer-review system)

### **Governance Challenges**

- How might we bridge the gap between isolated citizen health innovators and community bio-labs?
- How can we foster the convergence of these two forms of health democratization?
- How can we help them collaborate to build legitimacy and responsible governance mechanisms for participatory and open health research?

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# INTRODUCTION

## The Emergence of Citizen-Driven Biomedical Research

In the last several years, scholars and journalists have observed increasing examples of the democratization of medical research and innovation. Stories of citizens outside the biomedical research community leading efforts in disease research, funding, or development of therapeutics and medical devices have astonished some and empowered others. Such a disruptive movement offers the lay public new opportunities to guide the direction of biomedical innovation and enables individuals to generate and mobilize new knowledge. Citizen-driven biomedical research can be thought of as medical, clinical, and other health-related research driven and conducted primarily by citizens themselves - not traditional research institutions.<sup>5</sup>

Such research can take on a variety of forms, methods, and environments – from closed-loop artificial pancreases and other open source methods like Crohndology.com’s aggregation of patient input on disease management and treatments, to more traditional research environments like the crowdfunded clinical trials initiated by the Gray Family and Andy Woods. In this report, we will discuss each of these examples in detail. For now, it is important to establish the notion that citizens can drive, steer, and significantly contribute to scientific innovation – even in the face of seemingly insurmountable barriers like funding, knowledge-gaps, and legitimacy while preserving (and perhaps even enhancing) transparency, collaboration, and privacy.

One member of this emerging movement is Tal Golesworthy, a bright and resolved engineer who, suffering from a genetic disease damaging his heart, designed a surgical device that would save him and other patients from more traditional procedures with higher risk. To understand the genetic mechanisms and penetrance of her rare prion disease, Sonia Vallabh and her husband, Erik Minikel, left their consultant jobs and became published PhD scientists at the Broad Institute. And to find a cure for their daughters suffering of the rare Batten disease, a couple raised millions on a crowdfunding platform<sup>6</sup>. While these individuals are reshaping their involvement in health research and practice, they are raising new ethical, safety, and governance issues for policymakers, practitioners, and patients.

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<sup>5</sup> “Citizen-driven biomedical research” has also been referred to as: “participatory biomedical/health research”, “participant-led research”, and “patient-led research”. For more information on citizen-driven biomedical research, see The Young Foundation’s *Citizen-Driven Health* project, [<https://youngfoundation.org/projects/citizen-driven-health/>]; Eleonore Pauwels, “The New Bio-Citizen: How the Democratization of Genomics will Transform Our Lives from Epidemics Management to the Internet of Living Things” *The Wilson Center*, Policy Briefs (May 2017) [[https://www.wilsoncenter.org/sites/default/files/new\\_bio\\_citizen\\_democratization\\_of\\_genomics\\_transformation\\_our\\_lives.pdf](https://www.wilsoncenter.org/sites/default/files/new_bio_citizen_democratization_of_genomics_transformation_our_lives.pdf)]; and Eleonore Pauwels and Todd Kuiken, “Citizen health innovators: Exploring stories of modern health,” *O’Reilly*, (April 2017) [<https://www.oreilly.com/ideas/citizen-health-innovators-exploring-stories-of-modern-health>].

<sup>6</sup> <https://experiment.com>



While this participatory turn has no official name, the term “patient-” or “participant-led research”<sup>7</sup> (PLR)<sup>8</sup> has emerged from the science and technology studies (STS) literature to describe the movement:

“As in standard research, PLR is an activity that characteristically aims at the socially valued goal of producing generalisable health knowledge. However, it is distinctive in being initiated and conducted by the participants themselves, often using the tools of online social media. Many of the participants in PLR are patients suffering from the condition that is the subject of their research. However, PLR also includes participants who are not patients, but rather individuals interested in acquiring health information, whether about themselves or more generally. The PLR label applies to a very heterogeneous range of research activities. Often, they cannot be sharply distinguished from standard research, partly because of the tendency of some PLR projects to evolve over time and become entangled with standard research activity.”<sup>9</sup>

Inspired by developments in citizen science, in this report we also refer to new forms of participatory health research as “citizen-driven biomedical research and innovation.” Similarly, we call these citizen scientists by the term “citizen health innovators” or “bio-citizens.” From analyzing their own genetics and mastering genome-editing on simple bacterial and viral cells to prototyping surgical devices, these “bio-citizens” are using newly available biotechnologies and resources to better understand and improve their health. We have begun mapping their emergence and exploring their stories, as well as the ethical and regulatory landscape that surrounds them on the Citizens Health Innovators Project website.<sup>10</sup>

In generating new findings and products, these lay citizens have asserted their potential to create clinically useful knowledge to benefit themselves and others, who often belong to chronic and rare disease communities. Such citizen involvement in biomedical innovation promotes the injection of “experiential knowledge”<sup>11</sup> into the more traditional research sphere,

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<sup>7</sup> Effy Vayena, et al. “Research Led by Participants: A New Social Contract for a New Kind of Research,” *Journal of Medical Ethics*, (Mar. 2015), doi:10.1136/medethics-2015-102663 [http://jme.bmj.com/content/medethics/early/2015/03/30/medethics-2015-102663.full.pdf]; Effy Vayena and John Tasioulas. “Adapting Standards: Ethical Oversight of Participant-Led Health Research,” *PLOS Medicine*, vol. 10, no. 3; PLoS Journals (Mar. 2013), doi:10.1371/journal.pmed.1001402 [http://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1001402&type=printable].

<sup>8</sup> For the remainder of this report, we will use the acronym “PLR” when referring to “patient (or participant)-led research”.

<sup>9</sup> Effy Vayena, et al. “Research Led by Participants: A New Social Contract for a New Kind of Research,” *Journal of Medical Ethics*, (Mar. 2015), doi:10.1136/medethics-2015-102663: p. 1. [http://jme.bmj.com/content/medethics/early/2015/03/30/medethics-2015-102663.full.pdf]

<sup>10</sup> Project website found here: [https://www.wilsoncenter.org/program/citizen-health-innovators-project] and the map can be found here: [https://chipmap.wilsoncenter.org].

<sup>11</sup> “Patients’ organizations also collected, formalized, and circulated patients’ experience as a legitimate body of ‘experiential knowledge’ (Borkman 1976; Arksey, 1994) on their conditions, and became what Rabeharisoa and Callon (2004) called “experts of experience”. See, Vololona Rabeharisoa, et al.

which can offer new insights on a disease informed by those who experience it. However, despite the potential clinical utility of leveraging experiential knowledge, this type of understanding can conflict with more credentialed knowledge and the traditional research community. Questions about whether the knowledge and innovations produced by this growing movement will be recognized as legitimate by the traditional research community and regulatory institutions remain unanswered, as do novel concerns over the ethical and governance impacts of democratized biomedical innovation.

The convergence of three factors have contributed to this democratization of health research and practice:

- (1) vanishing barriers to entry,
- (2) the rise of access to personal genomic data, and
- (3) the emergence of crowdfunding platforms.

First, the barriers to entry to an array of genetic and biological techniques have decreased considerably — from using PCR machines, gene-editing kits, to portable genetic sequencers — along with the possibility to sequence a genome for about \$1000. Second, biomedical research is increasingly relying on personal genomic data to tailor diagnostics and therapies to groups of patients, creating the incentives for individuals to resort to personal genomics and learn about their own genetic blueprint. A third and possibly more important factor which contributes to this participatory turn is the access to financial backing that citizens recently gained through crowdfunding platforms. After raising about \$2,642,000 on experiment.com, the parents of Charlotte and Gwenyth Gray decided to hire their own research team to accelerate research in three promising treatment options for Batten disease, including gene therapy, cellular therapy, and small molecular therapy. Crowdfunding platforms enable citizens to fund the research of their choosing and significantly increase participant control of the direction of research into treatments and inventions, versus indirectly using taxpayer dollars to support federal funding of this work.

While the synthesis of these factors is not necessarily a silver bullet to new cures, it does enable us to imagine one. Which begs the question: what if it works? Will research and clinical experts acknowledge the findings produced? And what should be the role of government in these new participatory endeavors? After all, some of these are health conditions and diseases that the traditional research communities have largely ignored or considered insignificant and unaffordable to investigate.

## Governance Challenges: Embedding Responsible Governance and Conferring Regulatory Legitimacy to Citizen-Driven Biomedical Research

Knowledge legitimacy will ultimately have impacts on the governance and ethical oversight of this new movement as well. As knowledge and governance can be thought of as co-producing one another<sup>12</sup>, understanding how governance mechanisms handle the experiential knowledge generated by PLR will be key in identifying the future direction of this phenomenon and its oversight. How will traditional academic journals and government agencies assess the data derived from crowdfunded studies that may not have applied National Institutes of Health (NIH) rules for health research? If journals and agencies reject such data, does it even matter if the protocols established to produce the treatments and medical devices are accessible to other end-users? If citizen-driven biomedical studies are not seen as legitimate, will they be able to obtain Institutional Review Board (IRB) approval? Without a clear path to ethical approval, citizens who innovate in health research might not overcome the “chill factor” - a phenomenon described by DIY inventors as the fear to confront regulators by sharing the recipe for a new invention.

This dynamic of empowerment also presents complexity. The potential for patients to take an increasing role in their own diagnosis and treatment raises important questions: How does PLR transfer the responsibility to preserve safety and ethics to individuals? Who, in this

**While these groups may appear to be less risk averse, they have in-depth tacit knowledge of their conditions and a vested interest to make sure that a treatment or device will be effective, safe, and beneficial.**

participatory turn, is expected to deal with health-related regulatory and liability issues? The questions we raise should not lead one to think that medical research conducted by patients and non-traditional actors is de facto less safe, less reproducible, or unethical. While these groups may appear to be less risk averse, they have in-depth tacit knowledge of their conditions and a vested interest to make sure that a treatment or device will be effective, safe, and beneficial.

The press might cover the few memorable cases<sup>13</sup> of patients who self-experimented with unregulated gene therapy treatments. But those are not common practice. Most of the time,

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<sup>12</sup> Jasanoff, Sheila, editor. *States of Knowledge: The Co-Production of Science and the Social Order*. 1 edition, (Routledge, 2004).

<sup>13</sup> Kristen V. Brown, (2017). “Genetically Engineering Yourself Sounds Like a Horrible Idea – But This Guy Is Doing It Anyway,” *Gizmodo*, (29 November) [<https://gizmodo.com/genetically-engineering-yourself-sounds-like-a-horrible-1820189351>]; <sup>13</sup> Kristen V. Brown, (2017). “This Guy Just Injected Himself With a DIY HIV Treatment on Facebook Live,” *Gizmodo*, (18 October) [<https://gizmodo.com/this-guy-just-injected-himself-with-a-diy-hiv-treatment-1819659724>].

patients who produce knowledge and innovations address crucial user-centered issues. Often, their design is vetted by peers and doctors who have become their collaborators in a shared innovation journey. Nonetheless, we argue that it is important to think creatively about how to help citizens and patients share biomedical data, evidences, tacit knowledge, value trade-offs, and ethical concerns in ongoing conversations with regulators and society at-large.

We, as a society, are at a tipping point. We could build a new innovation ecosystem that ensures safe and responsible citizens' participation in health research, or, we could drive these emerging communities of innovators to the margins, underground, or out of existence. This report will explore the real and perceived legitimacy challenges faced by citizen-driven biomedical research in order to probe governance and ethical questions. PLR represents an exemplary case of tensions between credentialed and experiential knowledge<sup>14</sup>, a growing line of inquiry which should be investigated if appropriate oversight mechanisms are to be developed. Ultimately, experiential knowledge created by citizen-driven biomedical research may in turn impact governance<sup>15</sup>, and more work is needed to understand the dynamics of these two-entangled socio-technical systems. This study will provide new insights to design more appropriate governance strategies for citizen-driven biomedical research.

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<sup>14</sup> Vololona Rabearisoa, et al. "Evidence-Based Activism: Patients', Users' and Activists' Groups in Knowledge Society," *BioSocieties*, vol. 9, no. 2, (June 2014): pp. 111–28, doi:10.1057/biosoc.2014.2.

<sup>15</sup> Jasanoff, Sheila, editor. *States of Knowledge: The Co-Production of Science and the Social Order*. 1 edition, (Routledge, 2004).

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## METHODOLOGY

This project employs a combination of qualitative methods indicated for evaluating the perceptions of knowledge production in citizen-driven biomedical research, its legitimacy, and governance and ethical challenges in producing and mobilizing this knowledge. Established ethnographic, sociological, and STS methodologies are deployed to provide rich analysis of multiple data sources and triangulation of findings.

- *Interviews*: The project uses a mix of qualitative in-depth interviews and semi-structured interviews to probe broad perceptions around knowledge production and mobilization in citizen-driven biomedical research. This includes interviews with multiple stakeholders engaged in the process or evaluation (current or potential) of citizen-driven chronic and rare genetic disease research, including actors in and around the citizen-driven biomedical research, crowdfunders, regulators, and members of the traditional scientific community studying rare diseases. Participants were identified by utilizing existing relationships with actors and gatekeepers in each of the respective communities to aid in selecting and gaining access to potential interviewees, augmented by “snowball sampling” methods. Direct interview questions cover topics including perceptions and understanding of how PLR is conducted, perception of legitimacy and challenges to legitimacy in PLR, and perceived and experienced ethical and governance challenges with PLR. Qualitative analysis of interview data focuses on producing a descriptive understanding of the characters of challenges in knowledge production and mobilization in PLR from a co-production perspective, with consideration for impacts on ethical and governance challenges.
- *Document Analysis*: The investigators analyzed documents from both the grey and peer reviewed literature pertaining to citizen-driven biomedical research to explore perceptions around knowledge production and mobilization in PLR. Sources of data may include government documents and websites, policy reports and recommendations, academic publications about and resulting from PLR, white papers, and descriptions of PLR projects including those posted on crowdfunding platforms. Data sources were also identified by consulting with actors in the involved communities, utilization of archives, and searching other relevant resources such as crowdfunding platforms.
- *Case Studies*: Case studies like those described above were conducted for the project in order to explore individual cases of citizen-driven biomedical research related to chronic and rare genetic disease. Units of analysis for the cases include stakeholder perceptions of PLR and its legitimacy, perceptions of tacit knowledge and its role in advancing biomedical research, and perceptions of the current or desired roles of regulators and the traditional scientific community in engaging with PLR.

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## CASE STUDIES:

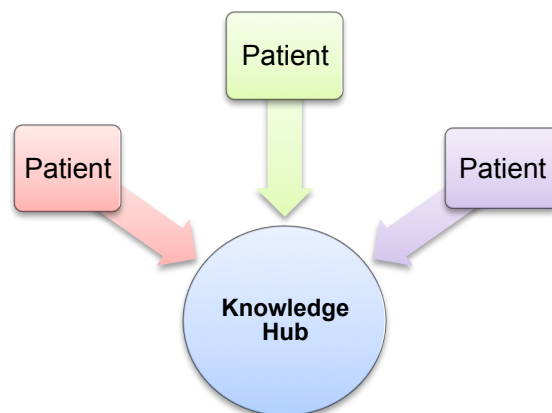
### A Few Empowerment Stories on the Health Frontier

#### The Health Pioneers

Sean Ahrens<sup>16</sup>

After being diagnosed with Crohn’s disease at the age of 12, Sean Ahrens faced years of painful and debilitating flare-ups, most of the time without clear reasons why. Crohn’s (and Colitis) is an autoimmune response that causes inflammation of the digestive tract (hence the painful flare-ups). In an effort to figure out what triggered his episodes, the first thing he needed to do was begin collecting massive amounts of data – not just his own data, but collect open-source data from others suffering from the same condition. Thus, Crohnology was born. Just a few years after Sean launched Crohnology in 2011, his site attracted thousands of patients from every continent of the world, who then banded together to advance medical knowledge of the disease by open-sourcing their data.

Patients contributed data points ranging from the treatments they take, when they started and stopped those interventions, and their overall feeling of health and wellbeing resulting from treatment. Beyond the aggregation of health data relating to Crohn’s disease, Crohnology provided a platform for patients near and far to connect with one another and potentially learn from each other’s disease management successes and failures. Perhaps the most interesting, and certainly the most extreme, aspect of Sean’s health pioneering occurred right before the start of Crohnology, when he willfully ingested parasitic worm eggs and proceeded to document his dosage and experience during his self-experimentation.



Adapted from a [photo](https://crohnology.com/about) on Crohnology.com. [https://crohnology.com/about]

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<sup>16</sup> Stephanie M. Lee, (2016). “[This Guy Swallowed Parasitic Worms on Purpose - Then Became a Published Scientist.](#)” *Buzzfeed News*, (20 August). [Crohnology: A Patient-Powered Research Network: website.](#)



Photo Credit: Sean Ahrens. Retrieved from Stephanie M. Lee, (2016), [“This Guy Swallowed Parasitic Worms on Purpose – Then Became a Published Scientist,”](#) *Buzzfeed*, (20 August).

Interestingly, he got the idea from an online forum (not dissimilar to what would turn into Crohnology), where other Crohn’s patients provided their own personal experiences with self-experimentation using parasites. Unfortunately for Sean, his experience did not match the claims of success and weekly improvements in health. However, one very big thing did come out of it – he became a published scientist in a renowned science journal, *The American Journal of Gastroenterology*. His article titled, [“Opening \(and Swallowing\) A Can of Worms to Treat My Crohn’s Disease,”](#) chronicles the acquisition of pig whipworm from Thailand, its journey from the jar to his gut, and the subsequent dosing methodology (12 doses all together, the first on March 17, 2010 and the last on August 15, 2010). Sean wasn’t entirely on his own though. His long-time gastroenterologist, which he shared with some of the patients who had recommended parasitic

worm treatment, would neither condone nor condemn his decision to self-experiment, vowing to continue to monitor his health even if he chose to ingest the unconventional treatment. Armed with the knowledge that his physician would continue to provide treatment as he always had, Sean drank the salty solution from a LED-flashing shot glass, on camera, for the world to see.

Generally, Sean’s engagement with biomedical research has not been confronted with or hindered by regulations or safety standards. He wasn’t promoting that others should follow his lead and take shots of parasitic worms they could buy off of the internet (he even wrote about the limited benefits from his alternative treatments). The parasitic worms were not a magic bullet that relieved him from his Crohn’s disease.

Of greater importance in Sean’s case than his documented self-experimentation is the call for crowdsourcing medical data on various aspects of Crohn’s so that others may use the collection to inform their own medical decisions. To address potential privacy and liability concerns raised by the use of open-sourced data from around the world to inform personal medical decisions (i.e., basing your decisions on data that has not been vetted for clinical accuracy), Crohnology’s website uses the following disclaimer:

“The data on this page is from personally submitted user reviews and ratings of treatments, and users who have tracked their health over time while taking these treatments. The data is of a small sample size of users and is subject to biases of side effects of treatments, perceived/expected efficacy, and more. For now, the data should be taken with a grain of salt.”

On the one hand, crowdsourcing open access to medical data from around the world creates vast opportunities for people suffering from painful diseases like Crohn's. In a world where pharmaceutical and other types of medical interventions are not one-size-fits all, the ability to reference what has worked for others (like taking beer out of your diet), things that have worked for some (such as vitamin B12), and things that have worked for few (e.g., ingesting parasitic worms) can provide great value.

On the other hand, privacy is always a concern when individuals are putting their personal health data into an internet-connected multi-user platform. However, Crohnology has been designed with a nod to privacy concerns. To have full access to Crohnology's data, participants must become a registered member of the site. Granted, all it takes to get full access is a name and email address.

## David Fajgenbaum<sup>17</sup>

In 2010, the tables turned for David Fajgenbaum, a 25 year old physically fit medical school student, who became increasingly fatigued, lymph nodes swollen, and odd red bumps began sprouting on his chest. After visiting the emergency room, his fears were confirmed, and he was told that his liver, kidneys, and bone marrow were not working properly. Since his doctors weren't able to provide a more clear diagnosis, Fajgenbaum decided to investigate, which led him to become one of the leading researchers in his field. Initially, his doctors believed a common form of cancer caused his condition. CT scans revealed David's body was overcome with swollen lymph nodes, which is typically a hallmark of cancer. After being told this, David's mind rushed back to a few years earlier, when his mother died of brain cancer.

A few weeks later, David was admitted to the hospital after suffering a type of mini-stroke and his blood vessels were leaking fluid, so much so that David gained about 70 pounds of excess fluid over the next two weeks, causing his brain to slow significantly. Luckily, his doctors decided to administer a very large dose of steroids, which reduced his excess fluids, and allowed his



Far left, David Fajgenbaum in 2004, in a football drill at Georgetown University, and how he looked in February 2011, two weeks after his third flare-up of the disease. Photo retrieved from: Kate Thomas, (2017), ["His Doctors Were Stumped. Then He Took Over,"](#) *The New York Times*, (4 February).

<sup>17</sup> Kate Thomas, (2017), ["His Doctors Were Stumped. Then He Took Over,"](#) *The New York Times*, (4 February). Jennifer Couzin-Frankel, (2016), ["A young doctor fights to cure his own rare, deadly disease,"](#) *Science Magazine*, (13 July).



liver and kidneys to function properly again. Unfortunately, that reprieve did not last long. While visiting his childhood home in Raleigh, North Carolina, one month after he was released from the hospital, his symptoms returned. This time, his doctors sent specimens of his lymph nodes to the Mayo Clinic where pathologists finally determined the cause of David's condition – Castleman's disease. It's no wonder why it took sending specimens to the Mayo Clinic for David to finally get a diagnosis. Castleman's disease is so rare that only around 8,000 people are diagnosed with it in the United States in a given year. Even rarer is the type that David suffered, multi-centric Castleman's disease, which only about 1,200 to 1,500 people are discovered to have in a given year in the US.

Interestingly, Castleman's disease occupies a type of no-man's-land space in medicine; doctors had no idea what caused it in patients like David. Some believed it could be a type of cancer, while others believed a virus could trigger it, and some even believed it to be a heritable genetic disorder. The only thing doctors agreed on was the prognosis – patients diagnosed with Castleman's had a 65% chance of dying within 5 years. David was undeterred and vowed to assist his physicians with finding an effective treatment. Over the next few years, dotted with alternating periods of relative health and painful relapses, David realized that the field of Castleman's research was in complete disarray (no wonder his doctors had no idea what caused it). He found variances in terminology making it extremely difficult for doctors, researchers,

**The field of Castleman's research was in complete disarray; no wonder his doctors had no idea what caused it.**

and patients to describe the condition and make comparisons across case studies, let alone actually *understand* it. This lack of coordination led David to meticulously curate his own data points on himself.

Armed with timelines, charts, and a spreadsheet of weekly samples that served as snapshots of his immune systems, David convinced his team of doctors to slice off a piece of his lymph nodes during his next relapse, test it, and save it for future research. This decision allowed him to piece together two parts of the puzzle: 5 months before he noticed his symptoms returning his T cells spiked (a sign that his body was preparing for a big fight) and about 3 months before his next relapse his body began producing more VEGF, a protein that instructs the body to make more blood vessels (yet another sign his body was preparing for 'the big one'). This led David to think that the problem was really that his body's internal communication system was telling his metabolism to produce VEGF and T cells when there was no big fight looming. If he could effectively shut down his mTOR pathway, the body's main communication line, then he might be able to keep his body from overreacting and producing excess VEGF and T cells. At this is the point, David began to self-experiment, but his doctors were not initially agreeable to this idea. His doctors were reluctant to collaborate with David as a patient even though he was also their colleague. Luckily, David prevailed; he stopped taking his cancer medications and began taking Sirolimus, a drug typically prescribed

for kidney transplant patients. David saw potential in Sirolimus because of its ability to target his mTOR pathway. A year later, David's weekly blood sample spreadsheet showed that his immune system was back to functioning at a normal level. With his health steadily improving, David returned to the coordination problem he found in Castleman's research, and started the Castleman's Disease Collaborative Network, a non-profit organization that works to coordinate Castleman's research. The organization's top priority was to identify the cause of Castleman's. Generally, single-mindedness is an undesirable trait in a physician, let alone a medical researcher.



Dr. Fajgenbaum, in blue shirt at left, and his patient Gary Gravina, right, who both have Castleman disease, having blood drawn last July at the Abramson Cancer Center of the University of Pennsylvania. Photo Credit: Nicole Bengiveno/The New York Times  
Photo retrieved from: Kate Thomas, (2017), "[His Doctors Were Stumped. Then He Took Over.](#)" *The New York Times*, (4 February).

Yet, David continues to prove his colleagues wrong and continues to push Castleman's research forward at a quick and steady pace. David's experience in traditional medicine allowed him to successfully navigate the world of rare medical diagnoses far better than most. He was able to identify problems with the current state of Castleman's research and convince his team of doctors that his proposed treatment was the best way forward. Even David, now a doctor, had difficulty convincing his doctors that his knowledge of the disease was legitimate

medical knowledge, regardless if it was acquired via non-traditional methods. Although David had a leg up on other health pioneers because he was himself a doctor, David came across other issues that span across citizen-driven biomedical research. In particular, he was confronted with poor scientific research on his type of Castleman's disease. Before David began researching Castleman's disease himself, much of the research and terminology was in complete disarray, if present at all. Varying terms were used interchangeably, which made slogging through scientific journal articles difficult even for him, let alone for a complete novice with little to no prior medical experience. But now, [David has made it his mission](#) to not only find an effective treatment and eventual cure for Castleman's disease, but to collaborate with other Castleman researchers in order to fill the gaps in research and bridge the divide between doctors and patients. The way forward is for doctors and patients to work together and encourage medical researchers to share their knowledge and data in order to create more cohesion and organization of medical information and research.

## Steven Keating<sup>18</sup>

In 2007, while pursuing his doctoral studies at the Massachusetts Institute of Technology's Media Lab, Steven Keating had an MRI as part of a study. His brain scan revealed a slight abnormality, but his doctors dismissed it beyond deciding it was worth monitoring. By his next follow up scan in 2010, his brain seemed normal. But, when he began smelling whiffs of vinegar in the summer of 2014, he thought back to the

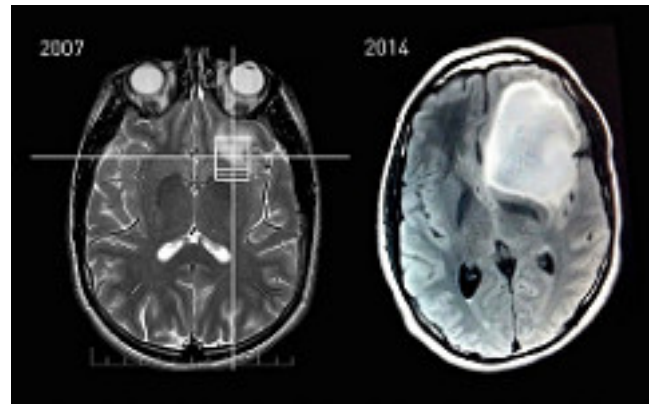


Photo Credit: Steven Keating's [Flickr album](#) linked in the health tab of his [personal website](#).

location of his brain abnormality (it was located near his olfactory, or smell, center). He advocated for his doctors to perform another MRI, and a short three weeks later, Steven underwent surgery to remove a cancerous tumor the size of a tennis ball from his brain. As Steven started his PhD in mechanical engineering, he became invested in curating his own medical information. By the time he turned 26 years old, Steven had collected an estimated 70 gigabytes of his own patient data. Steven had one big advantage over the average patient in the US: he knew exactly what medical information to ask for and how to navigate the medical field. He published much of his patient data on his [personal website](#), including a [10 hour video of his surgery](#), [paper health records](#), and his genetic sequencing from 23andMe. It was not easy though. Steven has

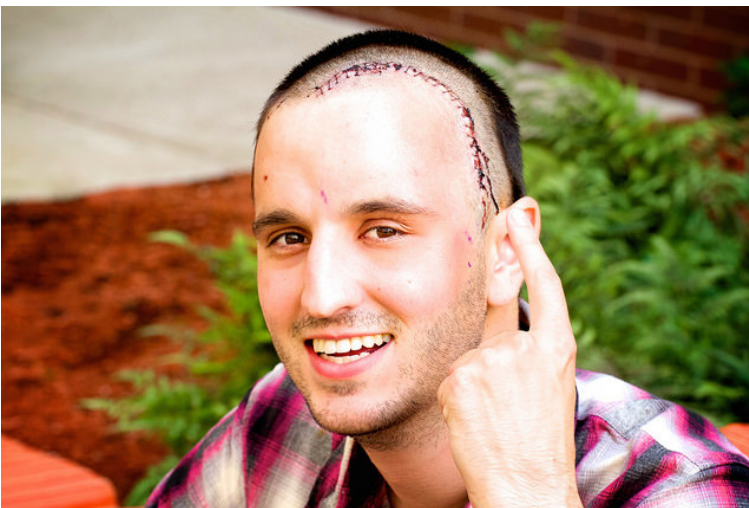


Photo Credit: Steven Keating's [Flickr album](#) linked in the health tab of his [personal website](#).

said, "The person with the least access to data in the system is the patient. You can get it, but the burden is always on the patient. And it's scattered across many different silos of patient data." Moreover, not all patients are like Steven, and may not have the medical literacy to know exactly what medical information to request and may not be able to bear the burden of navigating the various silos of information.

The prevailing culture in medicine is not conducive to

<sup>18</sup> Steve Lohr, (2015), "[The Healing Power of Your Own Medical Records](#)," *The New York Times*, (1 April). Julia Belluz, (2015), "[Meet the MIT student who filmed his own brain surgery](#)," *Vox*, (2 May). Steven Keating, MIT Media Lab, Mediated Lab Biography page: [<http://matter.media.mit.edu/people/bio/steven-keating>]. Steven Keating Personal Website: [<http://stevenkeating.info/main.html>].

sharing data with patients, often citing privacy and legal concerns. Information is power, and the power should be shared with patients. While increasing patient access to their personal medical information and health data is an admirable goal, it must be monitored to ensure patient privacy. While Steven may be comfortable with the video from his brain surgery being on the internet for anyone to see, he may be the exception, not the rule. Yet, Steven has been fairly open and encouraging of others to follow his lead and do the same – all in the name of patient empowerment. Again, patient empowerment is certainly a praiseworthy endeavor, but without adaptive regulatory and data-governance mechanisms, empowering patients with their personal medical information might make health data vulnerable to attack and potential misuse.

Information is power –  
power that should be  
shared with patients.

# health



**download health data**

If interested, below are links to some of the data! I've documented this entire process, straight from pre-surgery words, full surgery video, to post-surgery thoughts. Contact me for more scans/data/videos if interested (it's all open, there's just too much to post! 10-hour surgery video, tissue microscopy, genetic sequencing, tens of MRIs/scans, and more...we need a better way to store/access/use patient data!):

- [Flickr online album of images/short videos \(online link\)](#)
- [Short video of awake surgery \(13 MB\)](#)
- [Video of surgery \(10 hours\) shown in 2 minutes, time-compressed \(~ 235 MB\)](#)
- [Short video of CT repaired skull \(35 MB\)](#)

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Feel free to [contact me](#) if you have ideas on new data to collect!

Screenshot of the main page of Steven Keating's health tab in his [personal website](#). Taken on 01/02/2018. Steven has provided 70 gigabytes of his personal health data for anyone to download from his website.

## Dana Lewis<sup>19</sup>

As a young woman with Type 1 diabetes, Dana Lewis was constantly having to monitor her blood-glucose levels and determine whether she needs an insulin boost, and if so, how much. The number of decisions that diabetics have to make on a daily basis simply to stay alive is staggering, but Dana believes that she has reduced the hundreds of decisions that Type 1 diabetes patients must make a day to around six. Initially, Dana just wanted to make her continuous glucose monitor louder, because it failed to wake her up at night if she needed a shot of insulin. But just creating a louder glucose monitor did not satisfy her desire to be able to predict glucose levels hours into the future and create personalized recommendations for preventative actions. Dana decided that

she wanted to live the most normal life she possibly could without having to constantly poke and prod herself and developed a hybrid closed-loop artificial pancreas to regulate her glucose levels for her. Dana first created the “Do-It-Yourself Pancreas System” (#DIYPS) in December 2013. Dana leveraged her skills as a digital health analyst and enlisted the help of her husband, Scott Leibrand, who has expertise in computer networks.

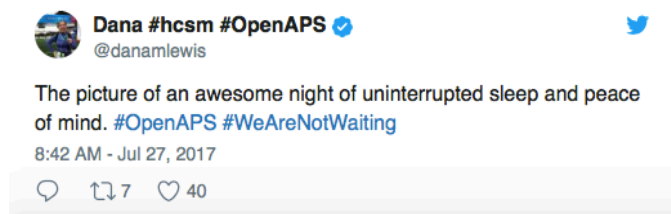


Photo Credit: Dana Lewis. Retrieved from her [August 7, 2017 blog post](#) on the DIYPS website.

<sup>19</sup> Rebecca Heilweil, (2017), [“This Woman Designed - And Texts - Her Own Pancreas,”](#) *Forbes*, (15 June); Clare McGrane, (2017), [“Geek of the Week: Dana Lewis built her own artificial pancreas, and is helping hundreds of other people do the same,”](#) *GeekWire*, (7 April). Also see, [“What is Living with an Artificial Pancreas Like?”](#) *Medical Futurist*. Also, see Dana Lewis and Scott Leibrand, (2017), [“Automatic Estimation of Basals, ISF, and Carb Ratio for Sensor-Augmented Pump and Hybrid Closed-Loop Therapy \(Autotune\),”](#) Poster presented at the *American Diabetes Association Scientific Sessions*, (10 June). (2017), [“Dana Lewis: Most Creative People,”](#) *Fast Company*. - “There have been no reports of unauthorized access to any patients implanted device, according to Abbott. The FDA says that the vulnerability allows an unauthorized user to access a device using commercially available equipment and reprogram it...The US Department of Homeland Security said that, “it is recommended that healthcare providers discuss this update with their patients and carefully consider the potential risk of a cybersecurity attack along with the risk of performing a firmware update...” This is a quote from: Alex Hern, (2017), “Hacking risk leads to recall of 500,000 pacemakers due to patient death fears,” *The Guardian*, (31 August) [<https://www.theguardian.com/technology/2017/aug/31/hacking-risk-recall-pacemakers-patient-death-fears-fda-firmware-update>].

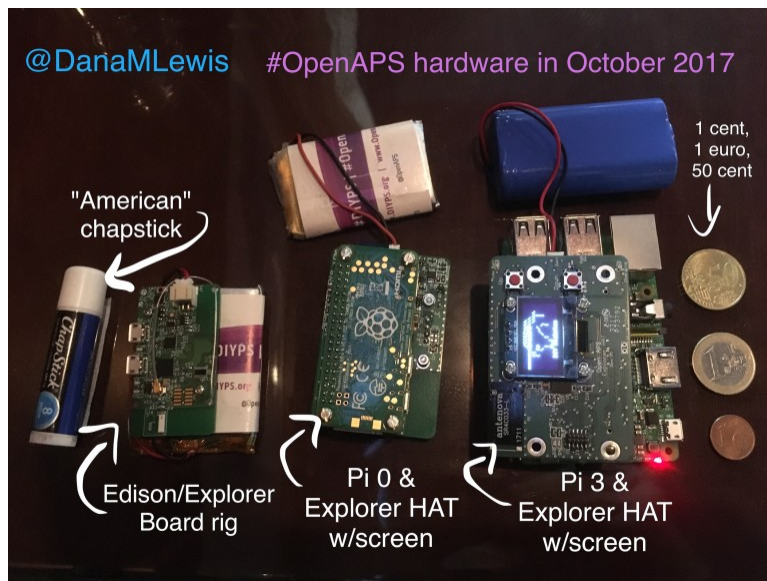


Photo Credit: Dana Lewis. Retrieved from her [October 22, 2017 blog post](#) on the DIYPS website.

hardware, such as a Raspberry Pi mini-computer, all the while using open source code and tools to communicate directly with her insulin pump.

This culminated in the ability for Dana to text her artificial pancreas when she needs to adjust her insulin levels. Her hybrid closed-loop artificial pancreas rig combines a small computer, radio stick, and battery in order to generate interoperability with her continuous glucose monitor and her insulin pump. For Type 1 diabetics, this sort of interoperability between medical devices is what will free them from the oppressive task of manually monitoring their levels. Every five minutes, the artificial pancreas pulls data from her insulin pump and her continuous glucose monitor, which is then combined and run through the algorithm that produces the output, the recommended basal rate. Now, Dana can simply text her artificial pancreas when she needs to adjust her levels - essentially creating an auto-pilot system for managing Type 1 diabetes. To date, more than 250 people with Type 1 diabetes have used Dana's tools to build their own systems.

As with any device that is connected to the internet, Dana's artificial pancreas could be vulnerable to cyber-attacks and hackers, as the most extreme examples, and internet outages more broadly. The most extreme of the three examples, a cyber-attack that targets internet-connected devices like artificial organs and pacemakers, is a potential [vulnerability](#) but not necessarily the most likely of potential problems. The most notable issue is likely Dana's ability to share her device with other diabetes patients simply because Dana came up with the idea, rather than a large bioengineering or medical device company. She is giving a product away for free that others could sell for profit. Moreover, because she seeks to disseminate the knowledge of the manufacturing process for her artificial pancreas design so others can build their own as well, she may incite interesting challenges for traditional medical journals taking the data generated by her device as legitimate. However, Dana continues to give talks at various

Together, they developed an effective algorithm that could automatically “tune insulin pump basal rates, ISF, and carb ratios” and could be used in the open source community. Dana advocates that the concept behind auto-tuning insulin pumps using data should be the norm rather than relying on traditional methods of guessing or weight-based estimations. She succeeded in creating a successful artificial pancreas by using the predictive algorithm from #DITPS and pairing it with off-the-shelf

institutions and presents her research to established groups like the American Diabetes Association. Thus, she appears to have discovered a remedy to the data legitimacy problem by increasing the number of participants, in traditional and non-traditional health research ecosystems, standing with her in support of her novel and necessary invention.

## Matt Might<sup>20</sup>

Imagine looking at your six-month old child whose developmental growth began to slow around three months after birth, describing your child's body as "jiggly". This is the story of Matt Might and his wife's journey to discover what was killing their infant son, Bertrand. Around the eight month mark, Matt's wife took Bertrand to his first developmental pediatrician appointment while Matt was settling in at his new job. After a long day at the faculty retreat, the pediatrician called to speculate



Photo Credit: Matt Might's ["About Us" section on the Overcoming Movement Disorder website](#). From top-left, Matt's wife, Christina, Matt, to bottom-left, Victoria, and Bertrand. (Their third child, Winston, is not pictured here).

that Bertrand had brain damage and scheduled a MRI for the following week with a pediatric neurologist. Fortunately, the MRI showed a healthy, normal infant brain. Although this could be good news to some, Matt was plagued with one nagging question: "what is killing my son?" And Bertrand's doctors were just as curious and concerned. After countless rounds of bloodwork, the lab reported only one anomaly: extremely elevated alpha-fetoprotein (AFP) relative to what it should have been for their son's age. Only two known disorders elevated AFP, and only one of those correlated with movement disorders: ataxia telangiectasia (A-T). Not only is A-T considered a fatal degenerative disorder, it is also considered not only incurable, but untreatable. This curiosity and concern on the part of Bertrand's doctors led them to ask Matt and his wife, "Are you two sure you're not related?" (they aren't).

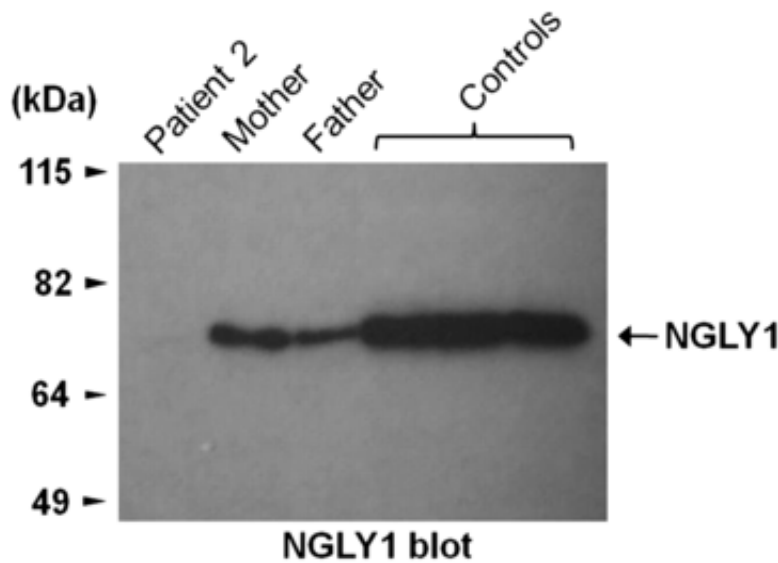
Trying to understand why so many of their son's doctors were asking them whether they were related led Matt to research how genes and mutations work to better understand his

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<sup>20</sup> Matt Might. ["Hunting Down My Son's Killer"](#); Matt Might and Seth Mnookin, (2014), ["One of a Kind: What do you do if your child has a condition that is new to science?"](#) *The New Yorker*, (21 July). Also see, "The ketogenic diet is a strict high-fat diet which forces the brain to switch from glucose to ketone bodies for its primary fuel." See Matt Might, "Hunting Down My Son's Killer", [<http://matt.might.net/articles/my-sons-killer/>]; and Matthew Might and Matt Wilsey. 2014. ["The shifting model in clinical diagnostics: how next-generation sequencing and families are altering the way rare diseases are discovered, studied, and treated."](#) *Genetics in Medicine*, Commentary, (1 January).

son's diagnosis since there were no other reported cases. His son was patient zero of a degenerative, fatal, incurable, and untreatable disease. Fortunately for Bertrand, he has one persistent father who refused to accept that his son was the only person in the world with A-T and decided to help find a treatment. In order to do so, he leveraged his knowledge of computer science, and realized that (on a basic level) computation and genetics aren't entirely dissimilar – genes are like the 'code' in the computer program. During his research, Matt became less and less convinced that his son did in fact have A-T: he didn't present in any of the ways mentioned in the A-T literature, and, eventually, the gene-test for A-T came back negative. So back to the drawing board. When Bertrand was around fifteen months old, oligosaccharides, chains of simple sugars, were found in his urine. Immediately, a small family of genetic disorders were implicated – Bertrand likely had inborn errors of cellular metabolism. Even though they did not know at the time which of the disorders Bertrand actually had (they now know that Bertrand actually created a new category of this kind of genetic disorder, a congenital disorder of deglycosylation), they did know that their son's life expectancy was cut down to about two or three years. Although there were some treatment options, unlike A-T, none of them were applicable to Bertrand's case. He was too far along for a bone-marrow transplant. So, back to the drawing board again. This is where Matt and his wife decided to experiment with hormone therapy and dietary changes. In order to reduce Bertrand's number of seizures, they decided to try a ketogenic diet; however, it only worked until the tonic seizures set in. At that point, they decided to try their "nuclear solution" - adrenocorticotrophic hormone therapy (ACTH). It worked, but Bertrand's hair began fading and falling out and he grew facial hair.

After a few more years and many more wrong diagnoses, Bertrand's true killer was identified by scientists and researchers at Duke University – he lacked the ability to produce the N-Glycanase 1 enzyme, which is crucial to fixing misfolded proteins. It is not surprising that it



"The dark bands in this ink blot indicate the amount of N-Glycanase 1. Bertrand is "Patient 2." Photo Credit: Matt Might's blog post, "[Hunting Down my Son's Killer.](#)"

took so long to accurately diagnose Bertrand. Considering that the discovery of rare genetic disorders is a long process of steadily eliminating possibilities, coupled with the fact that both Matt and his wife carry different NGLY1 mutations, the odds of Bertrand inheriting both mutations is somewhere around 1 in 4,000,000 births. Even though N=1 diagnosis discoveries are inherently difficult, this discovery process becomes more powerful when individuals suffering from a



condition share their experiential knowledge. Matt is working towards creating that reality.

Matt and his family are an extraordinary example of how the traditional medical discovery process could be significantly improved. But, improvement depends on acceptance by traditional medicine, which was initially suboptimal. Family involvement in the discovery process can be viewed as either helpful or problematic depending on the practitioner. Although they were the ones living with and caring for Bertrand on a daily basis when he was not in the hospital and experiencing their son's illness vicariously through him, experiential knowledge is not highly regarded like traditional (i.e., credible) knowledge. Bertrand fortunately has dedicated parents who refused to allow traditional methods for acquisition of knowledge to automatically override a patient's, or their family's, experiential knowledge.

**Bertrand fortunately has dedicated parents who refused to allow traditional methods for acquisition of knowledge to automatically override a patient's, or their family's, experiential knowledge.**

Now, Bertrand is 8 years old, in no small part due to his parent's devotion to investigating his condition. Perhaps in part for catharsis, Matt decided to vent his frustrations in a blog and inform others in the blogosphere about what helped them further the research and discovery process in hope that no other families would have to go through the same long and arduous journey.

Even though he knew that this was unlikely at best, he operationalized his blog post titled "Hunting Down My Son's Killer" to bring together other families affected by rare genetic diseases and provide a sense of hope. Hope, ultimately, would be a key factor in this case study. Hope can drive innovative, experimental, and sometimes risky biomedical research; but hope can also push patients and their families to take the first step towards bridging the gap between patients and their families, and health care providers, scientists, and regulators. Matt recognized this hurdle and overcame it by collaborating with another family with a child suffering from a rare genetic disease and authoring [an article](#) on their experiential knowledge in a traditional medical journal, *Genetics in Medicine*. Now they hope others living with and experiencing these diseases will take their advice and collaborate more closely with other patients and their families.

## The Gray Family<sup>21</sup>



Gwenyth and Charlotte Gray last year: Trish Alison Photography  
Retrieved from: Tiare Dunlap, (2016), "[Parents Fund Breakthrough Therapy That May Treat Daughters' Fatal Brain Disorder: 'We Were Told to Take Them Home and Watch Them Die'.](#)" *People Magazine*, (27 April).

of communication and motor skills, and even dementia. Children diagnosed with Batten's disease typically don't live past their 12<sup>th</sup> birthday, but the Gray family refused to give up hope. "We were told to just take them home and watch them die. But that was something that we just couldn't do." They refused to let a genetic neurodegenerative disorder render their daughters blind, bedridden, and severely psychologically impaired.

Instead of accepting defeat, Gordon and Kristen launched the [Charlotte and Gwenyth Gray Foundation to Cure Batten Disease](#) by leveraging his Hollywood producer connections. Stars like Jennifer Garner, Dwayne Johnson, Anne Hathaway, Rihanna, and Gwyneth Paltrow helped them reach their goal by crowdfunding \$3.5 million to cure Batten's disease. These funds helped the Gray family to establish a clinical trial for an investigative gene therapy at Nationwide Children's Hospital. Charlotte, then only 5 years old, became the first patient in the world to enroll in a clinical trial for an experimental gene-therapy. The treatment, if effective,

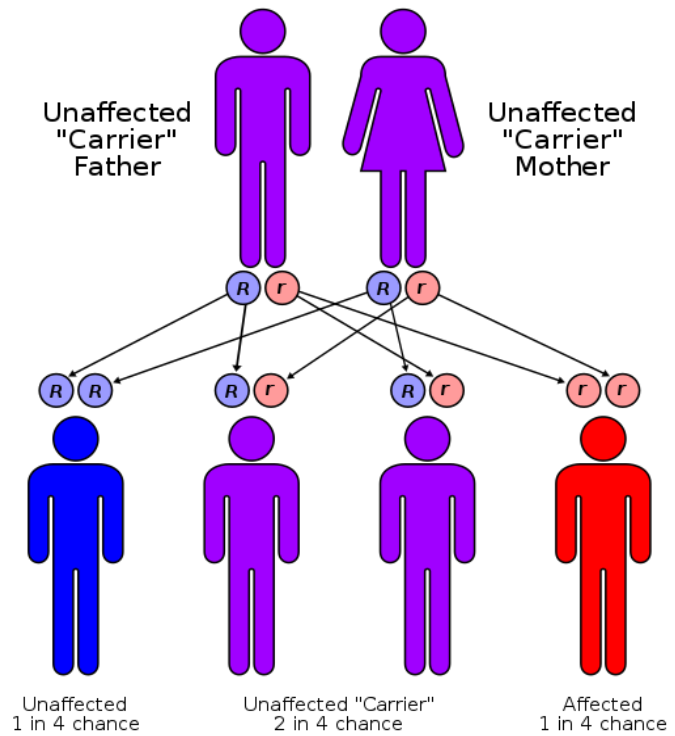
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<sup>21</sup> Tiare Dunlap, (2016), "[Parents Fund Breakthrough Therapy That May Treat Daughters' Fatal Brain Disorder: 'We Were Told to Take Them Home and Watch Them Die'.](#)" *People Magazine*, (27 April). Jerry R. Mendell, *Nationwide Children's Hospital*, (2016), [Batten CLN6 Gene Therapy](#), U.S. National Library of Medicine: Clinical Trial, (1 April). [Batten Disease Fact Sheet](#). National Institute of Health, Neurological Disorders and Stroke. [<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Batten-Disease-Fact-Sheet>]. Currently, there are 25 clinical trials reported for Batten Disease on [clinicaltrials.gov](https://clinicaltrials.gov). Ten studies are recruiting (the Gray family's trials is in this group), five are active but not recruiting, one is enrolling by invitation, one is terminated, seven are completed (three with results), and one was withdrawn. For more information regarding the clinical trials established for Batten disease, see [[https://clinicaltrials.gov/ct2/results?cond=batten+disease&Search=Apply&age\\_v=&gndr=&type=&rslt=](https://clinicaltrials.gov/ct2/results?cond=batten+disease&Search=Apply&age_v=&gndr=&type=&rslt=)].

will replace the mutated gene that caused Batten’s disease in Charlotte’s brain with a healthy gene transported by a virus that is not harmful to humans. Dr. Jerry R. Mendell, lead investigator in the clinical trial, says “the most direct way to correct a genetic disease is to restore what is missing and that is precisely what we have done in the work with the first patient [Charlotte] with this devastating disease.”

In early 2017, Charlotte underwent the one-time procedure and, although it is too early to make definitive statements on its effectiveness, the Gray family is optimistic. With the help of speech and occupational therapy, Charlotte is relearning how to walk and has begun to reconnect with her language skills – all of which were affected by Batten’s disease. In October 2017, Gwenyth became the second patient enrolled in the clinical trial. Unique to the Gray family’s experience is that crowdfunding significantly accelerated the clinical trial process. With \$1 million USD, they were able to hire a team of doctors and scientists committed to conducting research to treat Batten’s disease (CLN6) and begin the research phase immediately.

Since Batten’s disease affects an estimated 2 to 4 of every 100,000 live births in the United States, the rarity hinders the amount of research conducted on it. Thus, it’s not surprising that it took a wealthy movie producer to initiate the funding process for a clinical trial for his daughters’ disorders. But, this case study also exemplifies how crowdfunding can steer clinical trials and medical research. Historically, in the US, establishing clinical trials has existed within the realm of the traditional approach to medicine. Big pharmaceutical companies identify a market (i.e., people with rare genetic disorders with few treatment options) and then develop drugs to market it to that population. The clinical trial process tends to favor large pharmaceutical companies with experience and revenue from past products that have undergone clinical trials and received FDA regulatory approval. In the Gray family’s case, the ability to crowdfund \$3.5 million in one year helped them overcome that initial hurdle and establish a clinical trial on their own.



This image shows the heritable nature and rarity of Batten disease.

## Sonia Vallabh and Eric Minikel<sup>22</sup>

At the beginning of 2010, Sonia Vallabh's mother, a healthy middle-aged woman, had a sudden bout of blurry vision, a spike in blood pressure, and strange lapse of judgment while driving resulting in a minor traffic accident. A few months later, she was unable to feed herself, walk, or recognize her family members. By summer she was on life support and she passed away not long after. Following the autopsy, practitioners identified the disease that took Sonia's mother's life as a genetic prion disease called fatal familial insomnia, a rare and incurable genetic neurodegenerative disease. Since it was genetic, due to merely one wrong letter in one wrong place in the genome, Sonia had a 50-50 chance of having the same mutation. Without hesitation, Sonia and her husband, Eric Minikel, decided to have Sonia tested for the genetic marker. Unfortunately, she has it. "Does this mean I'll definitely get the disease?"

After finding out Sonia had the same genetic typo in her DNA that proved fatal in her mother, Sonia and Eric quit their jobs in law and city planning to become experts in fatal familial insomnia, more specifically, PRNP mutation D178N. They almost immediately began to familiarize themselves with the scientific literature in order to be able to answer some of the questions that doctors and scientists stumbled around. For instance, they learned that the question Sonia asked after learning her diagnosis was a question about penetrance, the probability of developing a particular genetic disease if you have a particular genetic mutation. Her doctors wouldn't be able to assess the penetrance of fatal familial insomnia,



Photo Credit: *Kayana Szymczak for NPR* - Eric and Sonia prepare materials for an experiment measuring prion protein in spinal fluid. They're both third-year Harvard graduate students doing research at the Broad Institute in Cambridge, Mass. Retrieved from: (2017), "[A Couple's Quest to Stop a Rare Disease before it Takes One of Them](#)," *NPR* (19 June).

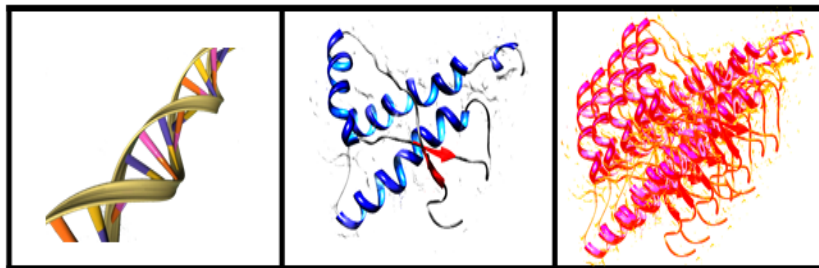
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<sup>22</sup> Eric Minikel, (2016) "[Does this mean I'll definitely get the disease?](#)" *CureFFI.org*, (20 January); D.T. Max, (2013), "[A Prion Love Story](#)," *The New Yorker*, (27 September); Matthew S. Lebo, Sheila Sutti, and Robert C. Green, (2016), "['Big Data' Gets Personal](#)," *Science Translational Medicine*, 8(322): pp. 322fs3, (20 January); Richard Harris, (2016), "[Big Data Coming In Faster Than Biomedical Researcher Can Process It](#)," *NPR*, (28 November). Also see, 23andMe, [Privacy Policy](#). [<https://www.23andme.com/about/privacy/>]; and Sonia Vallabh, (2017), "Prion Registry: an online tool to connect patients, families, and researchers," *Prion Alliance* (10 November) [<http://www.prionalliance.org/2017/11/10/prion-registry-an-online-tool/>].

but they would go so far to say that “the evidence suggests that...” As they would soon learn, from their own research, the penetrance of fatal familial insomnia is very high, around 90-95%. The evidence that her doctors referred to was a longitudinal study of three families with the mutation, and in each generation, all or almost all people with the mutation died of the disease. This is the reason why Sonia and Eric completely changed career paths, and dedicated their lives to finding a cure.

They began to look at Sonia’s family tree and noticed that Sonia’s mother seemed to be the first in living memory to die of a neurodegenerative disease; there wasn’t even a history of dementia in the family. Her mother was also the first South Asian to ever die of this particular subtype of prion disease, which led them to look into whether other scientists were researching whether the disease behaves differently in South Asians, or, if it was possible that more families carried the mutation – both reasonable questions. But, they found that only the families where everyone, or almost everyone, succumbs to fatal familial insomnia gets studied and published in scientific journals. As they would come to learn, they weren’t the first people to wonder about those sorts of questions. What they found out was the genetic researchers discover the mutations by identifying families where, generation after generation, about half of the people with the disease die. Thus, when the probabilities are determined based off of this kind of discovery process, the answer to Sonia’s question is tautologically 100%. But, this is a prime example of

ascertainment bias. Prion disease caused by Sonia’s exact mutation affects about 1 in every 100,000 people, and if the penetrance is close to 100%, then it seems that either the disease is more common than previously thought and under diagnosed, or, there are undiagnosed people walking around that won’t die from it. Clearly, Sonia wants to be in the latter group.



**PRNP is a gene in your DNA which encodes for prion protein**

**Prion protein or PrP is a protein on the surface of your cells**

**A prion is an infectious particle made up of misfolded prion proteins**

*Artist's rendering; protein images adapted from Ilc et al 2010 <http://goo.gl/WWBR7>*

Retrieved from: (2013), [“What are prions?”](#) Prion Alliance.

After Eric had become a successful bioinformatics analyst at Massachusetts General Hospital (MGH), he met other scientists and researchers that were trying to develop a massive reference dataset of rare genetic disorders. To help, Eric went around asking his colleagues at MGH and the Broad Institute, and many others, if they would be willing to let him merge all of their DNA sequence data into one giant database of genetic variation. Surprisingly, most

said yes. One of his colleagues at MGH, Daniel MacArthur, was working on a parallel dataset project with rare muscle disorders and they soon began working together; and Eric started working full-time in Daniel's lab. Unfortunately, Sonia's mutation was stubborn and wouldn't pop up no matter how large the dataset got. But, he noticed that some other mutations in the prion protein did show up, so he and Sonia started combing through the scientific literature in order to identify every single genetic mutation that popped up in the prion disease query. In the end, they came up with 63. This meant that these 63 mutations were present in almost 1 in every 1,000 people in Daniel's database, which meant that something was off, because the probability of genetic prion disease is around 1 in 50,000. But nothing was wrong with the DNA sequence data, so something had to be wrong with the diagnosis.

Since their research didn't turn up anything with the number of diagnoses, the best explanation they could come up with was that the penetrance of prion genetic mutations isn't as high as 90-95%. Maybe all prion mutations aren't created equally. Sonia and Eric presented a poster on their findings at the Prion 2014 conference in Trieste, Italy, and won the prize for best poster. "The research community decided we were legit." When they got back to Boston, they started calling prion surveillance centers, national authorities that perform autopsies, offer genetic testing, and collect statistics on prion disease; and while they were in Trieste, they got to meet many of the people who run prion surveillance centers. Within a few months, they received data on 16,025 prion disease cases, and their dataset grew to be ten times the size of the largest dataset in the current scientific literature. Then they contacted 23andMe, and after careful planning to protect consumers' privacy, the direct-to-consumer genetics company agreed to partner with them, allowing them to analyze data from over 600,000 people. Armed with vast amounts of data collected from prion surveillance centers, 23andMe, and the database at MGH, their hypothesis ended up being corroborated – a rare disease means there is a rare mutation.



Retrieved from: Eric Minikel, (2017), "[Prion Alliance honored with Research Models in Drug Discovery Award](#)," *Prion Alliance* (26 September). "The award recognizes [their] work to translate fundamental biological understanding of prions into a therapy for human prion disease. After accepting the award, [they] spoke about the profound ways in which preclinical models of prion disease have informed [their] efforts and [the] road ahead to the clinic. The funds from this award will support efforts to lay the groundwork for future clinical trials in prion disease."

While Sonia and Eric continue to research fatal familial insomnia, they are learning that not all genetic prion diseases are created equal and not all are as deadly or have high penetrance like the 90-95% that Sonia's doctors told her. Although Sonia and Eric have made great strides

in their research, their non-traditional beginnings in the field of medical research hampered their ability to really hit the ground running. No one took much stock in their hypotheses or gave their questions much consideration. It took Eric building a relationship with someone else in the hospital where he was working as a bioinformatics analyst before they would get access to the kinds of datasets they needed to continue their research on Sonia's genetic mutation. At that point, they still did not have a solid answer to Sonia's initial question, "So does that mean I'll definitely get the disease?" Beyond the legitimacy problem (i.e., getting traditional scientists and researchers to take them and their hypotheses and conclusions seriously), Sonia and Eric came across the accessibility of data problem that many of these case-studies have struggled with as well.

What propelled their research forward exponentially was their partnership with 23andMe, the direct-to-consumer genetic sequencing company. As with other consumer-based genetic sequencing, 23andMe users can opt-in or out of allowing their genomic data to be used for research. According to [23andMe's privacy statement](#), they only use and share information in three circumstances: to provide, analyze and improve their services; if the consumer has consented; and recruitment of external research and information shared with third parties. It seems that Sonia and Eric would likely be in the third category, which states that,

"We may share aggregate information with third-parties, which is any information that has been stripped of your [Registration Information](#) (e.g., your name and contact information) and aggregated with information of others so that you cannot reasonably be identified as an individual ("Aggregate Information"). This Aggregate Information is different from "individual-level" information ... In contrast, individual-level Genetic Information could reveal whether a specific user has a particular genetic trait, or all of the Genetic Information about that user. 23andMe will ask for your consent to share individual-level Genetic Information or Self-Reported Information with any third-party, other than our service providers as necessary for us to provide the Services to you."

After working through the privacy policies standards for not allowing third-party researchers to access individual-level information, Sonia and Eric were able to analyze more genomic information than ever before. Their partnership with 23andMe allowed them to conclude that Sonia's doctors, and the vast majority of the scientific literature, had the penetrance of fatal familial insomnia wrong. A rare disease, like the subtype of genetic prion disease present in Sonia and her mother, means there is a rare genetic mutation. Now, Sonia and Erik are continuing their research and have created a [Prion Registry](#) in collaboration with the CJC Foundation, the CJD International Support Alliance, the national surveillance center, and various clinics around the country and world to bring patients, families, and researchers together.

## Andy Woods<sup>23</sup>

At just 4 years old, Andy Woods' daughter Stellablue began complaining of cramps. At first, Andrea, her mom, who had just given birth to her little sister, thought Stella might have a milk allergy. But when they felt her side, there was something rock hard and big. An ultrasound at Bozeman Health Deaconess Hospital revealed a cancerous kidney tumor the size of a cantaloupe. Their doctor recommended that they take Stella to any out-of-state children's cancer center immediately. Andy abandoned his tile construction business, packed up his family and their dog, and drove 11 hours to Seattle. Like those parents mentioned above, Andy set out to learn as much about his daughter's cancer as he possibly could.

In order for Andy to be able to learn about Stella's cancer, he knew he would have to invest a lot of money into his re-education; money his family didn't have since Stella was undergoing treatment. So, Andy decided that crowdfunding would be the best way to raise the funds necessary for him to advocate for more research and supplement his education.

Andy used the online crowdfunding website, Consano.org, to raise the funds necessary for a summer internship in Portland, Oregon. He founded the Rare Childhood Cancer Advocacy Group and helped other families dealing with children diagnosed with rare cancers push for more research. But, he soon found out that big pharmaceutical companies do not consider uncommon cancers profitable, which means that clinical trials to develop drugs to treat rare cancers are rarely funded.

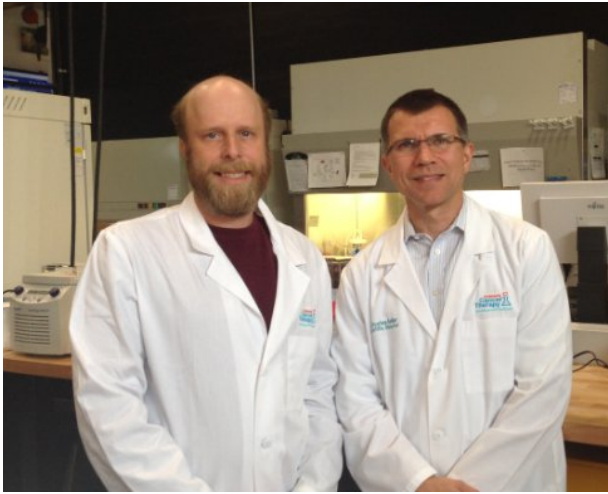


"Soren Woods, 4, center, and sister Stellablue, 9, in pink, sit with their dad, Andy, and mom, Andrea, at their home. Stellablue was diagnosed with a rare form of cancer five years ago. Andy has made it his mission to learn everything he can to help his daughter and other families around the country who have children with cancer." Photo Credit: Shawn Raecke / For the Chronicle. Retrieved from: Gail Schontzler, (2016), "[Determined dad fights daughter's rare cancer](#)," *Bozeman Daily Chronicle*, (19 June).

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<sup>23</sup> Gail Schontzler, (2016), "[Determined dad fights daughter's rare cancer](#)," *Bozeman Daily Chronicle*, (19 June); "[The Functional Genomics of Wilms Tumor: A More Effective and Less Toxic Treatment Strategy for Children with Anaplastic Wilms Tumor](#)," *Consano*; John Lauerma, (2016), "[The Montana Dad Who Fought Big Pharma to Get a Cancer Drug Trial](#)," *Bloomberg*, (29 June).





Retrieved from: Andy Woods, (2016), "[A study of Anaplasia in Wilms Tumor](#)," *LinkedIn* Blog Post (27 September). "Andy Woods, Summer Intern at The Children's Cancer Therapy Development Institute. Mentors: Dr. Charles Keller, Scientific Director and Dr. Noah Berlow."

During his internship, he would do hands-on research in a cancer lab at the Children's Cancer Therapy Development Institute. Consano was founded by Molly Lindquist, a Portland mother and breast cancer survivor, precisely to help support fundraising efforts for medical research. In 2011, Stella underwent a 13-hour surgery to remove a 7 pound mass. Once Stella made it through, Andy and Andrea were optimistic, as doctors had said that Wilms tumor has a 92% cure rate with chemotherapy. Unfortunately, after her tumor was sent to the pathology lab, the results were not good – Stella's cancer was advanced stage IV. The only positive news was that the Wilms tumor

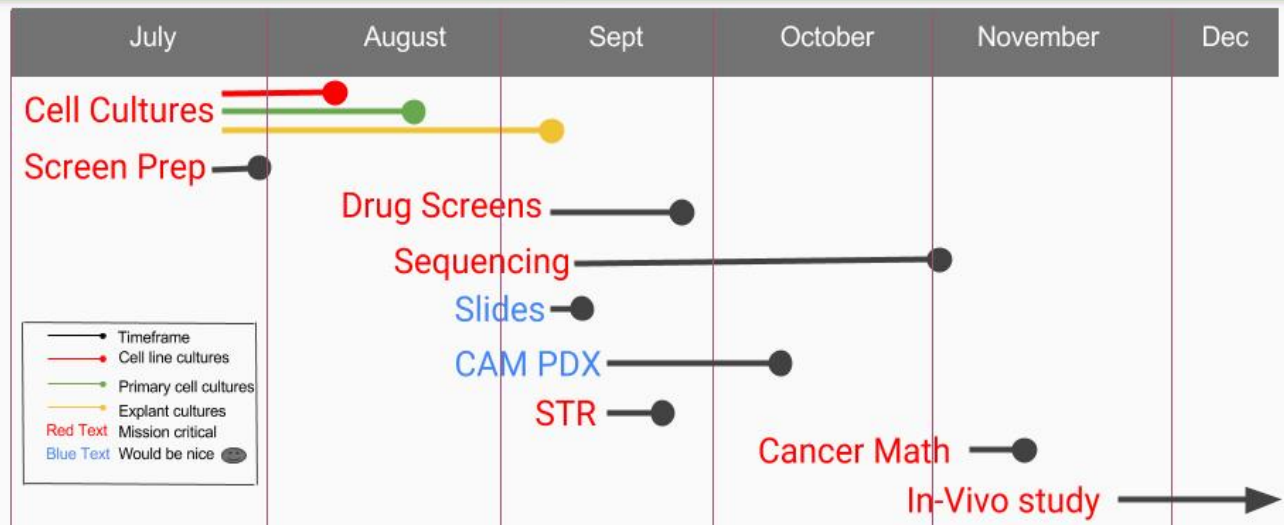
was anaplastic, which meant it would still respond well to traditional treatments. But more bad news followed, the cancer had spread from her kidneys to her lungs. Stella's doctor's believed she only had a 30% chance of remission. Soon after, she began an aggressive 33 week chemotherapy and radiation therapy. After 8 months, Stella miraculously went into remission. Then, just three short months later, the cancer came back in her lungs. Her doctors developed an even more aggressive treatment plan, one that would pump enough chemotherapy into her system that would essentially kill her. They would bring her back using her own stem cells collected from her blood. This therapeutic intervention is called autologous hematopoietic transplant. Now Stella's odds were at 15%. But after the extremely heavy treatment, Stella prevailed, and the next scan, and all subsequent scans after, showed no signs of cancer.

When Stella was about to undergo the transplant, Andy decided that he, not her doctors, was her best advocate since he had the time to dedicate to researching new therapies rather than relying on old, toxic ones. "Research is slow and cancer is fast." Though Andy was unsure where to start, he began by sending emails to scientists, researchers, and other families fighting Wilms tumor. This led him to eventually partner with the Children's Oncology Group, the US Food & Drug Administration, and one pharmaceutical company to begin clinical trials for a new drug treatment. The clinical trial began with 35 child cancer patients and remains an ongoing study. In the meantime, Andy kept advocating for more advanced medical research on rare childhood cancers and against pharmaceutical companies that resist new research into alternative cancer drug therapies.

**Research is slow and  
cancer is fast.**

# Wilms Tumor Project Roadmap/Timeline

Mission: To discover novel drug combinations that are effective for subpopulations of Anaplastic Wilms tumor patients.



[Consano project update \(9/15/2016\)](#)

Funding plays a large factor in the research and drugs that will reach clinical trial. Unfortunately, this system neglects some, like Andy Woods and his daughter. After abandoning his tile business in Montana, and uprooting his family and moving to Seattle, Washington (sometimes even living in a camper in the hospital parking lot), Andy crowd-funded his internship position to study at the Children's Cancer Therapy Development Institute in Portland, Oregon. Now Andy is his Stellablue's number one advocate because he has the time, and the knowledge, to dedicate to finding the best therapy for his daughter. Of course, difficulties arose with many doctors, scientists, and researchers that he reached out to never responding. But his perseverance is astounding as he continues to advocate for new clinical trials for drugs that promise improvements over what is currently available. Andy is adamant that the clinical trial process shouldn't be about the money – it should be about promoting health and always striving to create better treatments.

## The Community Biolabs

### Counter Culture Labs & The Open Insulin Project<sup>24</sup>

The [Open Insulin Project](#), launched by the community-based science group [Counter Culture Labs](#), crowdfunded its research in opposition to the soaring cost of insulin. One of Open Insulin's organizers, Anthony DiFranco, has a personal stake in the project; he's had Type 1 diabetes since his early 20s. Currently, he serves on the board of Counter Culture Labs, where he hopes to make open-insulin a reality. Since his diagnosis in 2005, Anthony has been interested in hacking diabetes by developing closed-loop continuous glucose monitoring systems and DIY insulin pumps (a la Dana Lewis). By 2011, he had co-founded Counter Culture Labs in Oakland, California, but making a bioreactor to create insulin seemed a remote possibility. Then, in 2015, Anthony met Isaac Yonemoto, who has a background in working with insulin, and Arcturus BioCloud, a biotech startup that could provide DNA synthesis services. This collaboration of patient, researcher, and technology is exactly what Anthony needed to jump start Open Insulin. The ultimate goal is free insulin for everyone who needs it.

Counter Culture Labs crowdfunded<sup>25</sup> the Open Insulin project in opposition to the soaring costs of insulin and seeks to democratize insulin production by circumventing intellectual property. The goal of the project is to develop a protocol for manufacturing insulin that would enable generic production. With predominately computer science backgrounds, the "biohackers" behind the Open Insulin Project are motivated by an open source philosophy. Yet, open source insulin doesn't necessarily mean free insulin. The meaning of free differs depending on the context.



Image retrieved from: [Counter Culture Labs' Projects](#) section of their website. Work on Open Insulin is conducted at Counter Culture Lab every Wednesday and Sunday. "Developing the first open source protocol to produce insulin simply and economically. Our work may serve as a basis for generic production of this life-saving drug and provide a firmer foundation for continued research into improved versions of insulin. [Support our crowdfunding campaign on Experiment.com!](#) Help make affordable insulin available to millions worldwide."

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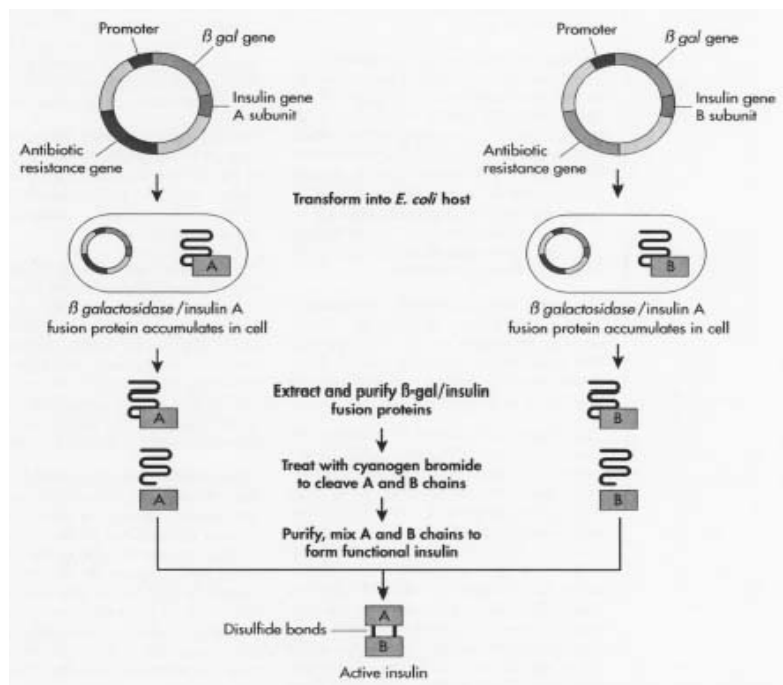
<sup>24</sup> Alexandra Ossola, (2015), "[These Biohackers Are Creating Open-Source Insulin](#)," *Popular Science*, (18 November); Lisa Martin, (2017), "[Oakland's Open Insulin Project Aims to Disrupt Diabetes](#)," *Make: Magazine*, (16 March); Miriam E. Tucker, (2015), "[Biohackers Aim to Make Homebrew Insulin, But Don't Try It Yet](#)," *NPR*, (15 July). Eleonore Pauwels. "Can the Open Insulin Project Increase Access to Insulin?" (forthcoming). – [The idea here is the "free insulin" is more like "free speech" rather than "free beer", but the goal is the reverse. The goal is to be able to pre-package the necessary materials and equipment, like what would come in a home-brew beer kit, but for home-brew insulin.] – Also see, L. S. Rotenstein, N. Ran, J. P. Shivers, M. Yarchoan, K. L. Close, (2012), "Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market?" *Clinical Diabetes* 30: pp. 138-150; and X. Hua *et al.*, (2016), "Expenditures and Prices of Antihyperglycemic Medications in the United States: 2002-2013," *JAMA*, 315: pp. 1400-1402.

<sup>25</sup> Open Insulin's experiment.com crowdfunding site: [<https://experiment.com/projects/open-insulin>].

For instance, “free speech” is not the same as “free beer.”<sup>26</sup> The Open Insulin Project might provide a “free speech”-like access to information about how insulin is manufactured. But, exercising freedom to disseminate information and translate that knowledge into affordable treatment alternatives relies on the assumption that the main barrier to manufacturing insulin cost-effectively is intellectual property. There are two aspects of intellectual property (IP) involved in insulin production: (1) the IP related to the amino acid structure, and (2) the IP related to the manufacturing process. In regards to (1), patents for human insulin, and many insulin analogues, ran out decades ago, recently expired, or will expire in the near future. As such, IP protecting insulin itself is not a barrier to open-source insulin. Although patents don’t necessarily protect the process of insulin manufacturing, (2) is protected by confidentiality. Trade secrets, such as the strain of microorganism used to express the insulin, the fermentation process, and the purification of the resulting protein, represent the greatest obstacle to open-source insulin. Because trade secrets don’t expire like patents, the manufacturing process is the main intellectual property barrier to developing insulin at competitive prices.

However, manufacturing only constitutes a very small component of the cost associated with bringing insulin to market. Insulin costs only around \$50-\$75 per gram to manufacture, but the market value of commercial insulin is well over \$1000 per gram. (The average cost of insulin in 2013 was \$13 per ml<sup>1</sup>, commercial insulin is typically formulated at 100 or 200 units/ml, and one international unit of insulin is equal to 0.0347 mg). Sales and marketing expenses are also lumped into the cost of insulin to consumers, but the biggest expense comes from

profits meant to offset the initial cost of developing the drug and achieving regulatory approval. Thus, the value of insulin manufacturing IP doesn’t lie in the process itself, but rather in the fact that regulatory approval for those manufacturing practices has already been achieved, which pushes outsiders like Anthony DiFranco from Open Insulin out of the market.



A diagram of the manufacturing steps for making insulin Retrieved from: [How Products are Made](#), Volume 7.

<sup>26</sup> The idea here is the “free insulin” is more like “free speech” rather than “free beer”, but the goal is the reverse. The goal is to be able to pre-package the necessary materials and equipment, like what would come in a home-brew beer kit, but for home-brew insulin.

The current structure of the regulatory process favors large pharmaceutical companies because it is significantly easier and cheaper for the original manufacturer to acquire approval than it is for someone like Anthony and Counter Culture Labs. Since any changes in the manufacturing process are subject to regulatory approval, the current system de incentivizes innovation that could improve upon the manufacturing process and decrease the cost of manufacturing. The built-in competitive advantage for big pharmaceutical companies allows them to start clinical trials faster and for less money. These regulations represent a significant financial barrier to entry for potential biosimilar producers like Open Insulin and necessitate high costs in order for biosimilar producers to recuperate investments. One potential solution to this problem would be to eliminate the competitive advantage given to big pharmaceutical companies and level the playing field in order to ensure the best medicines and medical devices make it to market. Moreover, leveling the playing field may also significantly reduce the cost of manufacturing since small companies, like Open Insulin, would have the opportunity to improve the manufacturing process.

#### Four Thieves Vinegar & The EpiPen Anarchist<sup>27</sup>



"Michael Laufer loads the 'Epi Pencil', his homebrew EpiPen alternative, before injecting himself with saline as part of the demonstration, in San Francisco, California, on September 14, 2016." Photo by Seth Rosenblatt/ *The Parrallax*. Retrieved from: Rosenblatt, (2016), "[EpiPencil hack costs a fraction of EpiPen \(exclusive\)](#)," *The Parrallax* (19 September).

Michael Laufer and the biohacker collective [Four Thieves Vinegar](#) has published open-access instructions on how to assemble an at-home apothecary lab to synthesize medications at home. The group has also published instructions on how to source and assemble your own epinephrine auto-injector (EpiPencil) for just over \$30 USD. The rapid injection device delivers epinephrine to reverse allergic reactions known as anaphylaxis, which can cause difficulty breathing and severe swelling – both of which are life threatening. Since exposure can

<sup>27</sup> Charles Piller, (2017), "[An anarchist takes on the drug industry - by teaching patients to make their own meds](#)," *STAT*, (12 October); Eliza Strickland, (2016), "[Hackers Offer a DIY Alternative to the \\$600 EpiPen](#)," *IEEE Spectrum*, (19 September); Peter Hess, (2016), "[Should You Build Your Own EpiPen?](#)" *Popular Science*, (21 September); Kristen T. Brown, (2017), "A DIY Pharmaceutical Revolution is Coming - If It Doesn't Kill Us First," *Gizmodo*, (2 August) [<https://gizmodo.com/a-diy-pharmaceutical-revolution-is-coming-if-it-doesn-t-1796865404>]; Chris Lo, 2017, "DIY Medicines: the anarchic fringe of the drug price debate," *pharmaceuticaltechnology.com*, (28 November) [<https://www.pharmaceutical-technology.com/features/diy-medicines-anarchic-fringe-drug-price-debate/>].

happen anytime, and allergic reactions can become life-threatening quickly, having quick access to an EpiPen is absolutely necessary. But access also includes the ability to pay for it, which became a problem in 2016. The EpiPencil was in direct response to Mylan hiking up the price of the EpiPen from under \$100 in 2007 when the company first acquired the product to over \$600 in 2016. Michael was outraged. So many people have severe allergies to substances like peanuts, shellfish, and bees and they all rely on carrying an EpiPen with them in case of exposure.

The Four Thieves Vinegar collective's mission statement stresses that access to life-saving medical interventions not only necessitates affordability, it necessitates that it be free. Their website reads: "People are disenfranchised from access to medicine for various reasons. To circumvent these, we have developed a way for individuals to manufacture their own medications...The main reasons for people being disenfranchised from medicines are: price, legality, and lack of infrastructure."

Although providing open-access to the knowledge required to manufacture medications like the EpiPencil is certainly admirable, many have professed concerns about patients building their own medical devices and manufacturing their own medications at home. Jennifer Miller, a professor of medical ethics at New York University, has even gone so far as to accuse Michael of "...basically saying, we



"EpiPencil components, clockwise from top left: The Auto Inject 2 and case, vials of epinephrine, 22-gauge luer lock dispensing needle, 1 mL luer slip syringe." *Photo by Seth Rosenblatt/ The Parrallax.* Retrieved from: Rosenblatt, (2016), "[EpiPencil hack costs a fraction of EpiPen \(exclusive\)](#)," *The Parrallax* (19 September).

should deregulate drugs, and allow anyone to make anything."<sup>28</sup> Granted, there are some potential problems with such an anarchistic, moral crusade to provide access to free medications. Four Thieves admits in the FAQ section of their website that making your own EpiPencil violates Mylan's copyright on the EpiPen, which means making your own at home is illegal. However, Michael and his biohacker collective believe that being forced to choose between following the law and staying alive is, at the very least, a false dichotomy. "If the choices presented to you are to die, because you cannot afford medication, or violate a copyright, which would you choose?"<sup>29</sup> Four Thieves argue that the state does not gain anything by enforcing the copyright because those who cannot afford the medication may be in danger and may create greater overall costs for the hospital and healthcare system.

<sup>28</sup> Peter Hess, 2(016), "[Should You Build Your Own EpiPen?](#)" *Popular Science*, (21 September).

<sup>29</sup> Four Thieves Vinegar: [Frequently Asked Questions](#) (FAQ).

Four Thieves' anarchistic, anti-establishment philosophical orientation makes it vulnerable in some ways (e.g., Michael is only a de facto leader behind the leaderless collective, which can result in disorganization and lack of achievable goals), but it also allows them to push against pharmaceutical companies that may be inclined to prioritize profits over patient access. The pharmaceutical industry is considered the locus of drug-making legitimacy in the US, as they have the capital to cover the costs of acquiring FDA regulatory approval for new drugs. Michael, along with his fellow Four Thieves biohackers, many of whom have never met face-to-face, are determined to “transcend the cult of the expert” that is perpetuated by what Michael sees as “unconscionable corporate profiteering by drug makers.”

**“Putting the idea out there, though, could be dangerous. It’s important that if we do these things, people trust the process.”**

**– Jose Gomez-Marquez**

Providing off-the-shelf kits for lab design, somewhat similar to at-home brew-your-own beer kits, only provides specific scientific knowledge – not broad, general chemical knowledge. This illustrates one significant weakness with Four Thieves' Apothecary MicroLab. They want to access to the necessary knowledge and equipment to make needed drugs at a much lower cost than it would be if purchased at the pharmacy. Still, one weakness in their model is that they would not offer any further knowledge to mentor potential participants and users. Some are more concerned about biosafety in DIY pharmaceutical products – such as making your own EpiPencil. In August 2017, someone speaking on the behalf of the FDA stated that, “It’s essential to remember that epinephrine auto-injectors are life-saving products, and it is critical that they are made to a high standard of quality so patients can rely on them to work safely and effectively.” More recently, in November 2017, feasibility and biosafety concerns have been raised about Michael Laufer and Four Thieves Vinegar’s mission.

“Some neutral observers who have seen (and been in a position to understand) the plans are skeptical that it could work. Moreover, expecting patients – mostly poor and dying ones, if they are uninsured and desperate enough to attempt it – to be able to build their own chemical lab and then create complex small-molecule drugs to treat themselves, is frankly dangerous, although in a legal and regulatory grey area, as Laufer is providing advice and instruction rather than distributing a product.”

Jose Gomez-Marquez of MIT claims that even disseminating the knowledge of how to make your own epinephrine auto-injector at home could be dangerous.

“Putting the idea out there, though, could be dangerous. It’s important that if we do these things, people trust the process. Otherwise, it becomes like snake oil. The worst that can happen is somebody that’s gullible out there tries this and fails, with disastrous consequences.”

The use of the snake oil metaphor is worth mentioning, if only because Four Thieves Vinegar derives its name from old folklore on concocting a vinegar solution to ward off the black plague.

Interestingly, Michael has not been stopped in his endeavor by pharmaceutical companies or the FDA thus far. Perhaps regulators do not give credence to the self-proclaimed “EpiPen Anarchist” and industry does not see either Michael or his collective as a threat to their business model. This could be a mistake for industry. EpiPen’s are necessary for many people to survive severe allergic reactions to common substances found almost everywhere. So when the price of a pack of two auto-injectors rise from less than \$100 to around \$600, it is not hard to understand why some people feel forced to explore producing them at home. However, while Michael’s work has not been wiped off the internet, it may be possible that the necessary equipment and substances will become more highly regulated to prevent people from having access to the items they would need to make their own EpiPencil at home.

### Biocurious Teens: Vardhaan Ambati<sup>30</sup> & Elodie Rebesque

Biocurious<sup>31</sup> is a community bio-lab in California that is dedicated to provide a working space for anyone to have access to equipment, materials, and mentorship from accomplished scientists and researchers. Eric Espinoza joined Biocurious’ Board of Directors in 2017 and has been providing mentorship to some of biology’s youngest rising stars.

When Vardhaan came into high school as a sophomore, he already knew that he wanted to cure cancer. While many high school students have fanciful dreams of what they want to accomplish in life, Vardhaan was already taking clear steps to achieve his goal. At that time, CRISPR was very hot and in the news everywhere. He read about the new technology’s ability to kill cells, so he decided to explore using CRISPR to target and kill cancer cells. In order to do this, he needed to figure out a way to specifically target cancer cells, and only cancer cells, so he needed to figure out a way to visualize cells that were CRISPR positive. Vardhaan went through the scientific literature and identified a few proteases that were heavily upregulated in metastatic cancers. He enlisted the help of one of his friends to visualize cells with quantum dots and make a construct that had CRISPR (to kill

He read about the technology’s ability to kill cells, so he decided to explore using CRISPR to target and kill cancer cells.

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<sup>30</sup> Vardhaan S. Ambati. 2016. “[A Permutable Nanotherapeutic Using Engineered CRISPR/Cas9: A Personalized Treatment for Cancer Heterogeneity and Viruses.](#)” *California State Science Fair*, Project Number S0501.

<sup>31</sup> [Biocurious](http://biocurious.org/about/)’ website: [http://biocurious.org/about/]



cells), a protease recognition site (to only kill cancer cells), and the ability to bind a quantum dot (to see which cells should die).

This is where [Biocurious](#) and Eric Espinosa came into play. Vardhaan was struggling to engineer the gene, and he needed a little help and guidance. With Eric's help, Vardhaan decided to do everything in vitro because he could move quicker and have clearer results. The problem he was encountering was that CRISPR-cas9 has a nuclear localization signal and can't enter the nucleus of a cell and cling to the DNA with the quantum dot attached. First, they engineered the gene so that the thrombin cleavage sequence would mimic the cellular protease and the BirA biotinylation signals adds biotin to a specific sequence allowing a stable complex to form with the quantum dot. And it worked. Then, they increased the complexity and used an ex-vivo assay with isolated sell nuclei and cytoplasm, and swapped out the thrombin cleavage site with a cancer protease site. However, they found that even a small amount of endogenous protease was sufficient to activate the CRISPR domain - meaning it wasn't specific enough to target cancer cells and only cancer cells. With this finding, they decided to pivot and only look at virally infected cells.

Many eukaryotic viruses carry a protease to process the viral genes. This protease is very specific and only present in infected cells. This answered part of Vardhaan's problem – he needed to be able to identify and target specific cells. So they once again swapped the thrombin cleavage site with a viral protease and discovered that it was still functional in their in vitro and ex-vivo assay. But, what Vardhaan really needed was to make cancer cells kill themselves, and destroy cancer cells from within. Vardhaan and Eric are now working together to identify the minimal domain of the clostridium pore forming region with GFP to identify the minimal sequence required to allow exit from the endosome. During endosome acidification, a domain of clostridium toxin undergoes a large conformational change and creates a pore in the endosome, which allows the N-terminal toxin to escape into the cytosol. But, the pore domain of the toxin is embedded in the membrane and the toxin uses a protease to separate the toxin from the pore to access the cytosol. And so they used transferrin so the cells would internalize the protein via receptor mediated endocytosis.

While this research is still in development, Vardhaan and Eric presented their findings at the Keystone Viral Immunity conference in Santa Fe, New Mexico on February 21, 2017. They are currently seeking collaborators that have expertise in virology to move out of the in vitro/ex-vivo phase and into an in vivo system. Although they still require additional human resources to help them further this unique approach to cancer treatment using CRISPR-Cas9, Biocurious has allowed Vardhaan to increase his knowledge and even present scientific findings at a conference before he even graduates high school. Granted, his research is still in the very early stages, therefore there are limited regulatory requirements at this point. What Biocurious has allowed him to do was bypass the hurdle that many bio-citizens encounter – access to biomedical equipment and mentors.

Elodie, a senior at Los Altos High School, has one of the most unique after-school activities for students her age – she walks to Biocurious, a community-based bio lab, where she is conducting research that could save her brother from painful medical treatments. Growing up, Elodie witnessed her brother suffering from sudden crises called pneumothoraxes, triggered by a disease where a lung collapses and separates from the chest wall. In severe cases, the best-in-class treatment is to create scar tissue on the chest wall as a grip to keep the lung in place. To say the least, it’s invasive and painful treatment. Elodie, not wanting to see her brother suffer through either the disease itself or the best-in-class treatment, she set off to Biocurious to develop her own vision, her own innovation, a sort of biological velcro. Biocurious was the perfect place for her, she had access to bioprinters, mentors, and pretty much everything she needed in order to leverage the inner mechanisms of proteins to bind lungs to the chest cavity.

For weeks, Elodie searched through the scientific literature to find the proteins that are responsible for helping cells bind together. After narrowing down the search to a few prime candidates, she genetically modified them to enhance their binding effects. Her bio-community

**Soon, she will start bio-printing the engineering proteins on a molecular patch, a thin matrix of collagen, to be placed between the chest and the lungs.**

helped her make sure her proof-of-concept was reproducible by obtaining three optimally engineered proteins that bind very tightly to lung cells. Soon, she will start using Biocurious’ bio-printer to print the engineered proteins on a molecular patch, a thin matrix of collagen to be placed between the chest and the lungs. Now, Eric Espinoza is helping her

to identify the best substrate for what she calls her biological double-sided tape. Like Vardhaan, Elodie has also not encountered specific regulatory requirements yet, but she will likely encounter them before Vardhaan does simply because her goal is to develop a clinical or surgical application, a better treatment for her brother than what is currently available. She is on a time crunch. Luckily, her mentors at Biocurious have helped her to make sure all of her ducks are in a row when she attempts to acquire regulatory approval for her novel pneumothoraxes treatment. She has already made sure her proof-of-concept is reproducible, which is the first thing she would be asked for if she tried to get this into a clinical trial.

## Health Makers & Makerspaces

Health care providers have been creating innovative solutions to medical problems since Florence Nightingale decided to start collecting information on British soldier mortality rates and curating patient records<sup>32</sup> – and even long before her. Now, the medical field is trying to provide a space for creativity. Despite the ever increasing use of technology within health care,

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<sup>32</sup> Louise Selanders, 2017, “Florence Nightingale,” Encyclopaedia Britannica (20 December) [<https://www.britannica.com/biography/Florence-Nightingale>].

there is still need for innovation. “Nurses fabricate solutions to everyday problems to increase safety, comfort, and efficiency of care; however, this ingenuity goes largely unsupported without space, time, and materials to bring practical solutions to everyday problems to fruition.”<sup>33</sup> The first medical makerspace in the U.S., MakerHealth Space, is located at the University of Texas Medical Branch in Galveston.<sup>34</sup> Within the makerspace, you’ll find equipment such as, 3D printers, laser cutters, and sewing machines.

### Tal Golesworthy<sup>35</sup>

Tal was diagnosed with Marfan syndrome, a genetic disorder that manifests in unusually long, slender bones, above average height, flexible joints, and various eye problems. Over the years, his aorta dilated progressively, always teetering the line that meant he would have to undergo surgery. Tal was not fond of the surgical option, to say the least.

“[They] anesthetize you, open your chest, put you on an artificial heart and lung machine, drop your body temperature down to about 18°, stop your heart, cut the aorta out, and replace it with a plastic valve and a plastic aorta. Most importantly, this surgery commits you to a lifetime of anticoagulation therapy”<sup>36</sup>

Tal leveraged his skills as an engineer in R&D and decided to think about the functioning of his heart as a plumbing problem – something he was familiar and comfortable with. So he set out to change the entire treatment for aortic dilatation. Rather than



Tal Golesworthy, 57, suffers from Marfan syndrome, a genetic, life-threatening condition that left his main artery in danger of splitting. He designed himself a made-to-measure knitted polyester sleeve to fit around the artery. Read more: Emma Innes, (2013), “[Engineer saves his own life and 40 others by inventing device to repair threatening heart defect](#),” *The Daily Mail*, (20 November).

<sup>33</sup> David Marshall and Deborah McGrew, (2017), “[Creativity and Innovation in Health Care: Opening a Hospital Makerspace](#),” *ScienceDirect* 15(1): p. 56.

[<http://www.sciencedirect.com/science/article/pii/S1541461216302233>]

<sup>34</sup> Rachel Nuwer, (2016), “[The First Makerspace in a Hospital](#),” *Popular Science*, (14 April) [<https://www.popsci.com/first-makerspace-in-hospital>].

<sup>35</sup> Geoff Watts, (2016), “[The Engineer Who Fixed His Own Heart](#),” *The Independent*, (7 November)

[<http://www.independent.co.uk/life-style/health-and-families/the-engineer-who-fixed-his-own-heart-a7397016.html>]; Julia Traver, (2017), “[‘Nothing Frightens Me Anymore’: How an Engineer Invented a Repair for his Heart](#),” *Not Impossible*, (17 January)

[<http://www.notimpossible.com/blog/tal/golesworthy/heart>]. Also see a journal article written by one of the core team members: Tom Treasure, (2013), “[Personalized External Aortic Root Support](#),” *Texas Heart Institute Journal* 40(5): 549-552 [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853825/>].

<sup>36</sup> Tal Golesworthy, (2011), “[How I Repaired My Own Heart](#),” *Ted Talks*, (October)

[[https://www.ted.com/talks/tal\\_golesworthy\\_how\\_i\\_repaired\\_my\\_own\\_heart#t-27565](https://www.ted.com/talks/tal_golesworthy_how_i_repaired_my_own_heart#t-27565)]

going in and cutting out the ascended aorta, Tal wondered if the pipe could be supported externally, allowing him to retain the original structure of his own heart and not need to spend the rest of his life on anticoagulation therapy.

Initially, he began organizing image acquisition from magnetic resonance and CT imaging machines, which he could use to make a model of the patient's aorta. After going through an iterative process of producing better and better models of his aorta, he then used his background in engineering to turn the model into a solid, plastic model using a rapid prototyping technique. Then, he used that plastic model to manufacture a porous wire mesh that perfectly fits the aorta. This is an example of personalized medicine at its best: relatively fast and cheap, plus patients no longer have to have parts of their hearts excised. Moreover, the easiest part of this new treatment is the surgical implantation, which made Tal happy.

This highlights an important feature of Tal's case study; health makers aim to come up with creative solutions to existing medical problems and make existing treatments better, safer, and more efficient. Tal's heart sleeve cuts the surgery time from six hours all the way down to two hours to implant his device. The existing treatment, the composite aortic root graft, requires a heart-lung bypass machine and total body cooling. His treatment alternative requires neither. But, how exactly does a process engineer who used to working on boilers find himself producing a medical device that transforms his own life, and subsequently, the lives of many others? The solution is in multidisciplinary team work. The core team included: Tal Golesworthy (process engineer), Dr. Warren Thornton (CAD engineer), Dr. Michael Lamperth (mechanical engineer), Prof. Peter Gibson (medical device engineer), Prof. Tom Treasure (cardiac surgeon), Prof. John Pepper (cardiac surgeon), Prof. Raad Mohiaddin (medical radiologist), Prof. Bob Anderson (cardiac morphologist), and Dr. Pete Schofield (catalysis chemist). Everyone on the team contributed in one way or another; Pepper was the cardiac surgeon that performed the surgical implantation on Tal, but to get to that point, they need Mohiaddin's expertise in order to get good enough pictures for Thornton to create the CAD model.

The biggest obstacle Tal came across was disciplinary jargon. His team consisted of two primary fields (medicine and engineering), which have drastically different terminology. It was difficult to overcome the language barrier at first, yet the institutional barriers presented the biggest hurdles. During the project, the Imperial College School of Medicine took over the Brompton Hospital, leaving bad blood between the two. Tal was working with both institutions, so the takeover generated problems that shouldn't have even existed. Bureaucratic problems snuck in behind the institutional hurdles. While the team had no qualms about the required Research Ethics Committee, some of the members had personal issues with seeing Pepper, an already renowned surgeon, succeed once again – so they created even more red tape in an attempt to slow his success. So much for the ethics committee ensuring ethical conduct in research (luckily, not all ethics committee operate in this way). By slowing down Tal's innovative progress based on personal, professional issues that are irrelevant to the production

of an aortic heart sleeve, the ethics committee seems to have conducted itself in an unethical manner – one that could’ve feasibly cost Tal his life. Another barrier is funding. Tal learned one lesson early on – don’t send organizations that fund biomedical research an engineering

**Tal learned one lesson early on – don’t send organizations that fund biomedical research an engineering proposal.**

proposal. “They didn’t understand it, they were doctors...it must be rubbish, they binned it.”<sup>37</sup>

After that the research team approached private funders with similar results. To entice potential funders, Tal started a company for his heart sleeve, [Exstent](#), and its main product is his personalized external aortic root support (PEARS). Finally, they secured institutional funding from the Polish Academy of Sciences.

Tal coined the phrase “constructive conservatism” to explain how some in the medical field are resistant to change and prefer to stay in their comfort zone based in tradition. They were resistant to an engineer coming up with an innovative medical solution. Moreover, there seemed to be sentiment throughout the UK medical field that since an engineer created the external aortic root sleeve, then that must mean it will never work, because a doctor or biomedical researcher didn’t come up with it. This line of thinking presents risks when it causes doctors to recommend long and risky surgical options when there are better, faster options available.

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<sup>37</sup> Tal Golesworthy, (2011), “[How I Repaired My Own Heart](https://www.ted.com/talks/tal_golesworthy_how_i_repaired_my_own_heart#t-27565),” *Ted Talks*, (October) [[https://www.ted.com/talks/tal\\_golesworthy\\_how\\_i\\_repaired\\_my\\_own\\_heart#t-27565](https://www.ted.com/talks/tal_golesworthy_how_i_repaired_my_own_heart#t-27565)]

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## TOPOGRAPHY OF INNOVATIONS & REGULATORY BARRIERS

The following topographical maps of each these case studies highlight the regulatory obstacles encountered by health innovators. The color orange represents the innovations produced; the color blue indicates traditional knowledge (e.g., doctors, journals, etc.); pink indicates patient experiential knowledge; purple indicates governance and ethical issues encountered throughout the process; and green indicates what is typically referred to as the “chill factor” and other barriers to innovation. We chose not to include flowcharts for the Biocurious Teens and Makerspaces because Vardhaan and Elodie have not delivered products yet and Tal’s innovative device has not made it to the United States.

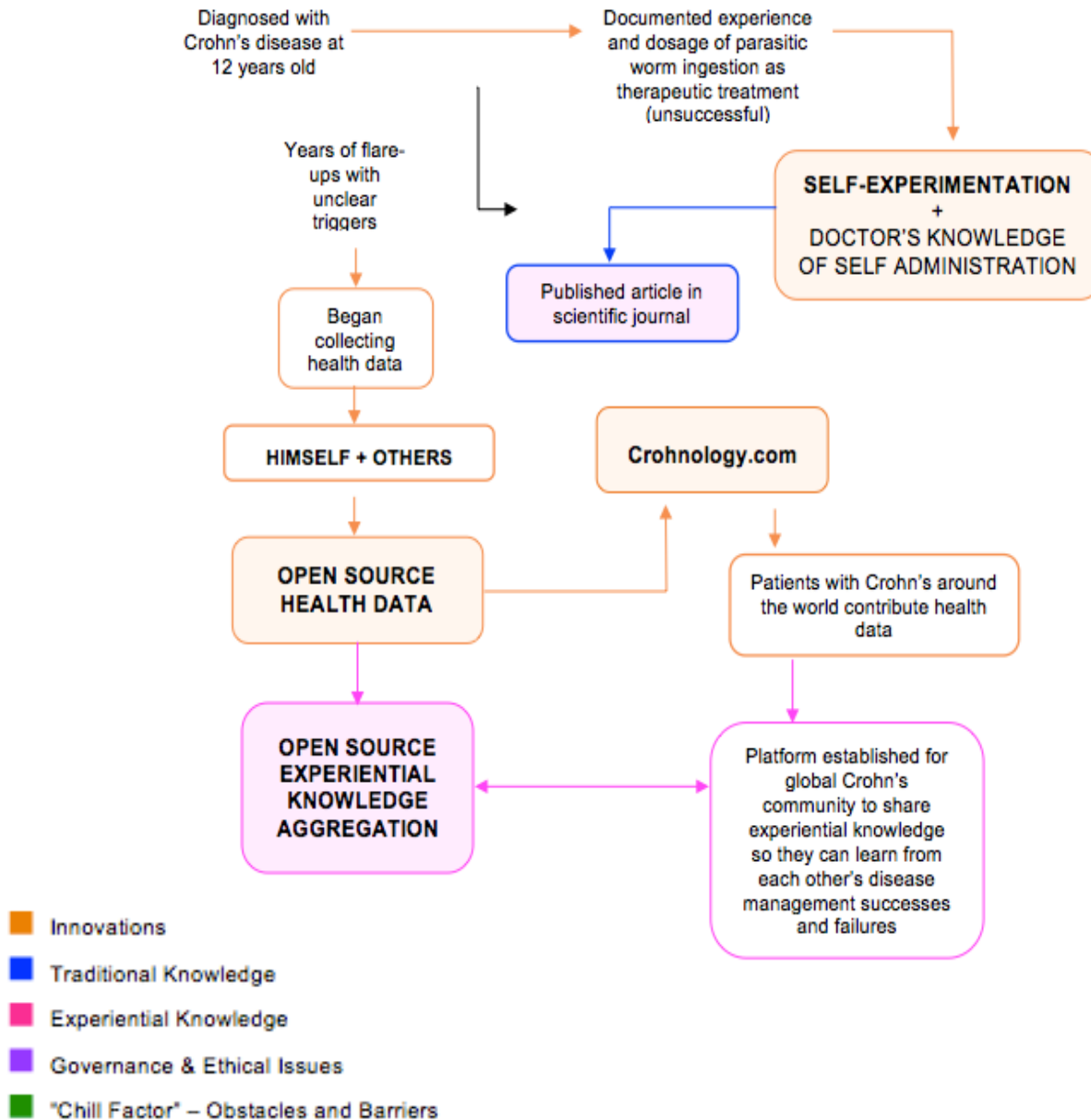
Based on our assessment of the case studies in this section, it has become clear that certain barriers and opportunities for innovation as well as governance and ethical issues play a role in participatory health research and innovation – even if traditional regulatory approval

**It has become clear that certain barriers and opportunities for innovation as well as governance and ethical issues play a role in participatory health research – even if traditional approval does not.**

does not. Specifically, barriers to innovation include, but are not limited to: the inability to quit one’s job to dedicate time and energy to finding alternative treatments, cures, and ways to navigate the medical/clinical field; the high cost of regulatory approval; and the cost and complexity of acquiring the necessary knowledge for medical and technological literacy, which may or may not be seen as legitimate by traditional actors.

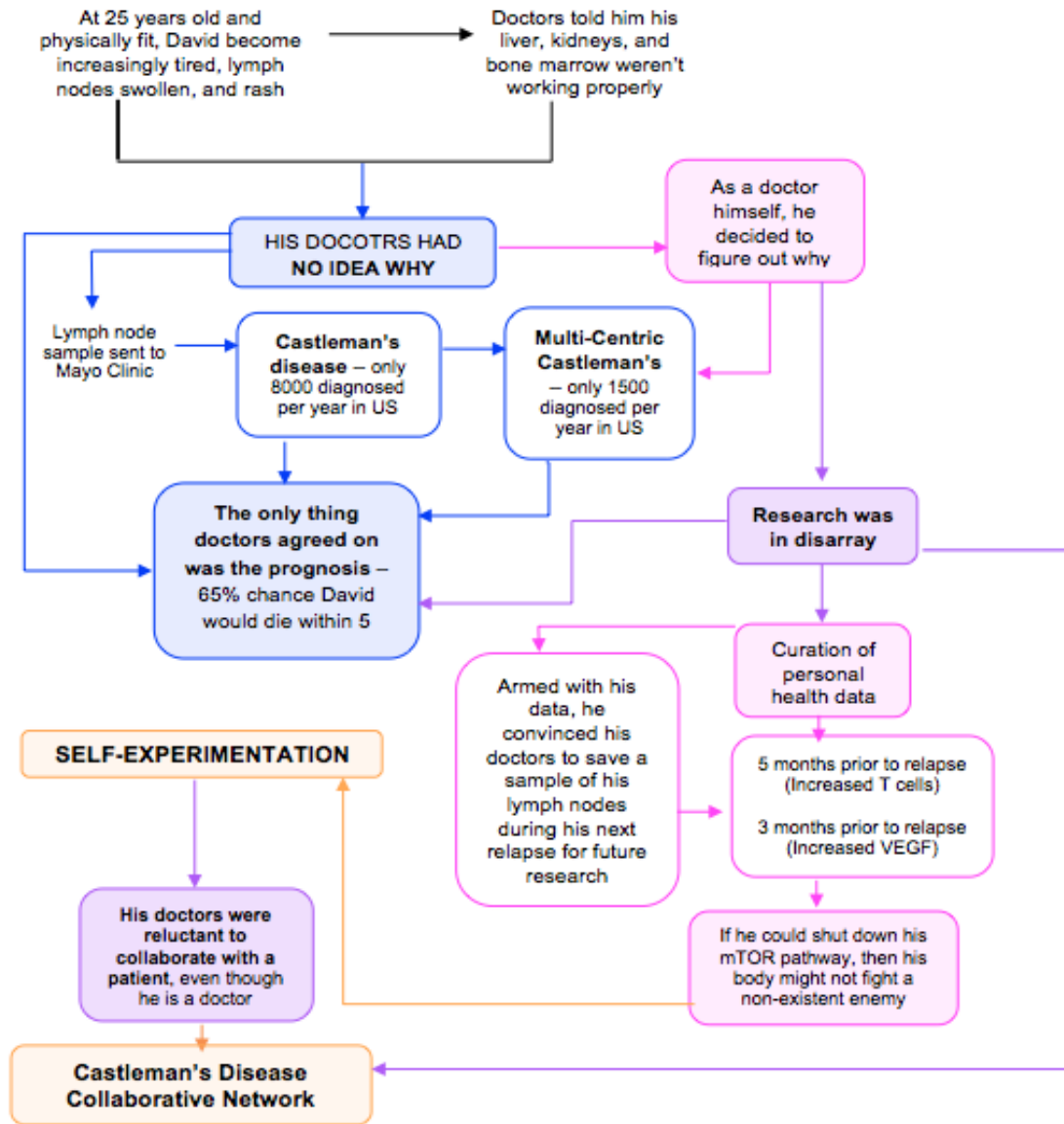
Opportunities found in our case studies include, but are not limited to: crowdfunding money for clinical research when and where the traditional clinical process allows little room for profit – steering biomedical research and the clinical trial process towards underserved disease populations; publishing experiential knowledge in academic journals and other traditional forums; and patient empowerment with ownership of their personal health data. But perhaps most interesting is the barriers and opportunities presented by health innovations in community bio-labs. We find these most interesting not because of the innovations themselves, but because the governance and ethical issues arise from the regulatory barriers held in place by traditional stakeholders like the FDA and large pharmaceutical companies.

## Sean Ahrens



This map of Sean's innovative journey shows no barriers to innovation. This is likely attributed to the fact that his doctors knew of his self-experimentation with parasitic worms and his subsequent journal article documenting the results. Moreover, since Sean's innovation is an open source aggregation of patients' experiential knowledge of living with and managing Crohn's, it falls outside the traditional regulatory structure.

# David Fajgenbaum

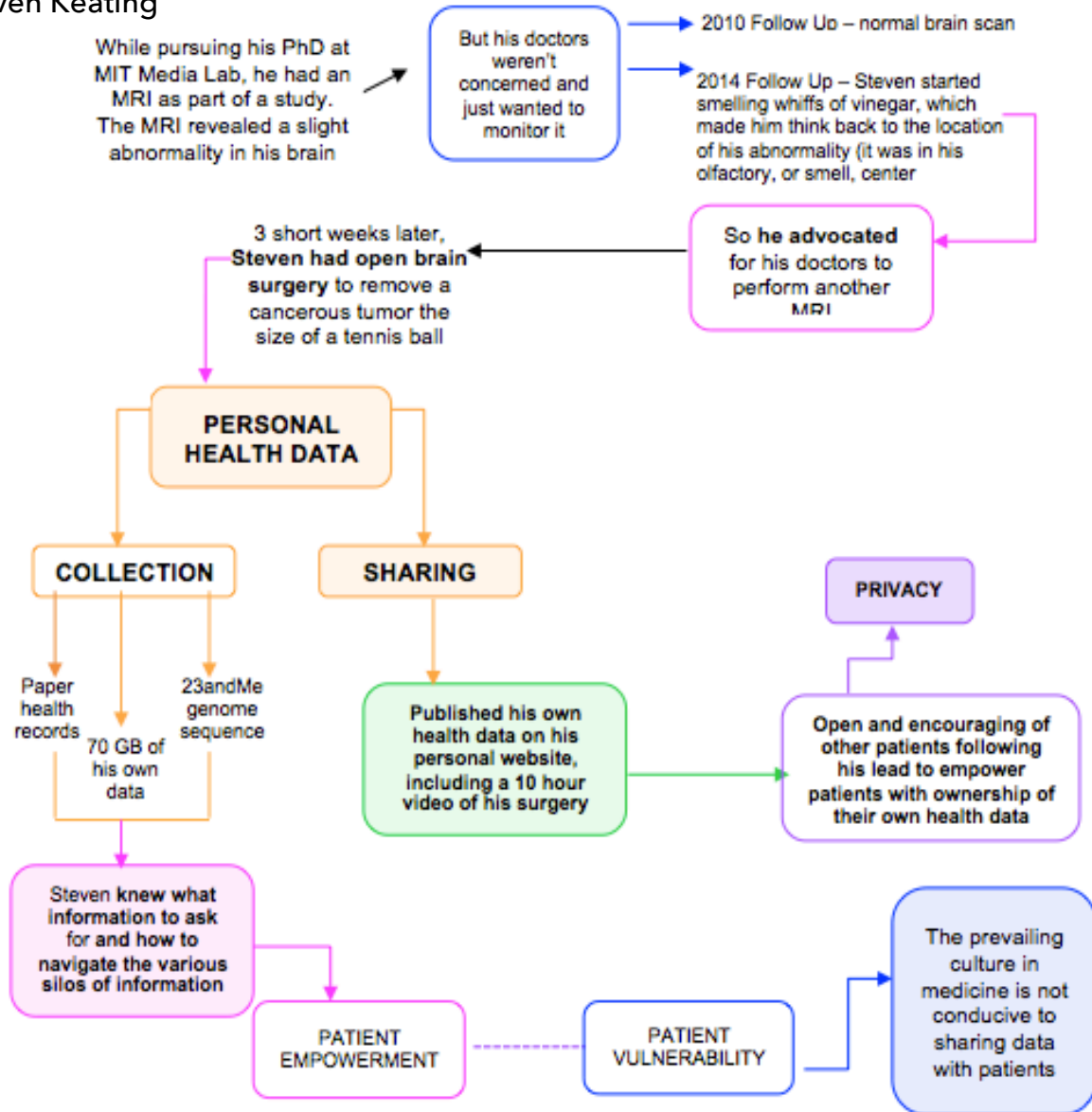


- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

As this case study map shows, even traditional scientific knowledge coupled with experiential knowledge presents obstacles. This forced David into self-experimentation, which allowed him to finally convince his doctors to take him off his cancer medications (since he didn't have cancer) and try an off-label use of Sirolimus, a drug typically prescribed for kidney transplant patients. One year later, David's blood work and personal health data showed his immune system was functioning normally.



## Steven Keating

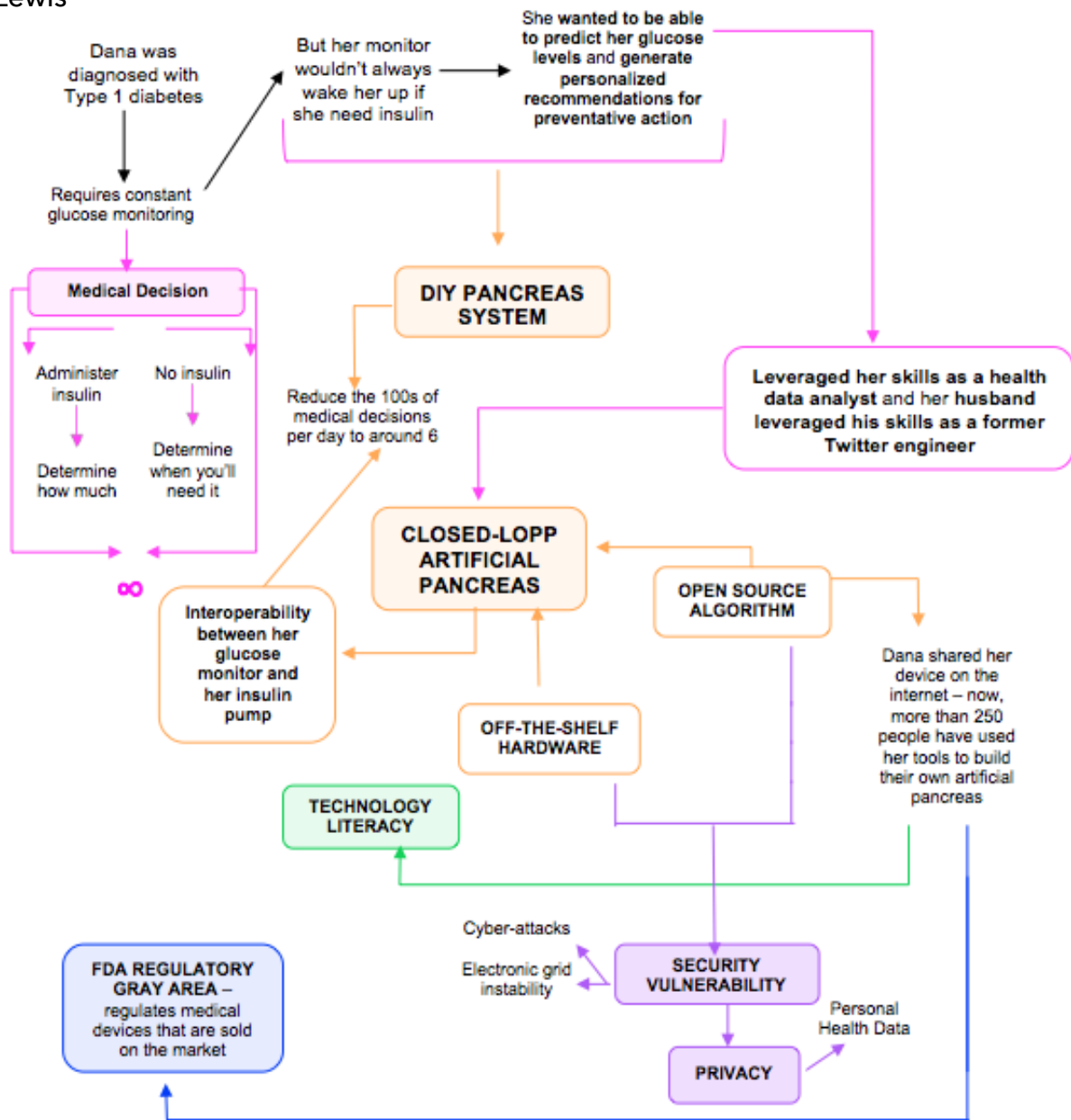


- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

This is the first case study map that shows the existence of a “chill factor.” In this case, the chill factor is tied to Steven’s self-publishing of his own health data, including a graphic video of his own brain surgery. Moreover, this chill factor is connected to one of the governance and ethical issues – not only did Steven publish his own data, but encourages others to do the same. However, this encouragement comes with

steep privacy concerns, in part, because some of the data he self-published was his personal 23andMe genome sequence. If everyone published their own genetic sequence on the internet, and there were not proper regulations in place to protect privacy and security, then that data could be used by malicious actors intending to use the data for harm. Another interesting aspect of this case is that Steven knew what medical information to ask for, while many other patients may not be able to navigate the medical field.

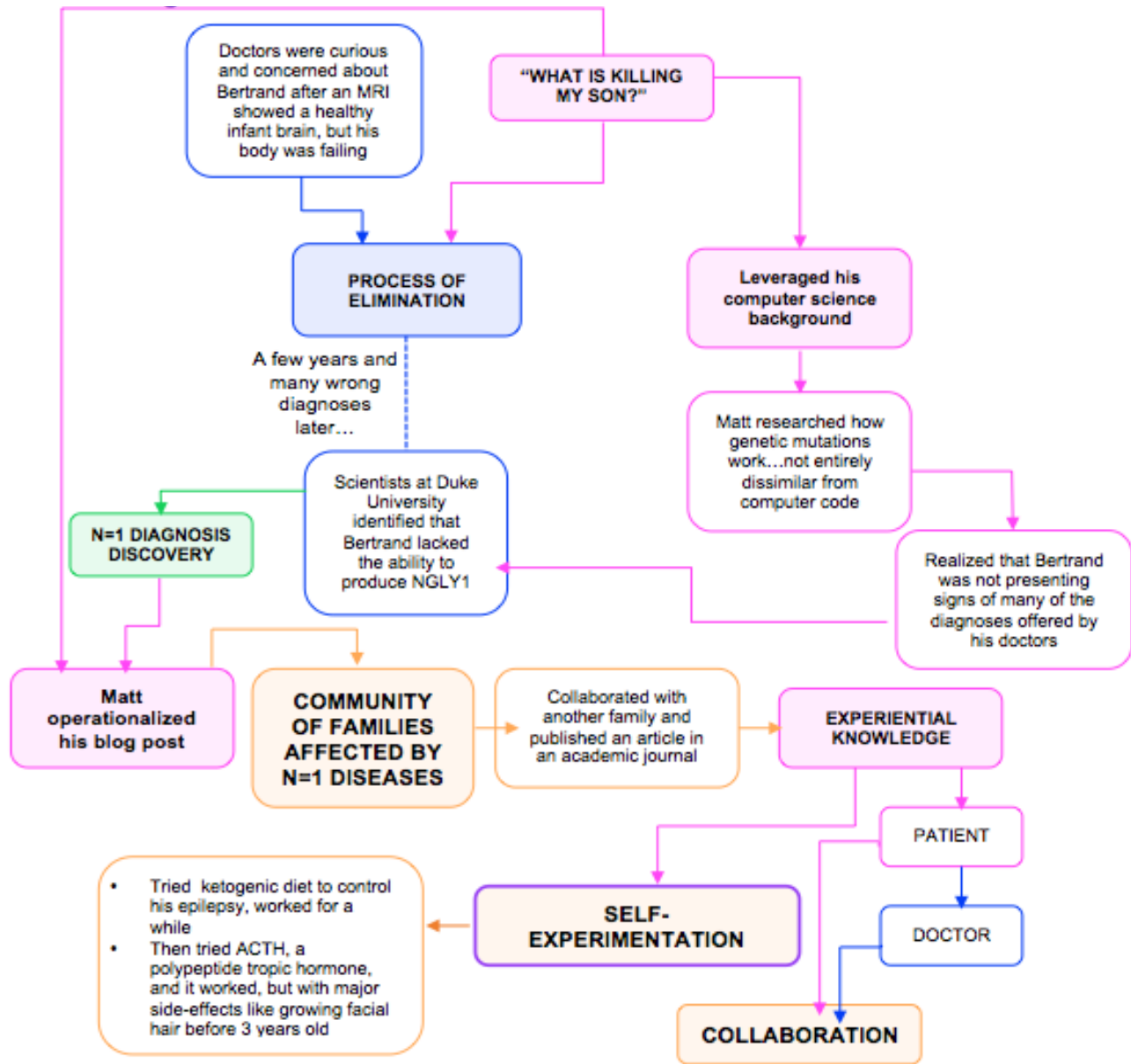
## Dana Lewis



- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

The main barrier to innovation is the technological literacy necessary to use Dana's tools to build your own artificial pancreas because, since she is not selling her product and published in online for anyone to use for free, it falls outside of traditional regulations. Thus, it seems that what matters to the FDA is whether anyone is making money off of new medical devices (or other products under their purview). This brings up an interesting point for further consideration – where is the line between self-experimentation and advertising or marketing of an open-access product?

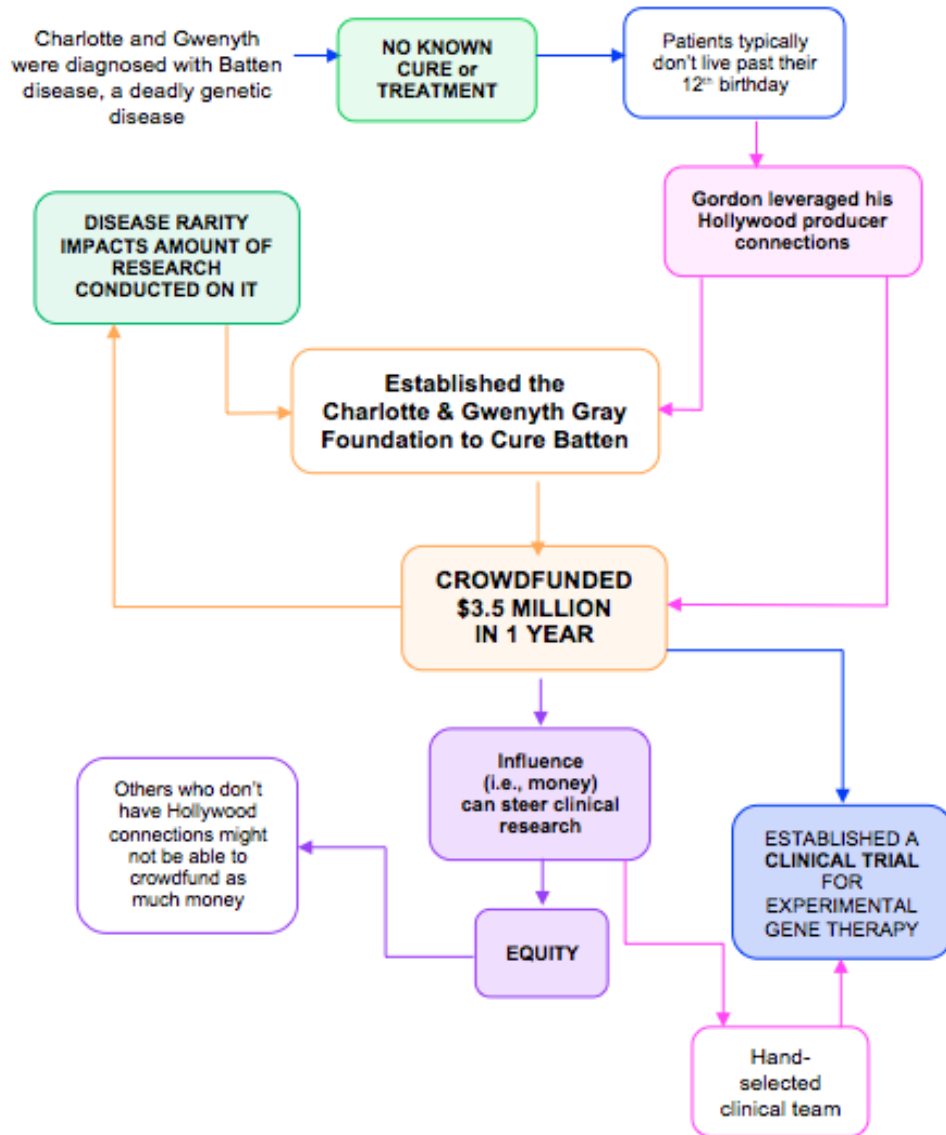
# Matt Might



- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

In this map of Matt's journey to find what plagued his son, it's clear that an array of roadblocks appeared before, but mainly after, the correct diagnosis was made. Matt also partook in self-experimentation with diet and hormones, both of which worked for a time. But, Matt was able to overcome barriers through collaboration with other families, which he created out of his open-access blog post, "Hunting Down My Son's Killer." Perhaps the most significant aspect of this journey was the collaboration between patient/family and doctors as well as collaboration between families affected by N=1 diagnoses. Moreover, it is possible that Matt's collaboration with Bertrand's doctors facilitated his successful collaboration with other patients.

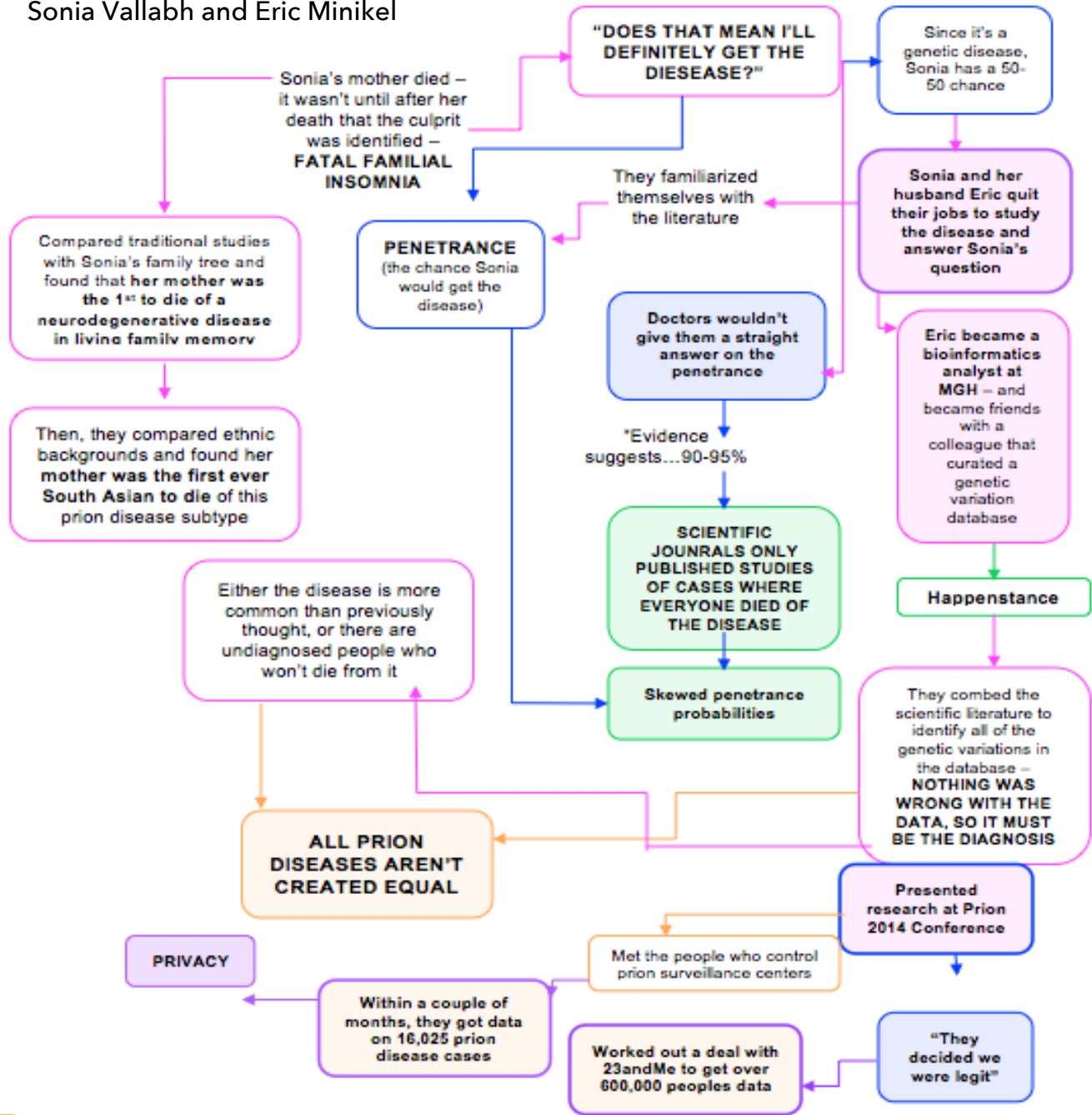
## The Gray Family



- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

The Gray family is perhaps the most straightforward of our case studies. This is likely due to the personal connections Gordon had to individuals with more money than the average citizen, which made raising the necessary funds to establish a clinical trial – a notoriously expensive process – easier and feasible. Granted, this pathway may well not work for other bio-citizens. But, this case study provides an exceptional example of how the clinical trial process sometimes neglects innovative rare disease treatments, considering few people will benefit, and how crowdfunding can steer money towards underserved populations and drive clinical research.

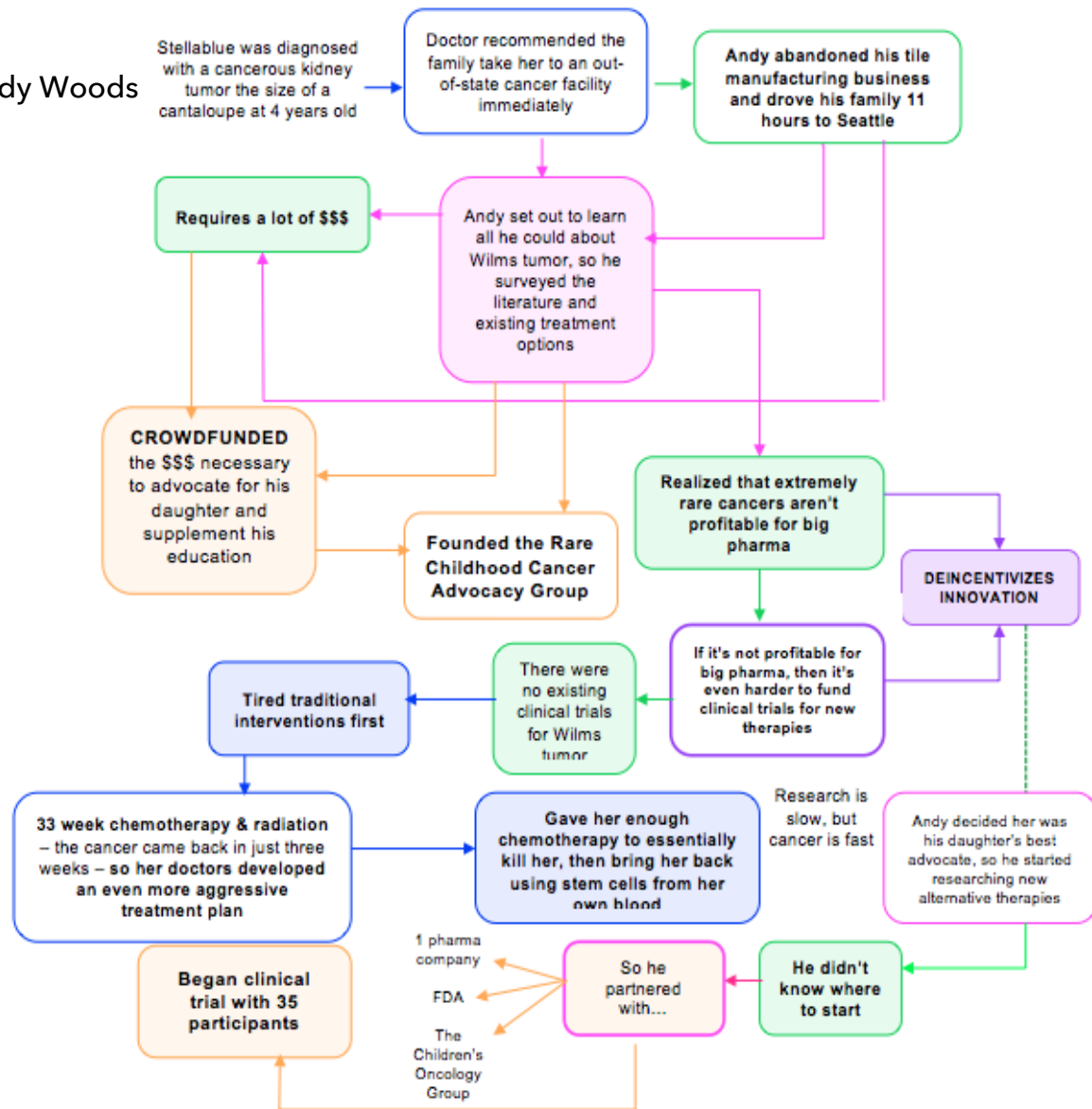
## Sonia Vallabh and Eric Minikel



- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

Sonia and Eric came across a few obstacles related to the quality of research on prion disease, which they were able to navigate through their cultivated relationships with other researchers and traditional stakeholders. Yet, not everyone will be able to quit their job; reliance on happenstance for their initial access to datasets may be difficult for others to replicate. Moreover, there are privacy concerns regarding their collaboration with prion surveillance centers and 23andMe.

## Andy Woods



- Innovations
- Traditional Knowledge
- Experiential Knowledge
- Governance & Ethical Issues
- "Chill Factor" – Obstacles and Barriers

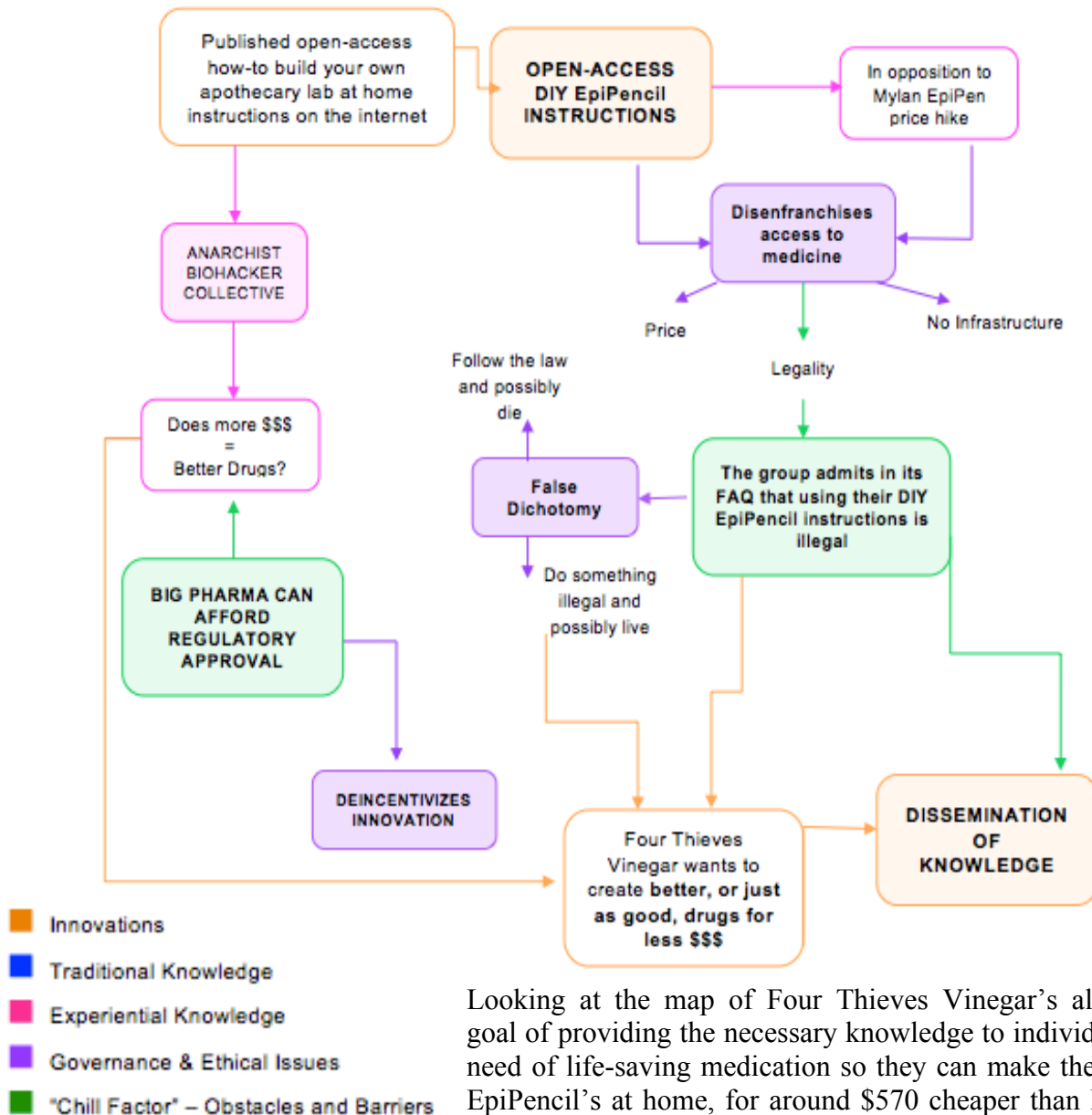
Andy Woods, out of all of our case studies, came across the most barriers, but overcame them by advocating for more research, partnering with other medical groups, patients, pharmaceutical companies, and even the FDA. Interestingly, he chose to go down a traditional regulatory pathway, seeking to establish an experimental trial for gene therapy. Generally pharmaceutical companies and the FDA

tend to be wary of testing experimental drugs like IMGN901 on children, even those who haven't responded well to traditional methods. Andy Woods managed to prevail and as of the writing of this report, the clinical trial has entered Phase 2.<sup>38</sup> Yet, how did he get connected with these groups that helped propel him into a clinical trial?

<sup>38</sup> "Lorvotuzumab Mertansine in Treating Younger Patients With Relapsed or Refractory Wilms Tumor, Rhabdomyosarcoma, Neuroblastoma, Pleuropulmonary Blastoma, Malignant Peripheral Nerve Sheath Tumor, or Synovial Sarcoma," Sponsored by the Children's Oncology Group, ClinicalTrials.gov Identifier: NCT02452554 [<https://www.clinicaltrials.gov/ct2/show/NCT02452554?term=IMGN901&age=0&rank=1>].



## Four Thieves Vinegar - DIY EpiPencil



Looking at the map of Four Thieves Vinegar’s altruistic goal of providing the necessary knowledge to individuals in need of life-saving medication so they can make their own EpiPencil’s at home, for around \$570 cheaper than Mylan, the copyright holder, sells it. Similar to Open Insulin’s flowchart, this map also shows governance concerns emerging from regulatory assessment, not necessarily the innovation itself. The primary regulatory barrier in the way here is Mylan’s copyright on the auto-injector. Unlike with Open Insulin, whose primary barrier was the intellectual property relating to the manufacturing process, this barrier means individuals that use their instructions and make their own EpiPencil’s are doing something illegal. Yet, the FDA has limited regulatory authority in this regard because the agency does not tend to regulate the dissemination of information, or, a medical device that is not being sold.

Firms Stave Off Generics, Costing Consumers Billions, Critics Say,” NBC News, (21 October) [https://www.nbcnews.com/business/business-news/drug-firms-stave-generics-costing-consumers-billions-critics-say-n447916].



## REGULATORY CONSIDERATIONS: A RESEARCH & REGULATORY TOOLKIT

In the United States, the Food & Drug Administration (FDA) is the primary regulatory authority for anything dealing with products sold to consumers. The National Institutes of Health (NIH) also provides guidelines for conducting health research; much of their recommendations are in line with FDA policies, but the primary difference between the two authorities is akin to the difference between policies and guidelines. Policies are requirements enforced through law, while guidelines are more like recommendations for research and development of emerging technologies.

### United States Food & Drug Administration (FDA)

The scope of the FDA's regulatory authority is quite broad, spanning from food, to human and veterinary drugs, to vaccines and other biological products, to medical devices intended for human use, to dietary supplements and even tobacco products.

| Foods  | Drugs                                     | Biologics                          | Medical Devices                                 | Electronic Products<br>(that emit radiation) | Cosmetics  | Veterinary Products          | Tobacco Products      |
|--|---|------------------------------------|---|--|--|------------------------------|-----------------------|
| Dietary Supplements  | Prescription drugs                        | Vaccines                           | Simple items like tongue depressors and bedpans | Microwave ovens                              | Color additives found in makeup and other personal care products | Livestock feed               | Cigarettes            |
| Bottled Water  | Non-prescription (over-the-counter) drugs | Blood and blood-related products   | Complex technologies such as heart pacemakers   | X-ray equipment                              | Skin moisturizers and cleansers                                  | Pet foods                    | Cigarette tobacco     |
| Food Additives   |   | Cellular and gene therapy products | Dental devices                                  | Laser products                               | Nail polish and perfume  | Veterinary drugs and devices | Roll-your-own tobacco |
| Infant Formulas  |   | Tissue and tissue-related products | Surgical implants and prosthetics               | Ultrasonic therapy equipment                 |  |                              | Smokeless tobacco     |
| Other food products (although the US Department of Agriculture plays a role in regulating aspects of some meat, poultry, and egg products) |   | Allergens                          |   | Mercury vapor lamps                          |  |                              |                       |
|  |   |                                    |   | Sunlamps                                     |  |                              |                       |

**Table 2:** FDA Regulated Product by Category (adapted from fda.gov)

Based on the case studies included in this report, many of the health innovations and bio-community products mentioned seem to fall within FDA regulatory jurisdiction. The exceptions include Crohnology, Keating publishing his health data online, disseminating the necessary knowledge to make your own EpiPencil, and other research conducted that doesn't result in the production of a new drug or therapy which include, Fajgenbaum, Vallabh and Minikel, and Ambati and Rebesque's research at Biocurious. However, the innovations that fall under FDA regulatory authority do so only on a superficial level. Since many of our health innovators and bio-citizens are not looking to market their products in the traditional sense, and are instead disseminating knowledge, publishing their own health data on the internet, or providing open-access to instructions on how to make your own EpiPencil at home, most of our case studies actually fall outside of FDA regulatory authority because the products are not being sold to consumers. Rather, many health innovators are providing access to their inventions for free.

|                  | Within FDA Regulation | Outside FDA Regulation |
|------------------|-----------------------|------------------------|
| Sean Ahrens      |                       |                        |
| David Fajgenbaum |                       |                        |
| Steven Keating   |                       |                        |
| Dana Lewis       |                       |                        |
| Matt Might       |                       |                        |
| The Gray Family  |                       |                        |
| Sonia Vallabh    |                       |                        |
| Andy Woods       |                       |                        |
| Anthony DiFranco |                       |                        |
| Michael Laufer   |                       |                        |
| Vardhaan Ambati  |                       |                        |
| Elodie Rebesque  |                       |                        |
| Tal Golesworthy  |                       |                        |

**Table 3:** FDA Regulatory Jurisdiction for Case Studies

As can be seen in table 3, more of the research and innovation exhibited by these case studies falls outside of FDA regulation (pink boxes) or exist in a gray area (gray boxes) than

those that fall under FDA regulatory authority (green boxes). The three cases that do fall under FDA regulation have something in common: they all either chose to establish clinical trials (The Gray's and Andy Woods) or they sponsored a postdoc to study potential treatments (Matt Might). Regardless of which road they chose, all of them crowdfunded the necessary money to push the research and drug discovery process.

On the other hand, seven cases fall outside of FDA regulation. Firstly, Tal Goleworthy's personalized external aortic support is only available in some areas around the UK; which means it clearly is not under FDA regulation given jurisdictional bounds. The biocurious teens, Vardhaan and Elodie, are similar; except they haven't made any devices yet nor have they gotten to the point where a treatment can be subject to clinical trials. Thus, they are similarly outside of FDA regulatory authority because the FDA regulates existing products, not works in-progress.

Dana Lewis' artificial pancreas exists in a regulatory gray area because, while she has made a type of medical device, she does not intend to market the device to consumers for profit and the device itself is composed of hardware that can be purchased by anyone. Unless the FDA starts to regulate open-source code or machine learning algorithms, the artificial pancreas seems outside of FDA authority. Anthony DiFranco and Open Insulin exists in the gray area because the FDA does not generally require extra regulatory approval for biosimilars;<sup>40</sup> although, they will still have to face the manufacturing process intellectual property problem. Since insulin and its biosimilars are already approved by the FDA, FDA regulatory approval is the least of Open Insulin's concerns. First, Counter Culture Labs must complete and perfect the yeast engineering and develop a technique for purifying it.<sup>41</sup> Then, and only then, will Open Insulin be able to address the regulatory barriers. Michael Laufer and 4 Thieves Vinegar has a similar issue as Open Insulin, where FDA regulatory approval is presents fewer potential obstacles to the democratization of insulin and EpiPencil's than the production and dissemination of the manufacturing process.

## Perspective of Regulators

On May 9, 2013, President Barack Obama issued an executive order titled, "[Making Open and Machine Readable the New Default for Government Information](#)," which states that,

“To promote continued job growth, Government efficiency, and the social good that can be gained from opening Government data to the public, the default state of new and modernized Government information resources shall be open and machine readable. Government information shall be managed as an asset

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<sup>40</sup> United States Food & Drug Administration, [Biosimilar Product Regulatory Review and Approval](#)

<sup>41</sup> Ruby Irene Pratka, 2017, “How Biohackers at Counter Culture Labs are Trying to Make Insulin more Affordable,” Shareable, (9 December) [<http://commonsfilm.com/2017/12/09/how-biohackers-at-counter-culture-labs-are-trying-to-make-insulin-more-affordable/>].

throughout its life cycle to promote interoperability and openness, and, wherever possible and legally permissible, to ensure that data are released to the public in ways that make the data easy to find, accessible, and usable. In making this the new default state, executive departments and agencies (agencies) shall ensure that they safeguard individual privacy, confidentiality, and national security.”<sup>42</sup>

This executive order helped pave the way for open data policy in the United States by directing the government, to the extent permitted by law (e.g. HIPPA), to release its data to the public in such a way that it is easy to find, access, and use. Congress enacted the 21<sup>st</sup> Century Cures Act [1] on December 13, 2016 as a ‘last will’ of the outgoing administration and outgoing Committee on Energy and Commerce Chairman, Fred Upton. The legislation gained attention by providing significant funding over time for the Obama administration’s flagship biomedical research programs, but performed several other notable functions.<sup>43</sup> The Cures Act prompted the FDA to establish an Innovation Initiative, which is aimed at making sure our regulatory mechanisms are modern and efficient to ensure that effective new technologies reach patients in a timely manner.<sup>44</sup> Among the bill’s other effects were defining “real world evidence and “patient experience data” for use in existing FDA regulatory mechanisms. Specifically, Title III Section 3002 requires the FDA to “issue new guidance regarding methods and approaches to be used in capturing and measuring patients’ experiences and perspectives.”<sup>45</sup> The FDA was tasked with address the following:

- (1) Methodological approaches that a person seeking to collect patient experience data for submission to, and proposed use by, the Secretary in regulatory decision making may use, that are relevant and objective and ensure that such data are accurate and representative of the intended population, including methods to collect meaningful patient input throughout the drug development process and methodological considerations for data collection, reporting, management, and, analysis;
- (2) Methodological approaches that may be used to develop and identify what is most important to patients with respect to burden of disease, burden of treatment, and the benefits and risks in the management of the patient’s disease;
- (3) Approaches to identifying and developing methods to measure impacts to patients that will help facilitate the collection of patient experience data in clinical trials;

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<sup>42</sup> Exec. Order No. 13,642, [Making Open and Machine Readable the New Default for Government Information](#), 78 Fed. Reg. 28111 (May 14, 2013), [<http://www.gpo.gov/fdsys/pkg/FR-2013-05-14/pdf/2013-11533.pdf>].

<sup>43</sup> Food & Drug Administration (FDA), Regulatory Information, [21<sup>st</sup> Century Cures Act](#), [<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentsstotheFDCAAct/21stCenturyCuresAct/default.htm>].

<sup>44</sup> Scott Gottlieb, (2017), [“FDA Plans to Help Consumers Capitalize on Advances in Science,” FDA Voice](#) (7 July), [<https://blogs.fda.gov/fdavoices/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/>].

<sup>45</sup> FDA, [Plan for Issuance of Patient-Focused Drug Development Guidance](#), under 21<sup>st</sup> Century Cures Act Title III Section 3002, [<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf>].

- (4) Methodologies, standards, and technologies to collect and analyze clinical outcome assessments for purposes of regulatory decision making;
- (5) How a person seeking to develop and submit proposed draft guidance relating to patient experience data for consideration by the Secretary may submit such [proposed draft guidance to the Secretary;
- (6) The format and content required for submissions under this section to the Secretary, including with respect to the information described in paragraph (1);
- (7) How the Secretary intends to respond to submission of information described in paragraph (1), if applicable, including any timeframe for response when such submission is not part of a regulatory application or other submission that has an associated timeframe for response; and
- (8) How the Secretary, if appropriate, anticipates using relevant patient experience data and related information, including with respect to the structured risk-benefit assessment framework described in section 505(d) of the Federal Food, Drug, and Cosmetic Act,<sup>46</sup> to inform regulatory decision making.

Section 3001 of 21<sup>st</sup> Century Cures defines “patient experience data” as materials which illustrate how a clinical condition affects individual patients’ lives, as well as individual patient’s preferred therapies for that clinical condition. These data can be “collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers).” The term “drug” appears several times in Section 3001, however the definition of patient experience data does not explicitly restrict this data to pharmaceutical therapeutics. Using patient experience data is not unprecedented in drug regulation, as FDA approved Exondys 51 in September 2016 in part utilizing this type of information.<sup>47</sup> Legislators describe “real world evidence” (RWE) in Section 3022 of 21<sup>st</sup> Century Cures as any drug performance data which does not come from randomized control trials. This information can originate from “ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities.” Notable examples of RWE include electronic health records, personal health devices and/or apps, billing records, and social media.<sup>48</sup> As defined by 21<sup>st</sup> Century Cures, RWE exclusively

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<sup>46</sup> See 21 U.S. C. 355(d) – “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug....A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.”

<sup>47</sup> Pulliam, S. & Mullis, B. (2017), “How the FDA approved a \$300,000-a-year drug its own experts didn’t believe worked,” Wall Street Journal. Retrieved on June 4, 2017: from [https://www.wsj.com/articles/how-the-fda-approved-a-300-000-a-year-drug-its-own-experts-didnt-believe-worked-1495116544]; U.S. Food and Drug Administration. (2016), “FDA grants accelerated approval to first drug for Duchenne muscular dystrophy,” Retrieved on June 4, 2017 from: [https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm].

<sup>48</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), “Real world evidence — What is it and what can it tell us?” The New England Journal of Medicine, 375(23): p. 2293.

applies to drug regulation (potentially including regenerative therapies). This type of data would aim to enhance the generalizability of clinical trial findings.<sup>49</sup>

21<sup>st</sup> Century Cures directs FDA to create a trial framework for implementing the use of RWE by the end of 2018. This draft framework would use input from the public (e.g. industry, academia, patient groups) and apply only to drugs. FDA will then publish guidance on when RWE will be applicable and how to best collect this data. However, in July 2016 the FDA published draft guidance on utilizing RWE in medical device oversight,<sup>50</sup> suggesting RWE could become applicable across FDA regulation. RWE may help address issues with current clinical trial designs, which require large patient cohorts and high costs but still lack generalizability.<sup>51</sup> However, existing sources of RWE were not designed to aid regulatory decision making and could present analytical challenges.<sup>52</sup> Patient experience data may be able to serve a similar role, but limited literature exists on the potential risks and benefits of using patient experience data in regulatory approval.

While these eight points appear promising, it is interesting that ‘patient experiences and perspectives,’ which the FDA has been tasked with measuring and analyzing, does not seem to

**Since RWE applies to drug regulation, many of these case studies wouldn't fall under this classification because not all citizen-driven biomedical research aims to produce drugs that will require regulatory approval.**

align with citizen-driven biomedical research and patient-led health innovation. Since RWE applies to drug regulation, many of the case studies in this report would not fall under this classification of research because not all citizen-driven biomedical research aims to produce drugs that will require regulatory approval. At best, the definitions of

these two terms – RWE and citizen-driven biomedical research – do not align; at worst, the FDA has been tasked with measuring and analyzing only a small subset of patient-led health

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<sup>49</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), “Real world evidence — What is it and what can it tell us?” *The New England Journal of Medicine*, 375(23): p. 2293.

<sup>50</sup> U.S. Food and Drug Administration, (2016), “Use of real world evidence to support decision-making for medical devices,” Retrieved on June 4, 2017 from: [<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>]; Hills, B. & Zegarelli, B. (2016), “21st Century Cures Act requires FDA to expand the role of real world evidence,” Retrieved on June 4, 2017 from: [<https://www.healthlawpolicymatters.com/2016/12/19/21st-century-cures-act-requires-fda-to-expand-the-role-of-rwe/>].

<sup>51</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), “Real world evidence — What is it and what can it tell us?” *The New England Journal of Medicine*, 375(23): p. 2293; Pazdur, R. (2016), “Evaluating FDA’s approach to cancer clinical trials,” (September 16), Retrieved April 9, 2017, from: [<https://blogs.fda.gov/fdavoices/index.php/2016/09/evaluating-fdas-approach-to-cancer-clinical-trials/>].

<sup>52</sup> Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray G. W., Gross, T., Hunter, N. L., . . . Califf, R. M. (2016), “Real world evidence — What is it and what can it tell us?” *The New England Journal of Medicine*, 375(23): p. 2293.

innovations within the broader scope of citizen-driven health research. Even more recently, in November 2017, the FDA released information about the self-administration of gene therapy.<sup>53</sup> According to that statement the,

“FDA is aware that gene therapy products intended for self-administration and ‘do it yourself’ kits to produce gene therapies for self-administration are being made available to the public. The sale of these products is against the law. FDA is concerned about safety risks involved. Consumers are cautioned to make sure that any gene therapy they are considering has either been approved by FDA or is being studied under appropriate regulatory oversight.” (Ibid.)

Based on the statement above, the FDA’s primary concern regarding DIY gene therapy kits does not seem based on consumer safety; rather, their concern seems to be with the sale of such kits to consumers. This is a theme present throughout the analysis of the case studies as well.

### Inspiration for Taxonomy as a Legitimacy-Building Tool:

The goal is to develop engagement channels between patients-innovators, crowdfunders, ethicists, and regulators to design adaptive oversight mechanisms that will foster a culture of empowerment and responsibility. Concretely, the authors of this report envision building a taxonomy of different forms of innovations where you would also find, in parallel, an assessment of the risk-benefit trade-off defined in collaboration between bio-citizens and regulators. By relying on this taxonomy, channels for crowdsourcing expert and tacit knowledge, reducing the ethics and legal uncertainty that patients face when funding, and sharing their protocols, data, or inventions, could be created. Broadly, this taxonomy seeks to address the follow questions:

- 1) *How can we create a safe space for health innovators and community bio-labs to share and experiment with their data, value trade-offs and ethical concerns in ongoing conversations with regulators?*
- 2) *How can regulators and crowdfunding platforms help bio-citizens modernize practices that will give legitimacy to their research, devices, and treatments?*

### A Crowdsourced System for Assessing Citizen-Driven Innovation

Participatory biomedical research breaks when there is no means of ensuring quality of data, such as the data that is derived from person-generated data (e.g. the data produced by Dana Lewis’ artificial pancreas) and self-reported data (e.g., the data on Crohnology.com). Yet, lack of quality control of data is one, but certainly not the only, concern related to citizen-driven biomedical research.

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<sup>53</sup> FDA, Cellular & Gene Therapy Products, “[Information About Self-Administration of Gene Therapy](https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm586343.htm),” [https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm586343.htm].

## Emerging Ethical Implications of Citizen-Driven Biomedical Research

- Lack of/uncertainty about adequate information and consent/assent in terms of potential harm and alternatives
- Limits of parental authority in enrolment of their child in citizen-driven biomedical research
- Endangerment of traditional social values such as dignity, privacy, and justice
- Inadequate and/or unnecessary risks by self-experimentation
- Peer pressure to participate in trial
- Exploitation of vulnerable individuals in desperate search of help
- Bias and distortion arising from the use of self-reported and self-collected symptoms and data
- Bias by heterogeneity of participants
- Lack of overview and difficult regulation of citizen-driven biomedical research by heterogeneity of participants
- Blurring boundaries between treatment, self-experimentation, and lifestyle driven enhancement
- Missing acceptance of citizen-driven biomedical research as an authentic mode of research: obstacles in conducting research and publishing results
- No regulations concerning quality control and security by undermining current state-of-art guidelines concerning professionalism and ethics
- Uncertainty on how to use results of citizen-driven biomedical research in terms of validity and evidence in clinical therapy
- Study enrolment with risks of harm in the light of inadequate methodology

Instead of trying to fit citizen-driven innovation into the existing regulatory framework, a more adaptive approach might help these citizens become literate in how to conduct research and help them identify the regulatory checkpoints.

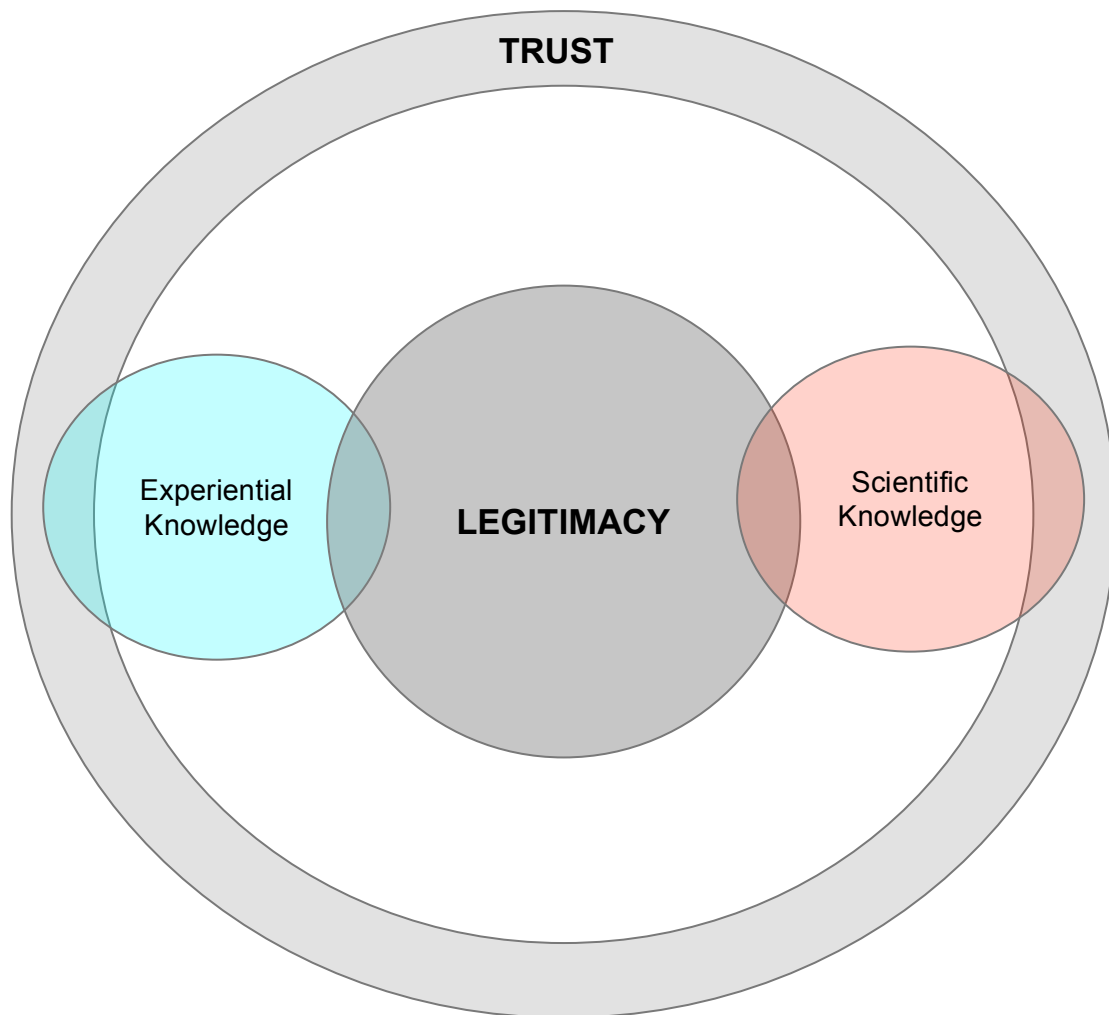
### Appropriate Responses to PLR include:

- To be adaptive when applying existing legal frameworks
- To gain a deeper understanding of current practices of citizen-driven biomedical research and comprehend that different activities within citizen-driven biomedical research may require different procedures
- To accept research issues outside of the scientific mainstream as a valuable means of contributing to generalizable health knowledge and provide scientific advice on research proposals through publicly funded panels of experts
- To promote co-design and shared decision-making amongst inventors (citizens/patients), regulators and crowdfunders
- To support reciprocal responsibilities of all inventors (citizens/patients), regulators and crowdfunders
- To support transparent and open manner of communicating about study design, results and their meaning
- To develop an online platform where citizen-driven biomedical research and inventions/innovations may be publicly registered
- To connect with other existing resources that can serve as a form of legitimacy-building such as crowdsourced biosafety and ethical expertise and co-authored publications between inventors and scientists/regulators



## The Legitimacy Issue: How can patient-led health innovations be taken seriously?

Traditionally, knowledge legitimacy has been tied to scientific knowledge; but citizen health innovators are beginning to change that paradigm and inject their experiential knowledge into biomedical research. Before bio-citizens will be seen as legitimate health innovators in the eyes of the traditional scientific and policy communities, they will need to overcome some obstacles and gain the trust of scientists and regulators.



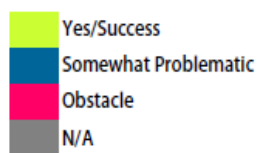
Thus, part of the regulatory toolkit must include a method for fostering trust between doctors, biomedical scientists and researchers, and patients. Bridging the gap between the perceived legitimacy of scientific, or credentialed, knowledge and experiential knowledge produced by patients and their families may increase the level of scientific innovation in the future.

# BARRIERS & OPPORTUNITIES IN DEMOCRATIZING HEALTH RESEARCH: AN ANALYSIS

As we alluded to in the previous section, knowledge and scientific legitimacy, patient-empowerment, and self-experimentation are perhaps the biggest obstacles and present some of the opportunities of democratizing health care research. In this section, we will break these issues down separately and discuss the obstacles and opportunities they present using our case studies as reference points. **Granted, this is a preliminary analysis that may be subject to change upon the completion of the project workshops to be held in March 2018.**

|                    |                  | Open-Source Data | Medical Data Acquisition/Collection | Access to Equipment, Hardware, etc. | Product (Device) - Innovation | Poor Research (or lack thereof) | N-of-1 Discovery (or extremely rare) | Self-Experimentation/ DIY | Experiential Knowledge | Knowledge Acquisition & Legitimacy | Privacy  | Dissemination (Knowledge/Data Sharing) | Crowdsourcing | Traditional Funding Source | Crowdfunding | Within Current Regulatory Structure | Clinical Trial | Safety Standards | Intellectual Property | Manufacturing Process |
|--------------------|------------------|------------------|-------------------------------------|-------------------------------------|-------------------------------|---------------------------------|--------------------------------------|---------------------------|------------------------|------------------------------------|----------|--|---------------|----------------------------|--------------|-------------------------------------|----------------|------------------|-----------------------|-----------------------|
| Health Pioneers    | Sean Ahrens      | Yes/Success      | Yes/Success                         | Yes/Success                         | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | David Fajgenbaum | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Steven Keating   | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Dana Lewis       | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Matt Might       | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | The Gray Family  | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Sonia Vallabh    | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Andy Woods       | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
| Community Bio-Labs | Anthony DiFranco | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Michael Laufer   | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Vardhaan Ambati  | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |
|                    | Elodie Rebesque  | Obstacle         | Obstacle                            | Obstacle                            | Obstacle                      | Obstacle                        | Obstacle                             | Obstacle                  | Obstacle               | Obstacle                           | Obstacle | Obstacle                               | Obstacle      | Obstacle                   | Obstacle     | Obstacle                            | Obstacle       | Obstacle         | Obstacle              | Obstacle              |

**Table 1: Global Perspective on Case Study Technologies - Barriers & Opportunities**



In the table above, green boxes represent successes and opportunities, blue boxes represent problems that can be overcome relatively easily, pink boxes represent barriers to innovation, and gray boxes represent non-existent barriers and opportunities. As table 1 shows,

knowledge acquisition and legitimacy presented the most problems for health innovators and bio-citizens. Another obstacle that hindered bio-citizen research is the current clinical trial process, which requires knowledge of the regulatory process and ample funds to acquire approval. Other issues of note include: traditional funding sources, the current regulatory structure and safety standards, poor research or lack thereof, crowdsourcing, and dissemination of knowledge and data.

## Knowledge & Scientific Legitimacy

Knowledge and scientific legitimacy will ultimately have impacts on the governance and ethical oversight of the bio-citizen movement. Since knowledge and governance can be thought of as co-producing one another,<sup>54</sup> understanding how governance mechanisms handle the experiential knowledge generated by participant-led research will be key in identifying the

**Knowledge and scientific legitimacy will ultimately impact the governance and ethical oversight of the bio-citizen movement.**

future direction of this phenomenon and its oversight. Specifically, we will address three key questions regarding the knowledge and scientific legitimacy of bio-citizens.

*How will traditional academic journals and government agencies assess the data derived from crowdfunded and open-source studies that may not have applied NIH rules for health research?*

Firstly, since none of our case studies involve research supported by NIH or conducted at a research institution, NIH rules for health research do not apply. So why would bio-citizens follow them? Even if we assume that the case studies in this report fall within this type of research, which some may and others may not, the research conducted in our case studies were not funded or supported by the NIH. Since the case studies in this report were not funded or supported by the NIH, they are not required to follow the NIH's guidelines. The *NIH Guidelines* are applicable to:

“Research that is conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid research from NIH, including research performed directly by NIH. An individual who receives support for research involving recombinant or synthetic nucleic acids must be associated with or sponsored by an institution that assumes the responsibilities assigned in the *NIH Guidelines*...Research that involves testing in humans of materials containing recombinant or synthetic nucleic acids developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects.

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<sup>54</sup> Jasanoff, Sheila, editor. *States of Knowledge: The Co-Production of Science and the Social Order*. 1 edition, (Routledge, 2004).

Participation includes research collaboration or contractual agreements, not mere provision of research materials.”<sup>55</sup>

Granted, Section I-C-1-a-(1) does state that even an individual conducting such research not funded or supported directly by the NIH must be associated with or sponsored by an institution; but, does this apply to self-experimentation? If so, how would individuals partaking in self-experimentation involving recombinant or synthetic nucleic acid molecules know that their research falls within NIH guidelines? Or, perhaps even more significant, how would bio-citizens know it might be a good idea to follow them since legitimate research institutions do? These questions must be considered when developing future guidelines for health research if the knowledge generated by patient-led research is to be considered legitimate by traditional institutions.

Secondly, it seems that the crowdfunding and open-source aspects of our case studies are the aspects of bio-citizen research that traditional academic journals are likely to find as the delegitimizing aspect – not simply the fact that the research might not have followed NIH rules. Peer review and replication are salient features of knowledge legitimacy; yet, peer review is typically acquired through the submission of research to reputable academic journals. If traditional academic journals and government agencies do not consider data derived from crowd-funded and open-source studies as legitimate, then the research will likely never receive the attention necessary for replication studies. Moreover, the rates of traditional sources of scientific funding continue to decline, which leaves both traditional scientists and non-traditional bio-citizens to resort to crowdfunding as a means for bringing in money for new research.<sup>56</sup> Thus, crowdfunding is in a position to steer the future of clinical research. This could potentially be both beneficial and harmful. While crowdfunding may be able to fund research on rare diseases that have traditionally been ignored by health research funders, if crowdfunding clinical research becomes the norm, then it may have the unintended consequence of allowing the public to decide what research is worth funding, which may be tied to emotional, social, and cultural perceptions.

***If journals and agencies reject such data, does it even matter if the protocols established to ensure the treatments and medical devices are accessible to other end-users?***

This question seems to particularly apply to the case studies of Sean Ahrens, Dana Lewis, and Steven Keating because their health innovation involves the production, curation, and dissemination of knowledge. In these case studies, the health innovations produced have been developed using experiential knowledge and subsequently published for other-end users on the internet. In the case of Sean Ahrens, his website Crohnology aggregates experiential

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<sup>55</sup> Reference to Section I-C-1a-(1) and I-C-1-a-(2) found in National Institutes of Health (NIH), *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, (April 2016); [[https://osp.od.nih.gov/wp-content/uploads/2013/06/NIH\\_Guidelines.pdf](https://osp.od.nih.gov/wp-content/uploads/2013/06/NIH_Guidelines.pdf)].

<sup>56</sup> Jarrett E.K. Byrnes, et al., (2014), “[To Crowdfund Research, Scientists Must Build an Audience for Their Work](https://doi.org/10.1371/journal.pone.0110329),” *PLoS One*, 9(12): e110329. [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4262210/>].

knowledge of Crohn's patients from around the world to help other patients see what disease management strategies have been successful and what has failed. Yet, this aggregation of experiential knowledge and data has not been vetted for quality assurance. If journals and agencies reject such data, it is still important for protocols to be established in

order to ensure the treatments and medical devices are accessible to other end-users because being rejected by traditional communities does not mean the data and knowledge produced is inherently illegitimate. It's only illegitimate because the community that has historically provided legitimacy to health research deems it so, perhaps in part because the research was not conducted by traditional scientists and researchers in traditional environments through traditional means. Most of our case studies have not been accepted by journals and other agencies, except for Sean Ahrens, Dana Lewis, Sonia Vallabh, and Matt Might, yet, almost all of the case study innovations are available to other end-users on the internet. Thus, regardless of acceptance by traditional institutions, establishing such protocols are essential to fostering legitimacy and trust.

**If traditional academic journals and government agencies do not consider data derived from patient-led research as legitimate, then the research will likely never receive the necessary attention for replication studies.**

***If citizen-driven biomedical studies are not seen as legitimate, will they be able to obtain Institutional Review Board (IRB) approval?***

**It's only illegitimate because the community that has historically provided legitimacy to health research deems it so.**

Obtaining traditional IRB approval is not likely unless citizen-driven biomedical research is seen as legitimate by the traditional scientific community. This is primarily due to the fact that if patient-led research is not accepted by the traditional medical/clinical community, then it is unlikely that the research will be sponsored by, or associated with, an institution with review boards. However, this does not mean that traditional

sources of knowledge legitimacy and IRB approval precludes citizen-driven biomedical research from obtaining peer-review in an open science setting. Moreover, simply the term 'Institutional Review Board' seems odd in terms of citizen-driven science because it is not always conducted at research institutions, which are the loci of IRB's.

## Patient-Empowerment

The dynamic of empowerment also presents complexity. Such participatory biomedical research represents an exemplary case of tensions between credentialed and experiential knowledge,<sup>57</sup> it is a growing line of inquiry that should be investigated if appropriate governance mechanisms are to be developed. The potential for patients to take an increasing role in their own diagnosis and treatment raises two important questions found below. To be sure, these questions should not lead one to think medical research conducted by patients and non-traditional actors is de facto less safe, less reproducible, or unethical. While these groups may appear to be less risk averse, they have in-depth tacit knowledge of their conditions and a vested interest and stake in making sure a treatment or device will be effective, safe, and potentially beneficial.

**While bio-citizens may appear to be less risk averse, they have in-depth knowledge of their conditions and a vested interest and stake in making sure a treatment or device will be effective, safe, and beneficial.**

### ***How does participatory health research transfer the responsibility to patients while preserving the safety and ethics of individuals?***

One example from our case studies of how patient-empowerment has preserved the safety and ethics of individuals is crowdfunding resources for clinical trials – one step to acquiring regulatory approval from the FDA. For example, Andy Woods used crowdfunding to supplement his education after his daughter was diagnosed with Wilms tumor so he could research alternative therapies after traditional and increasingly aggressive treatments failed. After identifying an experimental gene therapy treatment with the potential to wipe out the cancer from his daughters genome, he then partnered with traditional institutions like the FDA, cancer groups, and even one pharmaceutical company. This collaboration between patient (or family in this case), regulatory authorities, advocacy groups, and drug makers propelled him into a clinical trial, for which he hand-picked the clinical team. Andy's experience is also similar to another of our case studies, the Gray family. The Gray family used crowdfunding to entirely fund a clinical trial to cure Batten disease, which affected both daughters. Unlike Andy, the Gray family was able to crowdfund \$3.5 million in one year, which made the road to establishing a clinical trial that much easier. Although the Gray family also hired their own clinical team, dedicating funding to a postdoctoral researcher, the ample funds derived from his Hollywood producer contacts allowed them to progress in the process without much collaboration with regulators.

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<sup>57</sup> Vololona Rabeharisoa, et al. "Evidence-Based Activism: Patients', Users' and Activists' Groups in Knowledge Society," *BioSocieties*, vol. 9, no. 2, (June 2014): pp. 111–28, doi:10.1057/biosoc.2014.2: p. 113.

An example from our case studies of how patient-empowerment may not preserve the safety and ethics of individuals might be found in the cases of Steven Keating and Four Thieves Vinegar. In the case of Steven Keating, he was able to navigate the various silos of medical information, curate and aggregate upwards of 70 gigabytes of his personal health data, and subsequently published it all on his personal website for the viewing pleasure of anyone who found themselves there. He is open and encouraging of others to follow his lead; but, this patient empowerment could result in patient vulnerability, since not everyone will be able to navigate the medical field as easily as he was. Moreover, they may not be aware of the potential privacy concerns and risks involved in publishing, for instance, their entire genome sequence on the internet, as Steven did. In the case of Four Thieves Vinegar, if you consider following the law and being ethical to be one and the same, (i.e., one can't be ethical if one does not follow the law), then you will likely believe that using Four Thieves' EpiPencil instructions to avoid the exorbitant costs of Mylan's EpiPen renders you unethical, regardless of the safety concerns involved. However, if you believe that following the law and being ethical are not mutually exclusive (i.e., you can be ethical and not follow the law at the same time), then perhaps patient vulnerability is not a result of patient empowerment, but rather, a result of patient disenfranchisement. And if patient vulnerability is a result of patient disenfranchisement by means of restricting access to lifesaving medications to those who can afford to spend \$600 for two epinephrine auto-injectors, then using Four Thieves' instructions empowers patients to exert some control over their health.

***Who, in this participatory turn, is expected to deal with health-related regulatory and liability issues?***

**It seems natural for patients and citizens to share the burden of health-related regulatory and liability issues with their physicians.**

It seems rather intuitive that in collaborative and participatory research, both the patient and health care provider(s) would deal with health-related regulatory and liability issues together. The burden does not have to rest on one or the other. For instance, recall back to our case study on David Fajgenbaum and Matt Might. In Fajgenbaum's case, it may be possible that his team of doctors were not only reluctant to let him be involved in the discovery and treatment process, even though he is himself a physician, but that they were also reluctant for David to be involved due to regulatory and liability concerns. Typically, the regulatory and liability burden falls on physicians. But participatory research seems to necessitate sharing the burden with patients.

For patients to be fully empowered and owners of health-related research, treatment options, and all health-related data, it seems natural for them to share this burden with their doctors. In the case of Matt Might and his son Bertrand, Matt has done an exemplary job of creating and maintaining collaborative relationships with his son's vast team of doctors. However, doing so wasn't easy. It seems that pretty much from the very beginning of

Bertrand's story, Matt was dedicated to becoming clinically-literate in order to engage with his son's physicians on their level (or, at least, that was his goal). Imagine if Matt had not been so involved and had not shared his experiential knowledge with his son's doctors. Who would the liability be on then? It would likely have remained in its traditional place, with health care providers. It seems most natural in the age of patient-empowerment that health-related regulatory and liability issues should be navigated in the same collaborative and participatory nature as the research itself.

## Self-Experimentation

While the press tends to cover the most memorable cases of patients who self-experimented with unregulated gene therapy treatments, those are not common practice. Most of the time, patients who produce knowledge and innovate address crucial user-centered issues. Often, their design is vetted by peers and doctors who have become their collaborators in a shared innovation journey. Nonetheless, we argue that it is important to think creatively about how to help citizens and patients share this data, evidence, tacit knowledge, value trade-offs, and ethical concerns in ongoing conversations with regulators and society at-large. We will explore three fundamental questions regarding governance of self-experimentation.

***How are gray market treatments for unapproved or altered treatments (e.g., artificial pancreas, Open Insulin, and EpiPencil) not illegal? Or is this a case of there being no policy expressly forbidding it?***

The only case study that is in fact illegal is Four Thieves Vinegar's EpiPencil. In their frequently asked questions section on their website, the group explicitly states that using their instructions to make your own EpiPencil at home is illegal, not because it goes against FDA or NIH regulations and guidelines, but because it violates Mylan's copyright for auto-injectors, the epinephrine delivery method. Similarly, Open Insulin, while it aims to provide open-access to cheaply produced insulin in community bio-labs to avoid the skyrocketing prices of insulin in recent years, Open Insulin has not been able to overcome the regulatory barrier of the intellectual property associated with the manufacturing process of insulin. While Open Insulin does not fall directly under FDA or NIH regulatory authority, laws governing trade secrets have stepped in their place, and impeded their goal. Thus, if community bio-labs were to ignore trade secrets involved in the manufacturing of insulin, which already have regulatory approval by the FDA, then they would be partaking in something illegal simply for ignoring the acceptance of established processes. In the case of Dana Lewis' artificial pancreas, since her health innovation is open-access, meaning anyone can access her instructions on the internet and purchase the off-the-shelf hardware easily, and she is giving it away for free, her artificial pancreas does not fall within FDA or NIH regulations or guidelines.

***When experimental drugs are being used in a clinical setting (i.e., via the FDA's "Expanded Access" program) who is typically liable for damages to the patient? Can this be applied to liability concerns for self-experimentation?***



“Expanded access, sometimes called ‘compassionate use,’ is the use outside of a clinical trial of an investigational medical product (i.e., one that has not been approved by FDA)...Whenever possible, use of an investigational medical product by a patient as part of a clinical trial is preferable because clinical trials can generate data that may lead to the approval of products, and consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible (e.g., the patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials), patients may be able to receive the product, when appropriate, through expanded access.”<sup>58</sup>

Since physicians are typically the ones to apply for expanded access to an investigational drug or biologic for a patient, much of the administration and liability falls to them. First, the physician “must speak with the drug manufacturer to see if they will provide the investigational medical product for expanded access.”<sup>59</sup>

“After you get the agreement from the manufacturer to provide the investigational; product for use outside of a clinical trial, **you [the physician] will be responsible for managing the use of the investigational medical product and the patient’s medical care.**”<sup>60</sup>

Interestingly, on the same website, the FDA claims that they accept 99% of the expanded access requests they receive, but then go on to state that drug manufacturers have the authority to decline expanding access. Thus, even if the FDA approves the request, the manufacturer may decline, leaving no guarantee of expanded access.

If the physician is able to receive approval from the manufacturer, and though physicians are liable and responsible for managing the use of the investigational medical product and the patient’s medical care under FDA’s Expanded Access program, it may not easily transfer to self-experimentation. Although Sean Ahrens may be the exception and not the rule. Prior to Sean’s self-experimentation with parasitic worms as an alternative treatment for Crohns disease, he spoke

**Patient-doctor partnerships  
should be encouraged  
even in the face of self-  
experimentation.**

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<sup>58</sup> U.S. Food & Drug Administration, *Expanded Access (Compassionate Use)*, [https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm].

<sup>59</sup> U.S. Food & Drug Administration, “For Physicians,” *Expanded Access (Compassionate Use)*, [https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429624.htm]

<sup>60</sup> [Emphasis ours.] U.S. Food & Drug Administration, “For Physicians,” *Expanded Access (Compassionate Use)*, [https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429624.htm]

with his physician, whom he knew cared for other patients that self-experimented with similar worms for similar problems. Luckily for Sean, his doctor neither condoned nor condemned his self-experimentation and continued to provide medical care throughout. Patient-doctor partnerships should be encouraged even in the face of self-experimentation because physicians are required to care for their patients, even if the patient elects unconventional therapies. It would be harmful for doctors to choose otherwise, which would go against their professional ethical norms.

### ***Does the FDA provide any guidance or regulate self-experimentation?***

Until recently, pioneers of democratized health innovation had remained at the margins of our biomedical research and regulatory establishment. Yet, in the last few months, two individuals widely shared videos in which they injected themselves with unregulated gene-therapies. Josiah Zayner is one of the self-experimenters and the CEO of The Odin, a start-up that has a long-term mission of making genetic engineering available to consumers. For about \$200, Odin sells the gene-editing kits required to design gene-therapies at home. While a scientist is required to get approval to conduct research on humans, the U.S. government had not explicitly warned against self-experimentation by a scientist outside of a traditional research institution. Then, on November 21, the U.S. Food and Drug Administration issued a first-of-its kind [statement](#) on the practice:

“FDA is aware that gene therapy products intended for self-administration and “do it yourself” kits to produce gene therapies for self-administration are being made available to the public. The sale of these products is against the law. FDA is concerned about the safety risks involved.”

We must recognize the urgent need to build legitimacy, but also a tailored regulatory support for new forms of democratized health research. The way forward is not to promote radical, unregulated science, but to develop engagement channels where citizens, patients, ethicists and regulators are forced to rethink and design an adaptive oversight system that fosters empowerment and responsibility, rather than just adherence to the status quo. The only way to avoid a blanket ban on all self-experiments is to engage stakeholders, and it’s worth it.

## Privacy

Privacy will always be a concern when personal information is published, or stored, on the internet. In the age of citizen-driven biomedical research and private genome sequencing companies like 23andMe, protecting personal information like the data collected from at-home

**The critical factor  
is consent.**

genetic testing kits is more important than ever. All of us have the right to keep our genome sequences to ourselves; just as all of us have the right to publish our genome sequence data if we so choose. The critical factor here is consent. In a study published in the *European Journal of Human Genetics*, which

surveyed the attitudes, motivations, and preferences of research participants receiving personal genome sequencing results, the authors found that 57% of participants reported concerns related to potential privacy issues about their data.<sup>61</sup>

23andMe, one of the top genome sequencing companies, claims they have five key ways to ensure your privacy: meaningful choice, privacy by design, third-party sharing, data security, and research.<sup>62</sup> Meaningful choice means “you decide how your information is stored, used, and shared.”(Ibid.) Privacy by design refers to the types of information they collect (name, credit card, IP address, genetic, phenotypic, and familial information), how they store your information (personal and registration information is stored separately from your genetic information), and how they keep your research details private (your personally identifiable information is stripped from your genetic information when you opt-in for research). Interestingly, 23andMe’s third-party sharing section of their five pillars for privacy primarily focuses on considerations for children and incapacitated individuals who do not have the capacity to make decisions for themselves. For example, when an individual dies and they have received their genetic information, 23andMe claims, “we will only give their account information to individuals who are legally authorized to make decisions on their behalf, such as an executor, a personal representative, or a beneficiary of a deceased’s estate.”

They also claim to work very hard to protect your information from unauthorized access from law enforcement. In order to do so, their [Transparency Report](#) tracks the number of government requests for customer information, the number of instances where data was produced (in whole or in part) without the individual’s consent, and the number of users or accounts specified in requests received by 23andMe. As of September 15, 2017, the only country that has requested customer information has been the United States. According to their report, the US has submitted five requests for six users/accounts, but 23andMe has not fulfilled any of those requests. Not only will 23andMe not hand over personal and genetic information for unauthorized law enforcement requests, they will also not provide any person’s data (genetic or non-genetic) to an insurance company or employer. This point is of particular importance when it comes to privacy, and we will come back to this in this section. 23andMe’s fourth pillar for privacy, data security, “employs software, hardware, and physical security measures to protect the computers where customer data is stored...Personal information and genetic data are stored in physically separate computing

**As of September 2017, the U.S. is the only country that has requested customer information from 23andMe.**

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<sup>61</sup> SC Sanderson et al., (2016), “Motivations, concerns and preferences of personal genome sequencing research participants: Baseline findings from the HealthSeq project,” *European Journal of Human Genetics*, 24: 14-20 (see, p. 17). \*Note: While this study was conducted in Europe, which may have differing socio-cultural attitudes towards genome sequencing and personal data protection, we believe that this study is still relevant.

<sup>62</sup> See 23andMe’s Privacy Statement on their website [<https://www.23andme.com/privacy/>]

environment, which is in line with industry standards for security.” The final pillar is research participation. “If you choose to consent to participate in research, your data will be used to help power the work done by 23andMe scientists or third-party researchers working with 23andMe.”<sup>63</sup> Yet, just because storing identifying data in separate physical locations is in line with industry standards doesn’t mean it is adequate or sufficient for protecting personal information.

**“Medical big data can serve as a treasure trove of information for parties to use it to further their own economic interests.”**

– Hoffman 2015

Sharona Hoffman details how the HIPPA Privacy Rule,<sup>64</sup> the Privacy Act,<sup>65</sup> and numerous state privacy laws that govern the disclosure of medical records do not cover all data holders who make medical information publicly available.<sup>66</sup> Even though much of the medical data made available to the public has been stripped of many identification factors, many other remain (e.g., height, weight, age, gender, and even sometimes zip codes), at least a small risk of re-identification remains. Moreover, in cases like Steven Keating, he has taken no precautions to unidentify his medical data with himself, and encourages others to do so as well. The idea there is that if you publish your own health data, and others know it’s yours, then they may be able to help scour your data in the hopes aiding the discovery process, identifying others with the same disease, and identify potential treatment options. Steven is not concerned with any potential privacy concerns, but that doesn’t mean they don’t exist.

For instance, one potential risk to privacy with publicly available medical big data, either self-published or published by an institution like the Personal Genome Project, is discrimination and special, personalized targeting. “Medical big data can serve as a treasure trove of information for parties who will use it to further their own economic interests.”<sup>67</sup> Even

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<sup>63</sup> Thus, it would seem that Sonia Vallabh and Eric Minikel are third-party researchers working with 23andMe since they received 600,000 people’s data.

<sup>64</sup> 45 C.F.R. §§ 160.101-.534 (2013).

<sup>65</sup> 5 U.S.C. § 552a (2010).

<sup>66</sup> Sharona Hoffman, (2015), “Citizen Science: The Law and Ethics of Public Access to Medical Big Data,” *Berkeley Technology Law Journal*, 30(3): pp. 1741-1805. (p. 1764).

<sup>67</sup> Sharona Hoffman, (2015), “Citizen Science: The Law and Ethics of Public Access to Medical Big Data,” *Berkeley Technology Law Journal*, 30(3): pp. 1741-1805. (p. 1772) in reference to Narayanan & Shmatikov, *supra* note 167, at 26 (noting “increasing economic incentives for potential attackers”); Kate Crawford & Jason Shultz, *Big Data and Due Process: Toward a Framework to Redress Predictive Privacy Harms*, 55 B.C.L. REV. 93, 96-99 (2014) (discussing business use of big data to obtain personal health information about consumers); Danielle Keats Citron & Frank Pasquale, *The Scored Society: Due Process for Automated Predictions*, 89 WASH. L. REV. 1, 3 (2014) (stating that in today’s world

if re-identification were not possible, publicly available medical data self-published with no attempt to de-identify it with themselves, a trend emerging out of bio-citizenry, may make them vulnerable to discrimination by employers. It's not hard to imagine that an employer might do a quick Google search of you before hiring – this happens all the time. Now imagine Steven Keating looking for a new job, his potential employer Google's him and find the 70 gigabytes of his medical information, which details his struggle with a cancerous brain tumor. An employer might view this revelation as a company liability, because they very well may need to pay more for his health insurance, sick days, etc. if they hire him. As we know, many companies do take such things into consideration during the hiring process, even though they're not supposed to.<sup>68</sup> Yet, while employers are constrained by federal and state laws prohibiting discrimination based on a variety of protected classifications, including disability and genetic information,<sup>69</sup> publicly available health data may be a loophole for employers to exploit in subtle, undetected ways. Publicly available medical data can be viewed and used by *anyone*, meaning other patients, doctors, and even employers can access it and use it in decision-making processes. Patients who agree to publish their health data on websites such as the Personal Genome Project, or allow companies like 23andMe to use your data in research both inside and outside of the company, or self-publish their own health data on their personal website like Steven Keating, should be aware and understand that this data will be accessible to everyone – even their employers.

**Publicly available health data may be a loophole for employers to exploit in subtle, undetected ways.**

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“[p]redictive algorithms mine personal information to make guesses about individuals' likely actions and risks” and “[p]rivate and public entities rely on predictive algorithmic assessments to make important decisions about individuals”).

<sup>68</sup> Here we are thinking about employer discrimination of women, who may become pregnant, requiring maternity leave, and increased health care costs. “While few women file lawsuits, there are more discrimination claims submitted now than there used to be. In 2006, the Equal Employment Opportunity Commission (EEOC) received nearly 5,000 complaints of pregnancy-based discrimination—a [30 percent increase](#) from the previous decade. In 2010, there were more than [6,000 complaints](#) filed.” found in: Darlena Cunha, 2014, “When Bosses Discriminate Against Pregnant Women,” *The Atlantic* (24 September) [<https://www.theatlantic.com/business/archive/2014/09/when-bosses-discriminate-against-pregnant-women/380623/>]. Also see, Cynthia Thomas Calvert, (2016), “Caregivers in the Workplace,” *Worklife Law: UC Hastings College of the Law* [<http://www.worklifelaw.org/pubs/FRDupdate2016.pdf>].

<sup>69</sup> Sharona Hoffman, (2015), “Citizen Science: The Law and Ethics of Public Access to Medical Big Data,” *Berkeley Technology Law Journal*, 30(3): pp. 1741-1805. (p. 1773) in reference to Sharona Hoffman, *The Importance of Immutability in Employment Discrimination Law*, 52 WM. & MARY L. REV. 1483, 1489-94 (2011) (discussing the forms of discrimination prohibited by anti-discrimination legislation).

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## NEXT STEPS & CONCLUSION

### Community Bio-Labs as Catalysts for Responsible Innovation

Ultimately, experiential knowledge created by citizen biomedical research may in turn impact governance<sup>70</sup> and more work is needed to understand the dynamics of these two systems. Even though technological innovations and health research conducted by bio-citizens might not have a clear path to ethical approval or might not be able to overcome the “chill factor.” With the mentorship and peer-review culture they provide, community bio-labs could play an important role to explore how we might include bio-citizen innovations in responsible governance.

Three intersecting factors – access to technologies, mentorship and funding – are fuelling democratized health innovation. First, you can now find legal to buy online the rudiments of an amateur biology kit, from used [PCR machines](#) and [DNA synthesizers](#) to chemical compounds such as peptides and reagents. The mushrooming of consumer and community bio-labs also ensures exposure and mentorship into the technologies required for bio-engineering and personal genomics analysis. To cap it off, motivated patients have started crowdfunding selected clinical research strategies as a kind of “venture philanthropy” that can generate from several thousand to [several million](#) dollars.

Yet, empowerment often collides with hard truths. While intending to break new ground in underserved health domains, new forms of participatory health research suffer from a lack of legitimacy. Regulators tend to question the quality and scientific validity of experiments that occur outside of traditional clinical trials. Maybe, in some cases, rightly so. Another hard truth is that the potential for citizens to take a proactive role in their own diagnosis and treatments outside of traditional institutions probes many unresolved ethical issues: blurred boundaries between treatments and self-experimentation, peer-pressure to participate in trials, exploitation of vulnerable individuals, lack of oversight concerning quality control and risk of harm, privacy,

**Notwithstanding the concerns,  
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and more. The company [Wego Health](#), for instance, connects patients with research and pharmaceuticals brands that will ultimately pay them for helping recruit clinical trials’ participants. In this big pharma version of the gig-economy, the potential for these patients to enter conflicts of interest, while getting paid for their influence, is looming.

Notwithstanding the concerns, we should not simply disregard medical research conducted outside of traditional institutions as de facto less safe, less reproducible, or unethical.

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<sup>70</sup> Jasanoff, Sheila, editor. *States of Knowledge: The Co-Production of Science and the Social Order*. 1 edition, (Routledge, 2004).

Patients often have in-depth experiential knowledge of their conditions along with a vested interest to make sure that a treatment or device will be effective, safe and beneficial. Yet, facing regulatory uncertainty, they might not overcome the “chill factor.” The press has recently covered cases of biohackers who self-experimented with unregulated gene-therapies. But the stories encountered in community bio labs, such as Biocurious and Denver Biolabs, are different. As Eric Espinosa, Elodie’s mentor, mentioned in his interview: “The FDA is always at the back of my mind; we want our proof of concept to be safe and reproducible, and we will work towards that.”

The next step is to foster legitimacy for citizen-driven biomedical innovation by supporting citizens and patients to document and share their data, evidence, and ethical concerns in ongoing conversations with regulators and society at large. Because they respect [biological safety levels](#)<sup>71</sup> and function as a peer-review culture, community bio labs constitute an ideal ecosystem for mentorship in the most current bio-

**Foster legitimacy for citizen-driven biomedical innovation by supporting citizens and patients to document and share their data, evidence, and ethical concerns in ongoing conversations with regulators and society at large.**

engineering techniques and their related risk-benefit trade-offs.<sup>72</sup> These collective labs might be the perfect place to start a continuing dialogue about how to adapt our regulatory standards to a more democratized form of biomedical innovation. What we need is empowerment, but also more collective intelligence. If risks are properly managed without dampening the now more-democratized reality, we might all gain in the process.

“With the ready availability of tools such as...crowdfunding, a more-decentralized governance is needed for everyone, not just DIY biologists. Codes of conduct will be needed to establish appropriate norms for government funding and regulatory agencies, for people working both within and outside conventional research settings, for the directors of community labs and for the developers of crowdfunding platforms.”<sup>73</sup>

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<sup>71</sup> “Today, Genspace and other community labs around the world have their own advisory boards or can seek advice from the ‘Ask a biosafety professional your question’ portal (<http://ask.diybio.org>). The portal’s panels review proposals for projects and flag potential safety issues...In many ways, this proactive culture of responsibility is an advance on the post hoc scrambling that often occurs within the scientific establishment.” Found in: Todd Kuiken, (2016), “Learn from DIY biologists,” *Nature*, 531 (10 March): p. 168

[[https://www.nature.com/polopoly\\_fs/1.19507!/menu/main/topColumns/topLeftColumn/pdf/531167a.pdf](https://www.nature.com/polopoly_fs/1.19507!/menu/main/topColumns/topLeftColumn/pdf/531167a.pdf)].  
<sup>72</sup> (2017), “A boost from biohackers,” *Nature*, 552 (21/28 December) [<https://www.nature.com/magazine-assets/d41586-017-08807-z/d41586-017-08807-z.pdf>].

<sup>73</sup> Todd Kuiken, (2016), “Learn from DIY biologists,” *Nature*, 531 (10 March): p. 168  
[[https://www.nature.com/polopoly\\_fs/1.19507!/menu/main/topColumns/topLeftColumn/pdf/531167a.pdf](https://www.nature.com/polopoly_fs/1.19507!/menu/main/topColumns/topLeftColumn/pdf/531167a.pdf)].

## A Proposed Framework

|                                 | Type of Invention, Innovation, Intervention | Type of Evidence, Data, and Tacit Knowledge involved | Type of Data-sharing | Type of Trial or Evaluation | Type of Health Claims | Type of unexpected effects, negative results | Perceived Regulatory or Legitimacy Barriers (“Chill Factor”) | Type of Funding | Risks and Benefits Assessment By inventors (Thriving not just treating) and regulators | Governance and Ethical Issues (e.g. privacy, autonomy, group dynamics, interest of third party, e.g. children, etc.) |
|---------------------------------|---|--|----------------------|-----------------------------|-----------------------|--|--|-----------------|--|--|
| <b>Influencing Factors</b>      |   |  |                      |                             |                       |  |  |                 |  |  |
| Institutionalized or Bottom-up? |   |  |                      |                             |                       |  |  |                 |  |  |
| Collective or individual?       |   |  |                      |                             |                       |  |  |                 |  |  |
| Financial Incentives?           |   |  |                      |                             |                       |  |  |                 |  |  |
| Openness or in Competition?     |   |  |                      |                             |                       |  |  |                 |  |  |
| Level of Self-experimentation   |   |  |                      |                             |                       |  |  |                 |  |  |

**Table 2: Proposed Framework for Bio-Citizen Health Innovation – Inspiration from Stephen Friend/John Wilbanks for this taxonomy: “Collective and Personalized Memory”**



We are proposing this framework as a guide for citizen-driven biomedical research and innovation in community biolabs. This table is an effort to bridge responsible citizen-driven biomedical research and FDA's real-world evidence. This is an attempt to bridge responsible citizen health innovation in community bio-labs with the FDA'S real-world evidence. More research is needed to perfect this framework and assess its usefulness and feasibility.

## Challenges on Our Radar for Responsible & Democratized Health Innovation

How to bridge the gap between isolated citizen health innovators and community bio-labs? How to foster the convergence of these two forms of health democratization? How to help them collaborate to build legitimacy and responsible governance mechanisms for participatory and open health research? The two initiatives below might constitute interesting steps towards fostering the convergence of community bio-labs and open, participatory health innovation.

## Community biolabs as Catalysts for Responsible & Democratized Health Innovation

[TAKEDA HACKATHON](#) – Encouraging community bio-labs to build technical, scientific and safety standards in the development of research processes and in the collection of evidences?

On January 15, Takeda will launch Hacking Habenula, a crowdsourcing challenge that aims to leverage Big Data to determine which group of neuropsychiatric patients can benefit most from an investigational new drug. The drug activates GPR139 in the habenula and striatum, parts of the brain that are linked to a number of functions and disorders, ranging from pain processing to depression. Takeda seeks input from the community to uncover the critical insight that will help unlock the potential of this compound.

Powered by Brightidea, the challenge seeks to harness the power of Big Data and your bold thinking to solve real patient needs—and will offer a series of cash prizes to the most novel, strategic ideas.

Details on the challenge and how to participate will follow in early January 2018, including a direct link to sign up. In the meantime, join the discussion on Twitter at #HackingHabenula. We're excited to have you as part of this community of innovators, disruptors and apple-cart upsetters, and hope that you'll join the quest to help translate promising science into actionable solutions for patients.

[JUST ONE GIANT LAB](#) – Empowering networks of community bio-labs to share and assess scientific and biomedical research findings inside a virtual one giant lab?

Just One Giant Lab (JoGL) is the first research and innovation laboratory operating as a distributed, open and massive mobilization platform for volunteer-based, IP-free task solving. JoGL helps sync humanity onto solving our most urgent and important problems using Open Science, Responsible Innovation and Continuous Learning. JoGL partners with academic labs, companies, startups, foundations, NGOs and public services to create massive mobilization on distributed and participatory research programs for understanding and solving Health, Environmental, Social and Humanitarian issues.

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**The Citizen Health Innovators Project** focuses on developing regulatory and governance mechanisms for the fast-growing ecosystem of health innovators, built around maker spaces and community bio labs, to support responsible innovation in distributed networks. The Project also aims to unveil the conditions, barriers and opportunities for empowering citizens and patients who attempt to actively participate in the knowledge-production associated with biomedical research, in particular rare genetic diseases. It provides policymakers, regulators, philanthropists and funders (including crowdfunders) with an in-depth coordinated analysis of 1) the practices and methods of knowledge-production enacted by citizens and patients; 2) the ethical and governance challenges and barriers they face; 3) the potential mechanisms of legitimacy-building and responsible governance that could be adapted to fit non-traditional biomedical research. Such analysis should facilitate the development of alternative approaches to governance and ethical oversight, and generate materials for guiding citizens and patients towards responsible research and innovation. This project will finally create channels for constructive engagement and co-produced knowledge between citizens, regulators and (crowd)funders with the goal to foster responsible, inclusive and participatory health futures.

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