Data that Heals:
A Three Horizons Analysis

By
Lindsay A. Roxon

Submitted to OCAD University in partial fulfillment of the requirements for the degree of Master of Design in Strategic Foresight and Innovation Toronto, Ontario, Canada, April 2018

AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I authorize OCAD University to lend this thesis to other institutions or individuals for the purpose of scholarly research. I understand that my thesis may be made electronically available to the public.

I further authorize OCAD University to reproduce this thesis by photocopying or by other means, in total or in part, at the request of other institutions for the purpose of scholarly research.

ABSTRACT

You've got to think about big things while you're doing small things, so that all the small things go in the right direction. — Alan Toffler, Future Shock

In recent decades we have seen a major disruption to all major industries as a result of changing consumer demands, consumer empowerment, big data, and shifting demographics. Evidence of this can be seen in the disruption of major industries such as the automotive industry, retail, banking and manufacturing. Data is enabling a shift in power from large companies to smaller, emerging players.

Big Pharma has long enjoyed a privileged position, having grown with the healthcare system since its inception in the United States. We are at a moment in time where there is emerging capability to bring about radical change in the way that healthcare is delivered as a result of new technologies and the advancement of science. Digital Therapeutics and alternatives to pharmacological response to disease are becoming not only viable, but necessary, to contain costs and improve health outcomes. These changes are creating a risk of disruption for Big Pharma, if there is not a radical reassessment of organizational strategies and investment.

Using the Three Horizon's Foresight Methodology, this paper explores the needs, barriers and opportunities for each major stakeholder – pharma, emerging technology players, payers, patients and providers – given an overview to the present situation, the ideal future and presenting strategies to bridge these two horizons. The result is an understanding of the potential areas of disruption to health therapeutics industry and an understanding of how the pharmaceutical industry may adapt to build resiliency by transitioning and rethinking its core product, facilitating and partnering with emerging players, and moving towards a strategy of improving health outcomes (real value creation) rather than revenue increases and identifying new revenue opportunities in the process.

ACKNOWLEDGEMENTS

"Look at a stonecutter hammering away at his rock, perhaps a hundred times without as much as a crack showing in it. Yet at the hundred-and-first blow it will split in two, and I know it was not the last blow that did it, but all that had gone before." Jacob A. Riis

The splitting of this rock would not be possible if it were not for those who supported and encouraged me at every dip of the rollercoaster. In this case "all that had gone before" is not just my own work but that of all the wonderful people that support me whose own perseverance and perspective gives me mine.

Thank you to my family for always encouraging me to pursue any path that inspired me, and especially to question absolutely everything. Thank you also, for always reminding me that there is a light at the end of the tunnel.

Thank you to second family, my amazing friends, especially Kate and Hilary, whose courage, persistence, and bravery inspired me to try to understand more about healthcare and the rational side of the beast you face daily.

Thank you to all of my former classmates and colleagues at OCAD and Idea Couture whose perspective, smarts and inspired thinking taught me more than I ever thought I could learn in three years.

To all the faculty at OCAD's SFI program — especially Helen who shepherded through this process and provided her clear and insightful thinking at every turn, and Nabil and Kate for being incredible mentors throughout the program.

Table of Contents

List of Figures

List of Tables

ANALYTICAL TOOLS

Why a foresight study?

In order to uncover areas of potential disruption as a result of empowered emerging players in healthcare, it was necessary to look at not only the present situation but also some of the emerging changes, challenges, and opportunities on the horizon. This is critical for any large, entrenched, and complex system, not only because of breadth of opportunities for disruption and change, but also because of the time horizons upon which investments and planning are facilitated. The healthcare system, being extremely complex and entrenched, requires new patterns of thinking and frameworks to assist in navigating the uncertainty of the future.

"Shifting to a new pattern involves some form of strategic thinking and foresight." (Miller, 2007). Foresight can be classified into four types, according to the extent to which the decision maker has agency to do things and the degree of uncertainty they are facing. According to Anthony Hodgson, co-creator of the Three Horizon's method, the four types include Forecast Plans, Scenarios, Reflexive Futures, and Roadmaps. Hodgson and Sharpe developed the Three Horizon's model to fit into the Reflexive Futures category which fits into the High Uncertainty and High Agency in the quadrant below. (Hodgson & Midgley, 2015)

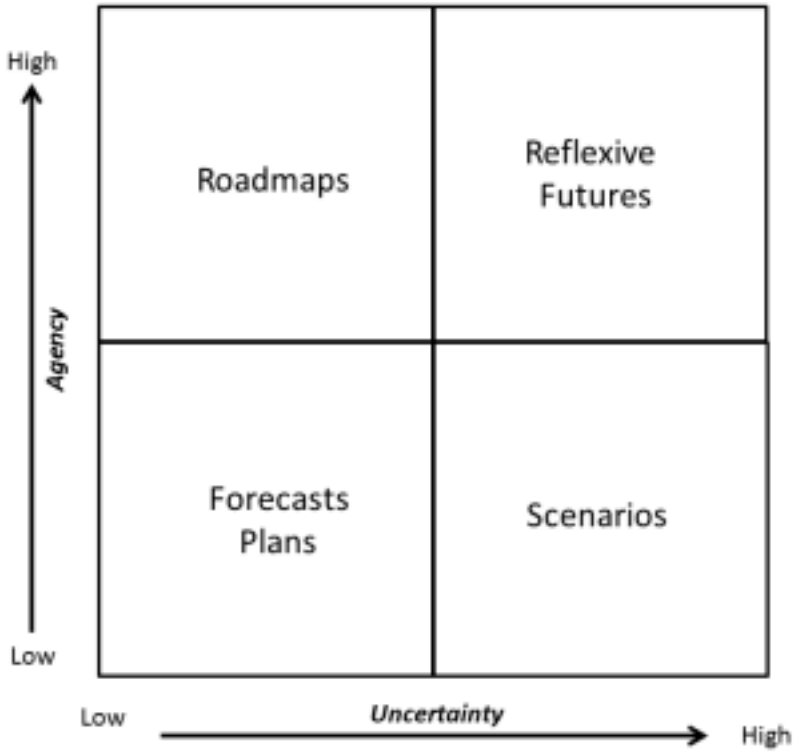

Figure 1 - Four Broad Categories of Foresight Method (Hodgson & Midgley, 2015)

Three Horizons Model

"Giants are not what we think they are. The same qualities that appear to give them strength are often the sources of great weakness." Malcolm Gladwell

In order to analyze the future of the pharmaceutical industry, the foresight framework "Three Horizons Model" was adopted. The Three Horizons model is useful in analyzing complex systems, especially those that involve many, large stakeholders that operate with different incentive systems, such as the healthcare system.

Operational research methods that are linear and algorithmic are useful in the more deterministic and predictive world of forecasts and extrapolation. Systems methods that account for dynamic feedback correlate better with the world of roadmaps, where performance on the pathway is subject to strong feedback influences. In the domain of scenarios, where there is high uncertainty, there is also increased dependency on human judgement, so approaches like critical systems heuristics and soft systems methodology fit well (Hodgson & Midgley, 2015).

The Three Horizons model was developed by UK Foresight Intelligent Infrastructure Systems (IIS) Project (Shultz, 2013). This tool helps us think about the future by helping us "group systemic patterns to identify which of the dominant patterns are no longer fit for purpose, how the emerging trends can shape the future, and what visionary action is needed to collectively move us towards a viable future." In a facilitated group environment, the model would allow us to gather perspectives from a large group of stakeholders, synthesize common understandings in order to prioritize action, and give the group a common language.

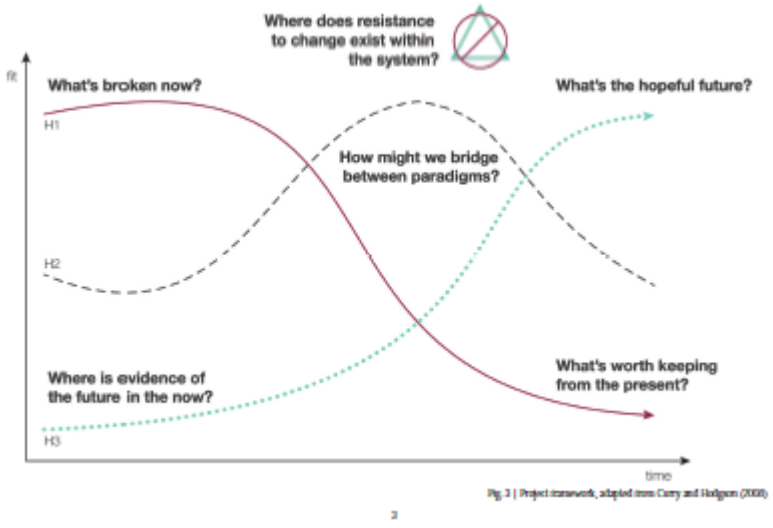

Figure 2 The Three Horizons (Hodgson & Midgley, 2015)

As a foresight methodology, the tool is used as an analytical framework to make speculative claims about the potential future and to guide future areas of study.

An alternative approach is to organise systems methods from the perspective of the three horizons. The qualitative distinctions between the horizons also suggests that different systems methods may be more suited to problem-solving and decision-making according to the horizon perspective adopted by the decision maker. A broad representation of this is given in Figure 4. This is not intended to be comprehensive or finalized, but rather to suggest an approach for further investigation (Hodgson & Midgley, 2015).

In the case of this study, the Three Horizons Model was used to structure research findings from the literature review. In place of a broad stakeholder discussion, the researcher used a literature review to get a sense of some of the major challenges facing the pharmaceutical industry today and some of the emerging opportunities for digital therapeutics as an alternative. This tool was chosen because it can accommodate a high-level system analysis while also offering the opportunity to dive deep into certain opportunities for intervention.

The Three Horizons Model looks at three large categories as can be seen in the table below: What is broken now? Where are we currently seeing evidence of the future? What is worthwhile keeping and how might we bridge that gap? Each section references critical nodes of the broader system that will be affected or may have to be disrupted in order to usher in the next generation of care. This exploration was done to provide a framework for understanding some of the challenges, barriers, and opportunities that exist across the healthcare ecosystem.

Horizon 1	*Horizon 2*	*Horizon 3*
Identify and repair self-defeating feedback. Identify missing necessary feedback.	Identify and displace self-defeating feedback and feedback that creates lock-in.	Challenge buried assumptions.
Seek optimisation.	Seek unmet need.	Seek new visions and patterns of viability.
Be efficient.	Be the disrupter.	Be the future.

Figure 3 Description of Three Horizons (Hodgson & Midgley, 2015)

In order to answer these questions, a variety of other research methods are employed, including a literature review, horizon scanning, and trend analysis. The findings are organized along the lines of the questions laid out in the table above in order to generate new insight, reframe existing problems, and identify opportunities for further investigation or research. The image below illustrates how a Three Horizons method may look during the research visualization process.

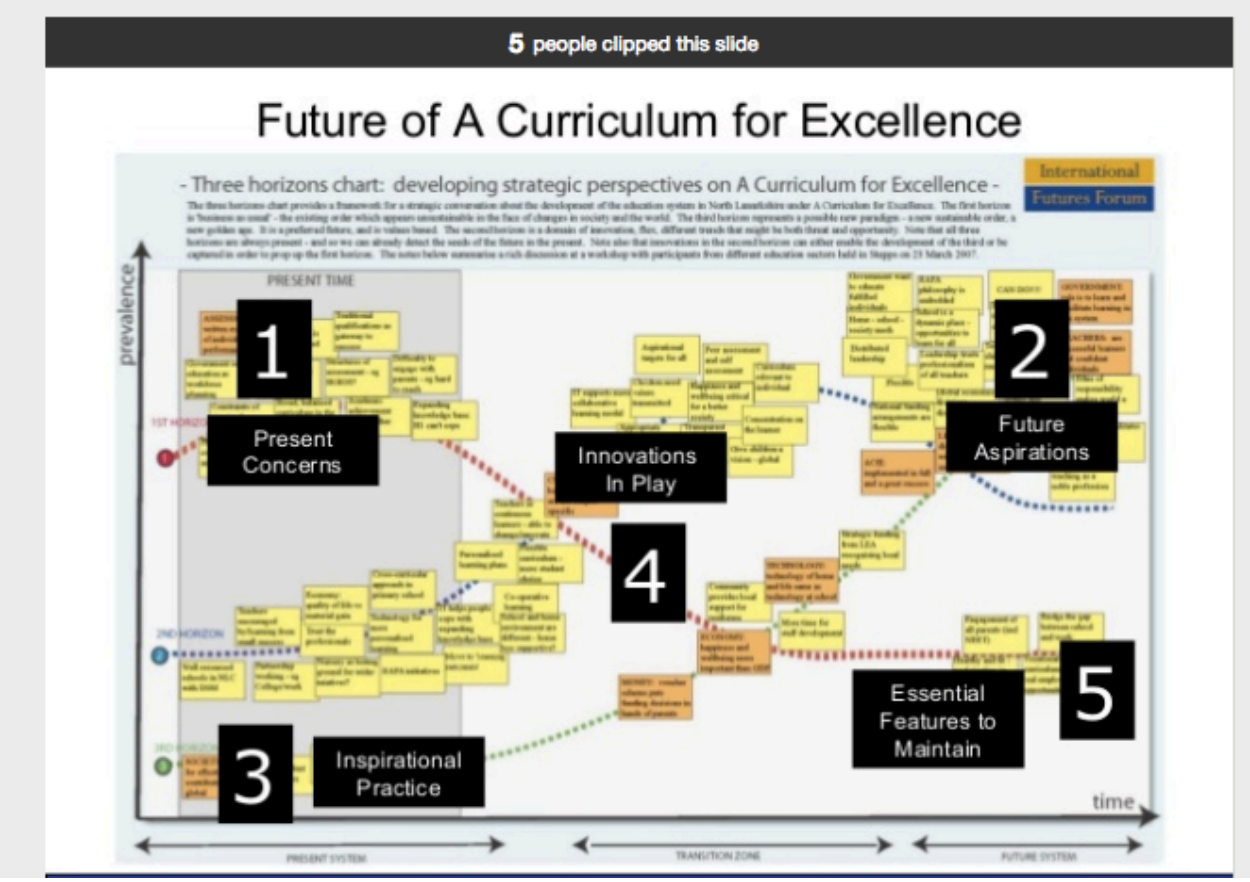

Figure 4 Three Horizons in Practise (Hodgson & Midgley, 2015)

Literature Review & Environmental Scan — A literature review and environmental scan was conducted over the course of two years, spanning journals, newspapers, magazines, newsletters, and technology reviews. The review resulted in a wide array of information that gave insight into some of the broader challenges, as well as hope and opportunities for the future of the healthcare system. Quotes and personal points from authors and experts were leveraged in place of points of view that would have been gathered from an interview. The literature review was largely used to inform the First Horizon, "What is broken now?" and "Where do we see evidence of the future?"

Horizon Scan & Trend Analysis — A horizon scan and trend analysis was done in conjunction with the literature review. A scan is a tool used to identify emerging changes. According to Wendy Shultz, a high-quality scan has the following three qualities: it identifies an emerging issue that is objectively new even to experts; confirms or is confirmed by additional scan hits; and has been identified in time for social dialogue, impact assessment, and policy formation. (Shultz, 2013) These scan signals helped to inform the Third Horizon, and to give a sense of some of the ways in which individualized medicine and digital therapeutics are likely to evolve. The scan was organized into the VERGE framework as a means to understand the potential impacts and implications; eventually the key points were used to bring context to the potential future and an understanding of what the ideal future might be (Visionforesightstrategy.wordpress.com, 2018).

Systems Diagrams & Archetypes — Systems thinking thought leader and researcher, William Braun, introduces the systems archetypes in his paper Systems Archetypes. Their purpose is to give "insight into patterns of behaviour, themselves reflective of the underlying structure of the system being studied." (Braun, 2002) The archetypes can be used both to diagnose and to give perspective on a problem. They help us recognize patterns of behaviour that are already present in the organizations and can give some insight into underlying systems or processes which may be invisible, informal, or deeply embedded in a systems structure. In order to breakdown the complexity of certain aspects of the healthcare system and especially the relationships between different actors within the system, the researcher uses systems archetypes and process diagrams to help characterize some of the behavioural patterns within the system.

Three Horizon Contents Summary:

FIRST HORIZON

What is broken now?

This section explores the development of the pharmaceutical industry and aspects of the ecosystem in which it operates that are creating barriers to innovation, encouraging incremental rather than the necessary transformational approach to innovation.

1. Discovery - Pharma and risk adapted corporate players/funders

The process and cost of discovering and innovating new treatments and cures is disincentivizing pharma to take a radical approach to therapeutic innovation and instead focus on prolonging profitability of current assets, investing in marketing and "blockbuster" medications rather than pursue innovative or truly individualized therapies.

- The Drugs Don't Work: *Im*precision Medicine – a description of the development of the evolution of pharmaceutical industry and the drug discovery process. This section explores how the growth of pharma alongside regulatory bodies and the broader healthcare system evolved into the current system.
- Generics Industry – an exploration of the ways in which the generics industry may inhibit pharmaceutical product innovation.

2. Payers, Access & Commercialization - Government and Hospitals and other major purchasers

This section explores existing processes and structures of commercializing treatments and how these act as inhibitors to innovation. It outlines key needs and barriers for payers as they strive to improve health outcomes, healthcare efficiency while managing risk and promoting safety.

- The Clinical Trials Process – a description of the Clinical Trials process and the ways in which it protects health and safety, but also inhibits drug innovation.
- Paying for and Approving Digital Therapeutics – a description of some of the challenges faced by payers in leveraging the potential of digital therapeutics.
- The Cost of Personalized Therapeutics – a description of the cost inhibitors for pharmaceutical companies to commercializing innovative, personalized medicines.

3. The Data Ecosystem - Tech, or tech enabled Health players

The data ecosystem that connects individuals to other stakeholders involved in facilitating treatment decisions. This section explores the current state of the ecosystem and highlights where there are gaps and challenges and opportunities for digital therapeutics in the future.

- Barriers and Potential for Digital Therapeutics – A discussion of the potential and challenges that are facing digital therapeutics.
- The Data Infrastructure is Fractured - Protocol and Real-World Evidence – an exploration of the current state of data infrastructure and how the broken aspects prevent the prevalence of pharma alternatives.
- Data Security & Ownership – A discussion of the current status of data security and the challenges that would need to be addressed to facilitate the next generation of cures.

4. Care Delivery – Patients and Clinicians

With the other sections focusing on the systems, processes and infrastructure of the healthcare system, this section focuses on the ways in which these tensions come to life at the point of care.

- Challenges in Adapting and Adopting – a discussion of the processual challenges in adopting digital and alternative therapeutics in regular practise.
- Lack of Alignment Between Providers – this section highlights gaps in education and details the misalignment between need, understanding and innovation.

Where is there evidence of the future in the present?

1. Discovery - Pharma and risk adapted corporate players/funders

This section explores how the process of discovery may be shifting and the directions it could possibly take in the future.

- Innovation in Precision Medicine -- This section explores how technology innovations are driving new approaches to treatment and care in the pharmaceutical industry.
- Leveraging Digital Technologies – This section explores current use-cases for digital technologies in pharmaceutical products.

2. Payers, Access, & Commercialization - Government and Hospitals and other major purchasers

In this section, the researcher will explore signals that point to a potential change in the way that reimbursement, commercialization and access may shift in the future.

- Bedside Pharmacy – If successful, bedside pharmacy may have an impact on the way that drugs are manufactured and personalized for patients, disrupting the drug manufacturing process.
- 3D Printed Drugs – 3D printing has the potential to radically change the way that drugs are manufactured and distributed by changing the supply chain, creating new opportunities for stakeholders outside of the pharmaceutical industry.

3. The Data Ecosystem - Tech, or tech enabled Health players

This section will explore signals that point to change within the data ecosystem and how this may create more viable options outside of pharmaceutical products.

- Disruption from Non-traditional Players – Stakeholders outside the bounds of conventional healthcare providers are beginning to enter healthcare and may radically shift the way that care is provided.
- Direct to Consumer Healthcare – This section speaks to the emergence of consumer healthcare products that are driven by data and may create disruption.
- Bypassing Biological Trials – New capabilities in AI and machine learning may enable researchers to simulate potential drug responsiveness, reducing financial barriers to generating clinical data and commercializing medicines.

4. Care Delivery - Patients and Clinicians

This section will explore potential changes in the way that care may be delivered and the ways in which perspectives and values in care may change given the shifts in the healthcare system.

- Global Perspectives – A description of how the Chinese government is leveraging digital technologies to promote a preventative approach to care.
- Digitally Savvy and Empowered Patients – A description of how patients' sense of ownership and responsibility may change in the future.

THIRD HORIZON

What's the hopeful future?

- Better treatment – Leaders in healthcare are looking towards a future where better, more personalized treatments are available by any means necessary. This will include working with emerging stakeholders to facilitate improved, innovative approaches to treatment.
- More cost-effective system – Cost-effectiveness is a both a goal and necessity for a viable, sustainable healthcare systems in the future.

1. Discovery

This section explores the future of drug discovery and the delivery of innovations.

- Empowerment and New Channels of Discovery – New capabilities are creating hopes for a new model of drug discovery that would allow for new channels of discovery, and empowerment to create more discoveries outside of pharmaceutical companies
- Providers with time to provide care – The hopeful future is that care can be improved not only at the systemic level but at the provider level, where the impact is experienced by patients.

2. Payers, Access, & Commercialization - Government and Hospitals and other major purchasers

The hopeful future for payers, access and commercialization is one in which medical treatments are more affordable, and accessible by more patients.

- Creating Equity – This section explores the hopes for improved access and equity of the quality in patient care.
- Affordable – In lowering the costs of care and making it more affordable, payers are looking for a means to create lower premiums to reduce the economic burden of care.

3. Data Ecosystem - Tech, or tech enabled Health players

This section explores the hopeful future for the data ecosystem that would facilitate open data networks and secured data for patients.

- Privacy & Openness – a key hope for the future is that future data ecosystems will be one in which privacy and openness are supported to allow for more access to information that would allow for more stakeholders to have the ability to innovate.

4. Care - Patients and Clinicians

This section explores the future of care and the ways in which more personalized treatments can be facilitated at the provider level.

- Integrated Problem Solving – the ability to create possibilities for integrated problem solving and intelligence sharing is critical to facilitating the next generation of treatments and medical discovery.
- Caring for Chronic Diseases – the creation of models of care to both prevent and care for chronic diseases, has the potential to create a large impact in improving health outcomes, potentially shifting or relieving the reliance on medications.

What's worth keeping from the present?

- Protecting Primary Care – Given all the shifts in responsibility, capability and ownership, this section explores the importance of protecting and promoting primary caregivers in the wake of disruption and facilitating a means to be educated, and prescribe beyond pharmacological response.
- Data Transparency and Ownership – The increasing importance of data in the provision of care means that awareness needs to be placed on individual privacy and security for personal data. In addition, it requires advanced methods for sharing and opening data sources to create pathways for innovation.

SECOND HORIZON

How do we bridge the gap?

Critical Tensions – Key tensions that emerged through the research that are likely to shape the direction of the future.

Scenarios – Short vignettes to bring to life some of the tensions and opportunities that may manifest in the future.

Summary of Findings – A summary of key findings: Incentives, Risks and Opportunities for each stakeholder.

Strategic Roadmap – A comprehensive set of recommendations directed at the pharmaceutical industry to continue to build resilient business models moving into the future.

Conclusion – A summary of findings.

Data that Heals

The pharmaceutical industry has long been a subject of contention. As a for-profit industry made up of monolithic organizations, histories of scandal such as the Thalidomide scandal of 1961, complex incentive structures and a virtual monopoly in the provision of drug treatments, many stakeholders within healthcare, government and consumers of pharmaceutical products have come to question whether the role that pharma plays in healthcare to a be one that is positive or negative.

Recent advances in technological developments have led to an increased ability to capture, store and analyze data through the use of digital tools that combine digital devices and machine learning. The proliferation of data is currently outpacing scientists' ability to leverage the data in a meaningful way. However, at some point this is likely to change. There are currently many companies that are working to create novel approaches to disease diagnosis and management that have the potential to reduce reliance on pharmacological interventions. The rise of chronic diseases has increased the cost of healthcare to a point that it is virtually unsustainable. It is estimated that by 2025, chronic diseases will affect nearly half of the American population. (49%). (Fightchronicdisease.org, 2018) Digital Therapeutics offer the potential for effective, cheaper alternatives that are targeted at areas that are not well addressed by the current healthcare system and pharmaceutical companies including chronic disease. (Joyce, 2018)

> Importantly, digital therapeutics tend to target conditions that are poorly addressed by the healthcare system today, such as chronic diseases or neurological disorders. In addition, they can often deliver treatment more cheaply than traditional therapy by reducing demands on clinicians' time. And all the while, more evidence is emerging to demonstrate their value in clinical terms. (Joyce, 2018)

In the development of this report, the researcher reviewed trends, drivers and signals that may indicate a necessary change and capability of digital therapeutics to uncover areas of potential disruption for pharma. Through a thorough scan of technology and innovation magazines, health blogs, and newspapers, and review of records of contemporary discourse around health with respect to pharmacological interventions this report attempts to synthesize where there are changes and potential disruption to pharma by digital therapeutics and non-traditional players.

This scan and literature review resulted in four key findings:

1) It was widely apparent that our current approach to healthcare delivery is no longer working. Much of care is suboptimal with unsustainable costs, and many treatments are ineffective and only add to existing healthcare challenges.
2) New technologies have the ability, for the first time, to provide a new level of precision. Our ability to collect many new kinds of data engenders hope that we will gain new understandings of the body and ways we may be able to heal it.
3) Personalization seems to be one advancement that could solve some of the inefficiencies of the healthcare system; the increasing availability of detailed data will make personalization a more effective process.
4) Innovation seems to be emerging from outside the realm of pharma R&D and is beginning to be led by technology companies. If data is truly the gateway to the next wave of treatments, pharma may not be best poised to lead treatment in the future.

Health outcomes are affected by more than available treatments. Health is also affected by provider decision-making and, of course, lifestyle factors. However, this report will focus on the opportunities that may come from focused use of detailed patient data in an effort to create more multimodal approaches to curing illness that extend beyond pharmacological approaches. It acknowledges and explores potential barriers, pain points and outlooks for pharma and risk adapted players in innovation. These same areas of vulnerability are also opportunities for emerging players from the technology sector to begin to play an increasingly large role in delivering care.

This project is concerned primarily with the future of healthcare in North America. While the cost and payer negotiation process is different in the United States and Canada, the impact of pharmacological innovation is similar in both countries. Where there is a difference, the text will reference how this may affect the universal healthcare model (Canada) versus a privatized system (United States).

Using the Three Horizons Model, this report will highlight the most powerful points of change occurring at the various levels of the system that expose why it is necessary for pharma to radically innovate, not only its products but business model in order to remain resilient moving into the future.

This analysis is far from exhaustive; because of the breadth of signals taken into account, there are most certainly gaps. Further analysis may explain nodes of change at even deeper levels. This study is intended to provide a starting point; to present perspective on some of the big changes and to highlight opportunities for further investigation of specific areas.

The intention is to present the reader with a deeper understanding of how data and data capturing tools are democratizing the process of innovation in medical science. It will provide an understanding of how this may serve to disrupt pharma in the future.

Summary of Findings from Literature Review

The literature review, in combination with horizon scanning, created a theoretical scaffolding that will be carried through the rest of this report.

First, in assessing the present and future state, it is important to look at four major groups of stakeholders that occupy four key functions in the medical treatment innovation system.

1. **Discovery – Pharma and risk adapted corporate players/funders**
    - It is critical to understand (at least broadly) how drugs are developed and brought to market and how the current system has created innovation barriers for pharma and risk adapted corporate players/funders.

As for-profit entities, pharma is incentivized to remain profitable and retain market control. In order to do this, they work to ensure exclusivity and access of their products, they attempt to secure and elongate profits from existing assets. Pharma is faced with the tension of balancing the cost of innovation with potential for profitable outcomes, which acts as a barrier to innovation and reinforces the need to protect assets.

2. **Payers & Access - Government and Hospitals and other major purchasers**
    - Payers determine which drugs are made accessible, to whom and for how much. Within this category this report will explore how the economics of drug commercialization are creating innovation barriers for pharma.

Government is interested in decreasing public expenditure on healthcare via improved health outcomes and affordable therapeutics. Private payers are similarly incentivized to improve health outcomes and efficiencies to increase profitability and lower payout costs. However, they face less risk as they're able to pass through costs to the broader system.

3. **Data Infrastructure & Ecosystem - Tech, or tech enabled Health players**
    - New capabilities to collect, digitize, and integrate data are contributing to a shift in the way that treatments can be tracked, monitored and instigated, creating opportunities to create real world evidence to support drug efficacy and opening up opportunities for technology companies to play a significant role in the future of medical treatment.

Technology companies are interested in clearing regulatory hurdles for digital therapeutics and in the meantime demonstrating potential use-cases for digital therapeutics to gain credibility, iterate to improve product quality and begin to attract investors and generate profit.

4. **Care/Treatment Delivery - Patients and Clinicians**
    - While the first three categories that will be discussed reference "back-end" aspects of the healthcare system, this section will explore how these tensions come to life at the point of care delivery.

Patients and physicians are principally concerned with improving health outcomes and increasing the availability of affordable efficacious options.

These sub-categories, while not an exhaustive list of stakeholders or structures within the system, will help shape the reader's understanding of some of the major leverage points within the system to catalyze change or lead to disruption in the future.

Secondly, the literature review exposed the deep, highly entrenched nature of the innovation barriers experienced by pharma. It has revealed that pharma may not be best poised to make significant shifts that will enable more access to better care. The current model has had both positive and negative impacts on society, but it is clear that the role of pharma in advancing science needs to be reconsidered. If pharma cannot learn to better leverage data to create more effective, less harmful medicines, is it possible that non-traditional players may be able to play a disruptive role to bypass these challenges that are so entrenched in the current, risk-adapted system.

Thirdly, the current paradigm of care is a primarily social and values-driven movement that takes aim at individualizing health as a way to improve outcomes, in a way that happens to be

intrinsically aligned with a neoliberal approach to health and care. This is not the only way or even necessarily the best way to improve health outcomes; this simply presents one perspective that is symbiotic with the pharmaceutical business model. As more treatment options become available, there may be a disruption to not only the way that diseases are treated but also a shift in values away from an individualized approach to one that is collective and preventative.

Related concerns of Major Stakeholders:

The stakeholder matrix below was developed for this report to show the interrelated concerns and incentives faced by some of the major stakeholders concerning the advancement of therapeutics. This should bring to light the tensions in the system which will be brought to light later in the report.

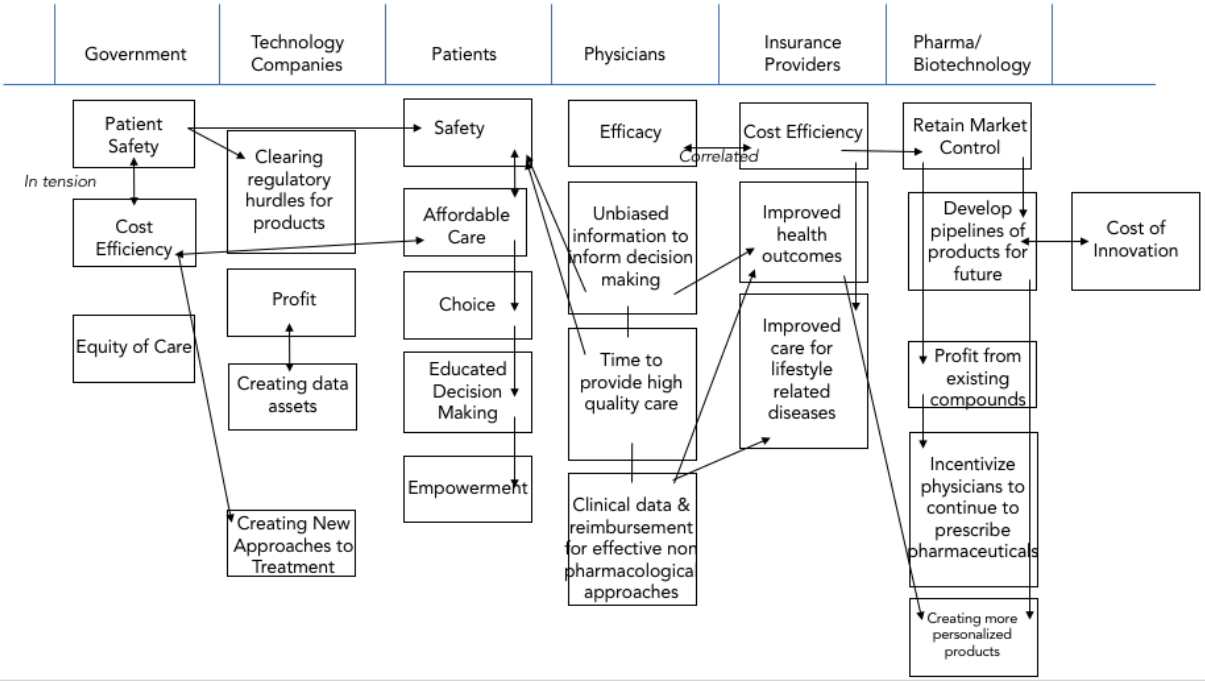

Figure 5 – Stakeholder Matrix – Lindsay Roxon

These stakeholders have been grouped into the nodes of the system: Discovery, Access, Data Ecosystem, and Care. Each section will discuss the ways in which the stakeholder is incentivized to behave now and, in the future, and how this impacts their ability to innovate, disrupt and remain resilient moving forward.

First Horizon

In the first horizon I will examine the current state of the medical system's advancement toward precision medicine through the analysis of broad social, political, technological, economic, environmental, values trends and historical development that address the following subsections: What's broken now? Where is there evidence of the future in the present?

This analysis will provide an overview of some of the larger forces at play in the medical system that are reinforcing, incentivizing a system that is unconducive to innovation and is vulnerable to disruption from emerging players. The intent of this Horizon is to understand a series of barriers, and the baseline from which we are currently working that will need to be addressed by the Second Horizon.

According to Wendy Shultz, in a Three Horizons Analysis, the First Horizon is dominated by four key characteristics.

First Horizon (H1) Characteristics from Wendy Shultz (Shultz, 2017):

- Today's dominant patterns — accumulations of past decisions and designs
- H1 systems are fully integrated with surrounding culture "locked in"
- Well-established ways of dealing with problems frame approaches to new challenges
- Barriers addressed in the Three Horizons Analysis are typically dominated by quantitative sense of time as a limited resource.

1.0.0 What's broken now?

The findings reported in this section are representative of the results of research conducted through a literature review and horizon scan. The sections below detail the innovation challenges that pharma is currently facing, and some of the ways that practitioners and administrators are attempting to address the gaps.

> Every day, millions of people are taking medications that will not help them. The top ten highest-grossing drugs in the United States help between 1 in 25 and 1 in 4 of the people who take them. For some drugs, such as statins -- routinely used to lower cholesterol -- as few as 1 in 50 may benefit. There are even drugs that are harmful to certain ethnic groups because of the bias towards white Western participants in classical clinical trials. (Schork 609-611)

1.0.1 Discovery

The role of Pharma and risk adapted corporate players

The pharmaceutical industry has evolved alongside the healthcare system. In order to capitalize on new capabilities in data proliferation to create customized medications and treatment plans and remain resilient in the face of emerging players, there are significant hurdles to overcome. The hurdles are largely systemic in nature, relating to the way our healthcare system, and specifically the knowledge gathering process, has evolved alongside the pharmaceutical industry in the 19th century.

The Drugs Don't Work: *Im*precision Medicine

The evolution of Pharmaceutical Industry and Risk Adaption

Over the last 150 years, formalized healthcare systems have developed around the world (Sheingold & Hahn, 2014). The structure, regulation and delivery of healthcare varies by country, but what is consistent is some understanding that health is of universal importance to both the state and individual. The evolution, structure, and values of the formal healthcare system can be seen in parallel to greater societal and economic movements such as industrialization (Sheingold & Hahn, 2014).

In the United States and Canada before the 1900s, healthcare was largely informal until economic and social influences drove the development of health infrastructure. These influences included the rise of accidents and injuries during industrialization and need to prevent productivity losses.

In 1940, penicillin was brought to market, revolutionizing healthcare (Sheingold & Hahn, 2014). At around the same time there was an economic boom. In order to compete for workers, businesses began to offer health insurance to cover incidental costs of care. The Economic Bill of Rights introduced the concept of the right to appropriate medical care. While it still took decades for this to be represented in more tangible terms, it marks the beginning of a change in values that still persists today in most healthcare structures. (Sheingold & Hahn, 2014).

By the 1950s, the price of hospital care doubled with an explosion of new services being offered, including vaccines, medications, and organ transplants (Lawrence, 2011). The increase in complexity and rising cost of healthcare services made it very difficult for individuals to cover the cost of their medical care. As a result, non-profit insurance organizations began to form to help cover healthcare costs. This trend continued in the decades that followed, creating a dynamic relationship between the increased cost of care services and the specialization of those services. In the decades that followed, the United States' economic growth facilitated rapid advances in medical science and discovery (Lawrence, 2011).

In the 1960s, health insurance became unaffordable for many Americans, which led to the creation of the federal and state coverage for those who qualified: Medicare and Medicaid. In the 1970s, as inflation rose, and new medical treatments and advanced surgical practices cost more, many people could not afford the premiums for basic health coverage through not for profit agencies (Lawrence, 2011).

With people living longer and receiving treatments that were continually increasing in cost, Medicare and Medicaid were no longer adequate to cover healthcare costs; this spurred product diversification in the insurance industry. There was an increase in privatization in order to manage costs (Lawrence, 2011).

By the 1980s the complexity of the system and the variety of treatment options had nearly doubled the price of treatments. This trend continued into the 1990s, when medicine became more specialized, precise, and complex with the introduction of biologics. In the current decade,

healthcare costs are creating a burden on public systems and governments and can be largely out of reach of individuals in the United States.

Pharmaceutical companies experienced tremendous growth over this time period as well, transforming from chemical and dye companies, apothecaries and chemists to drug production companies. This period saw the introduction of the world's first blockbuster drugs (a pharmaceutical that reaches over one billion dollars in sales) and a series of lifesaving vaccines. However, after a number of pharmaceutical product scandals, government regulations were implemented to provide greater oversight of the drug commercialization process and make a clear distinction between chemical companies and pharmaceutical companies.

> The Thalidomide scandal of 1961 prompted an increase in the regulation and testing of drugs before licensing, with a new amendment to US Food and Drug Administration (FDA) rules demanding proof of efficacy and accurate disclosure of side-effects for new medications (the Kefauver Harris Amendment) being implemented in 1962. Likewise, the 1964 Declaration of Helsinki put greater ethical strictures on clinical research, clearly cementing the difference between production of scientific prescription medicines and other chemicals. (Walsh, 2010)

These regulations formed the foundation of the system on which pharmaceutical companies operate today. They illustrate a continuous tension in the healthcare system between innovation and risk aversion to protect the health and safety of patients.

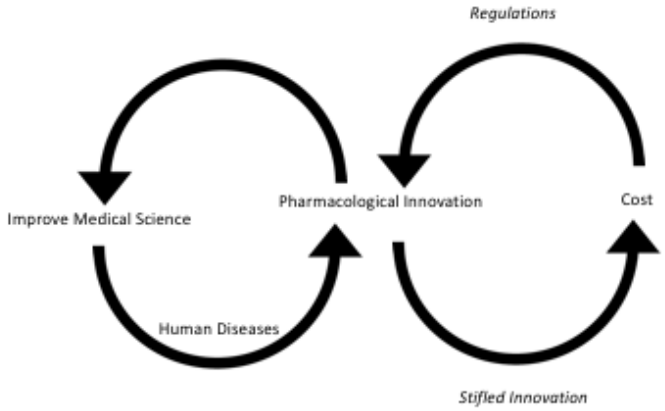

Figure 6 -- Eroding Goals (adapted from William Braun "System Archetypes) (Braun 2002) – Lindsay Roxon

> Fordian methods enabled more rational methods of mass production, and increasing understanding of biology and chemistry enabled drug candidates to be chosen systematically rather than discovered serendipitously. This 'golden age' of drug development took place in the broader landscape of the post-war boom, a general context of massive improvements in standards of living and technological optimism that characterized the 40s to the early 70s, as well as the science-boosting competition of the cold war. As the barriers to entry in drug production were raised, a great deal of consolidation occurred in the industry. Likewise, the processes of internationalization begun before the war were continued – in 1951 alone Pfizer opened subsidiaries in nine new countries. (Walsh, 2010)

With new regulations in place, innovation became increasingly difficult as a result of the cost associated with commercializing drugs.

> But whilst there were some breakthroughs, the enormous expense and risks involved in R&D caused many to merely ape their competitors, trying to get a cut of market-share using "me too" formulations rather than innovating novel medications. For example, AstraZeneca's popular proton pump inhibitor Nexium (esomeprazole), released in 2001, is merely a purified single isomeric version of an older drug which happened to be losing patent protection. Patents, or the lack of them, became a problem for the industry. (Walsh, 2010)

The new regulations alongside the broader needs of society for generalized medicine, pushed pharmaceutical companies to pursue *blockbuster* drugs that would net their business over $1

billion in sales (Walsh, 2010). Many of these drugs were competitors, or copies of existing drugs that offered marginal benefits, but were already proven to have broad marketability (Walsh, 2010). This acted as an inhibitor to pharmaceutical innovation; while there were significant strides made in the latter part of the 20th century in certain disease areas (especially cancer), the approach of marketing mass medicines continued (Walsh, 2010).

The introduction of biologics, or complex molecule drugs that are derived from an organic source such as human, animal or microorganism in the 1970s led to breakthroughs in the treatment of more complex diseases like cancer and autoimmune disorders. However, the costs of these complex molecule drugs are creating major challenges for payers, especially as the incidence of chronic or lifestyle diseases (such as autoimmune disorders) continue to rise. This remains a major profit center for pharma, as these medications are more difficult and costly to replicate by generics companies while many other generic versions of previous single molecule drugs have been readily distributed in place of originator products.

> For a long time, there was little economic impetus for industry to market drugs solely to responders when its existing pharmacoeconomic models incentivized companies to sell as much drug to as many patients as possible, regardless of whether those receiving medication were responders or non-responders. By definition, commercial drug development is driven by the profit incentive as much as by whether patients fail to respond to a therapy. (Schellekens et al., 2017)

The result of this is a system in which meaningful innovation is stifled; it encourages pharma to maintain a commercial strategy of pursuing the low hanging fruit of high profit, broad application therapies in order to maintain profits and deliver value to shareholders (Schellekens et al., 2017). While many pharmaceutical companies are continuing to invest in R&D, the likelihood of discovering a blockbuster has decreased, so pharma is being forced to leverage

other strategies to continue to encourage growth – including increasing prices and extending patents. It also discourages the development of very niche or personalized treatments that would not have the desired return on investment.

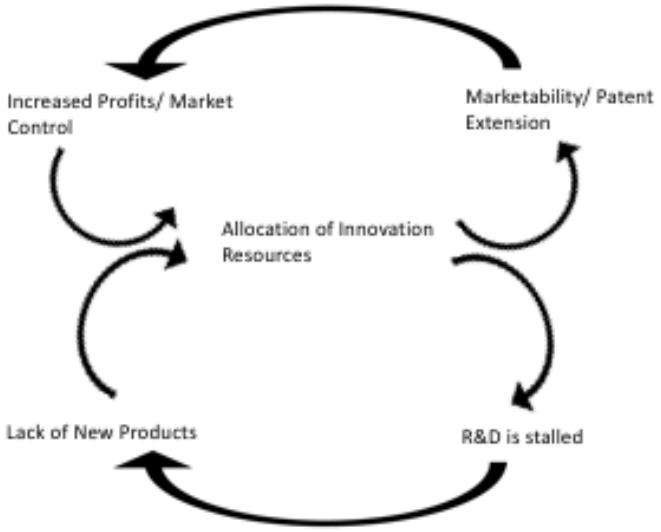

Figure 7 - Success to the Successful- Lindsay Roxon

As they have continued to adapt to manage the risk in product innovation, the cost of innovation has increased.

As this report will go on to discuss, the changes required to allow pharma to overcome innovation barriers and pursue the development of personalized products is difficult and costly, requiring a large departure from existing practices and a retooling of the entrenched systems. These barriers, if not addressed, may leave pharma vulnerable to disruption by emerging players

that are approaching disease management using data-based tools, devices and preventative methods that have the potential to be less risky.

Barriers for Pharma in Innovating in Digital Therapeutics

While aware of the opportunities in innovating in digital therapeutics, Pharmaceutical companies have been slow to invest because their R&D process is lengthy and costly. In addition, pharmaceutical companies are not currently equipped to take on a new process to innovate and research.

> "On average, it takes at least ten years for a pharmaceutical product to complete its journey from discovery to the market, and the average cost to shepherd it through this process is $2.6 billion.[5]Digital-solution innovators move more quickly. Their devices require the latest technologies coupled with a user-centric, iterative design process, which means their R&D teams must adopt an agile approach, welcoming and incorporating fresh feedback on ever-evolving user preferences. Approaching R&D in this way is a skill that many pharmaceutical companies would have to build in order to compete in delivering digital therapies." (Joyce, 2018)

In addition to this, the profit incentive is not as attractive. Digital therapeutics are currently not protected by the same patent protection that pharmaceutical products have. Meaning that any innovation could potentially be copied by a competitor. While technology companies are built to continually iterate and sustain in spite of the nature of the competitive, unprotected environment, pharma in incentivized and structured to invest in protected, relatively secure, market-proven and protected assets. (Joyce, 2018)

> "Another disincentive is the pharmaceutical model itself. In most countries, patents give drug manufacturers 20 years or more of protection from generic competition. Regulators do not afford the same protection to devices. Competitors can avoid infringing design patents and enter the market quickly by making incremental changes to the technology they use. Add to these factors the massive differences in manufacturing and distribution, and producing digital therapeutics starts to look very different from producing pharmaceuticals." (Joyce, 2018)

However, many pharmaceutical companies, recognizing the value and the likely future that will be disrupted by emerging players are beginning to consider partnerships with technology companies that are built to thrive and compete in the technology sector. (Joyce, 2018)

> For this reason, many, if not most, true digital-therapeutics companies have attracted at least one investor or partner from the sector. Roche, for example, recently purchased mySugr, which seeks to treat diabetes. In the long term, more pharmaceutical companies may well have their own digital-therapeutics lines. But in the short term, partnerships may be the most likely way forward, especially for digital devices that act as extension therapies by using data and patient engagement to offer insights into the effectiveness of those therapies. (Joyce, 2018)

Pharma is seeking technology solutions that leverage and capitalize on their therapies like digital pills that encourage adherence and create value for patients and physicians by generating insights and tools that improve the effectiveness of their therapies. This however, is a small step into the potential that digital therapeutics and tools have to offer. (Joyce, 2018)

1.1.2 Payers Access and Commercialization

Government/Hospitals and insurance companies:

Payors including government/hospitals and private insurers are principally concerned with ensuring that medicines are safe and effective. The process by which medicines are

commercialized and approved for public consumption was introduced as a means to ensure public safety and appropriate oversight of the pharmaceutical industry. However, this model is proving to be outdated now that all the low-hanging fruit of molecule production have been developed, and research and development (R&D) move toward more personalized medicines. This section will explore different facets of the process of drug commercialization which drives costs and inhibits innovation.

The Clinical Trials Process

> Randomized controlled trials (RCTs) are considered the sine qua non of applied biomedical research. The objective evaluation of the benefits and problems associated with novel clinical interventions by directly comparing them with standard or sham (placebo) interventions allows claims to be made about the ultimate effectiveness and utility of those interventions. (Lillie et al., 2011, pp. 161-173)

The purpose of clinical trials is to collect necessary data to validate the safety of a medication, its impact on quality years of healthy life and ultimately to justify public and private investment in drug reimbursement. This is determined by an algorithm that factors in quality of life, length of life, public healthcare expenditure, and cost of investment. The clinical trial is vital to the commercialization of any drug, as this data is used by the FDA to generate approvals for drugs to reach the mass market.

The cost of running a clinical trial is in the billions of dollars: "on an average, the research and development journey of these new drugs that make it to market takes around 12 years and cost more than € 1.5 billion" (Fusi, 2017). However, the data generated at clinical trials is not always reliable.

> Conventional phase III trials involve thousands of people. The intervention being tested is often given at random to one group while another group receives a sham treatment,

> such as a sugar pill or the standard treatment that physicians would give such patients. Because scant data are collected on factors such as genetics, lifestyles and diets, the results of these trials often indicate the need for yet another study to validate the effectiveness of the intervention among the apparent responders and to establish the underlying mechanisms. (Schork, 2015)

In addition, trial design has been historically very limiting as trial sample groups are somewhat arbitrary; they may focus on a particular demographic and fail to achieve sufficient breadth in the study. That may misrepresent the data, thereby making it irrelevant for large portions of the population.

> Essentially, our understanding of biology suggested that treatments worked through common mechanisms that were set apart from random variation. This assumption was substantially correct for approaches such as cytotoxic chemotherapy that target generic disease mechanisms, and it enabled considerable progress to be made in treating cancer. Towards the end of the twentieth century, concerns arose regarding the potential inhomogeneity of therapeutic effects because of socio-political characteristics such as race or sex. Many clinical trials were designed and analysed to examine such differences. Although motivated by politics and social justice rather than scientific fact, only minimal changes were actually made to the design of such trials — which was probably appropriate given the weak biological basis for differences that can be attributed to these superficial characteristics. (Biankin, Piantadosi & Hollingsworth, 2015)

In some ways, providers are always searching for supplementary data to help with clinical decision-making and treatment planning. They essentially run their own trials with patients they treat, understanding that medications may not be safe or effective for every individual; physicians have few indicators to use in order to determine treatment efficacy beyond trial data.

While scientific capability is widespread across academic research centers, start-up biotechnology companies, other private and public sector entities and independent researchers, the regulatory structures and associated costs required to commercialize a product make it very challenging to innovate and develop outside of the conventional structures of the pharmaceutical industry. In addition, many discoveries never make it to market because they fail at different

parts of the clinical approval process. This doesn't always mean that they would not be effective for segments of the population, but may not reach them due to marketing environment, timing, and other factors. "Each year, there are only a couple of dozen new drugs licensed for use. But in their wake, there are hundreds of thousands of candidate drugs that fail to clear these hurdles" (Fusi, 2017).

In addition, while drugs are being developed they are also under patent protection, which further stifles innovation over the course of the 10-year drug development process by preventing other manufacturers from commercializing or developing the same compound. This is in addition to 20-year patent protection. "New drugs, like other new products, are frequently under patent protection during development. The patent protects the salmon calcitonin sponsor's investment in the drug's development by giving them the sole right to sell the drug while the patent is in effect" (FDA, 2013).

With the improved ability to collect and analyze patient data, there may be new, cheaper avenues for treatment validation and achieving clinical data. Clinical trials, as they are currently designed, are a principal contributor to the cost of drug development and discovery. They are also designed to generate data that will support public safety and efficacy on a broad scale rather than the identification of side effects and individual responsiveness. More precise and improved treatments provide an opportunity to make the healthcare system more efficient by increasing the efficacy of treatments and reducing readmission due to adverse events and side-effects. However, this value can only be realized if the systems of reimbursement, distribution, and commercialization are also retooled.

Generics

Payers are typically focused on trying to keep costs manageable and treatment accessible by encouraging and incentivizing the use of generic brands, which are significantly more affordable. Innovation challenges and incentives for pharma are further exacerbated by their struggles to maintain profitability amid looming patent expiration and the resulting increase in competition from generics.

> The evolving payer initiatives to reward generic use have also led to the erosion of branded drugs. Payers are becoming more effective in their efforts to influence the way prescriptions are issued and dispensed by pharmacists (Tuttle et al., 2004). In response to rising healthcare spending, governments in developed economies are supportive towards generic production to keep costs under control and to make public health system sustainable. (Song and Han, 2016)

However, this creates a tension in the system that encourages pharma to find legal loopholes to extend patents, further encouraging a strategic game of controlling market share through marketing and corporate strategy rather than focusing efforts on R&D and innovation.

> Patents are the primary tools that the research-driven companies use to establish and maintain their brands in the marketplace and provide a window of opportunity to enforce the exclusivity of the inventions. (Song and Han, 2016)

With these tensions constantly at play in the healthcare system, pharmaceutical companies are incentivized to protect their products and extend patent protection. While this is a profitable strategy, it demonstrates pharma's vulnerability to innovators entering the market. With the costly path to commercialization, protection rather than innovation remains the strategic imperative. With digital therapeutics gaining credibility, pharma could be vulnerable to

disruption, since pharma does not have strategic protection against alternative modalities including digital therapeutics.

Paying for Individualized Medicine

With a recognition that the "low hanging fruit" of molecule production has been captured, pharma is increasingly moving toward more individualized medicines or personalized medications that are customized based on genetic profiling. While this appears to be an opportunity, there are significant challenges in making individualized therapies (within the context of pharmaceutical products) viable and affordable. While there are ways to create more individualized medicines, the existing networks through which drug manufacturers can develop and commercialize drugs make it costly and ultimately inaccessible for the majority of patients and payers (Schellekens et al., 2017).

> In current reimbursement systems based on perceived value of a treatment, the limited markets for precision or personalized drugs will be similar to molecularly targeted orphan indications like lipoprotein lipase deficiency. This will drive up drug prices, rather than reduce them. (Schellekens et al., 2017)

As more diseases are fractionalized and eventually understood at a unique level, the economics around treatment and care may be forced to undergo a large shift. A useful proxy may be to look at the ways in which molecules for orphan drugs or rare diseases are developed.

> In the few papers discussing affordability and cost-effectiveness, several solutions are suggested with the common theme being better collaboration between the diagnostic and pharmaceutical companies, regulators, funding agencies, payers and patients. However, it is difficult to imagine how such aspirational solutions will lead to cost control, considering the underlying causes of spiraling drug prices. (Schellekens et al., 2017)

There are 7,000 different types of rare diseases; almost 10% of the American population lives with a rare disease. ("Rare Diseases Foundation - The Ryan Foundation", 2018) It is estimated that 350 million people worldwide are living with rare diseases. As our understanding of disease becomes more precise we will continue to see a branching of types and subtypes of diseases considered common, such as breast or lung cancer; however, the current drug approval process is much too slow to accommodate the treatment needs of patients. ("Rare Diseases Foundation - The Ryan Foundation", 2018)

> It is estimated that 95% of all rare diseases do not have any FDA approved treatments, and there are currently less than 400 treatments approved by the FDA for the nearly 7,000 rare diseases which have been identified. According to estimates from the NIH, it will take 10,000 years at the current rate of FDA drug approvals to find therapies for all people suffering from rare diseases. ("Rare Diseases Foundation - The Ryan Foundation", 2018)

Individualized medicines offer some hope for individuals who suffer from these diseases, but the economics are still quite challenging and may require a complete overhaul of the supply chain in order to make these approaches more sustainable.

> The current pharmaceutical system is far too complicated, expensive, time-consuming and inflexible to provide medications tailored to individual patients", according to Schellekens. "In the second half of the 20th century, medications were generally developed for large groups of patients. Now that the patents for these drugs have expired, pharmaceutical companies are focusing on drugs to treat rare diseases and for specific populations, such as patients suffering from cancer or chronic illnesses. The prices for these drugs are exceptionally high; treatments that cost more than € 100,000 are no longer the exception. (Schellekens et al., 2017)

While specialized molecules are privileged in the regulatory process in that they are fast tracked by the FDA, the research and development process and market sizes typically make the costs of

these drugs inhibitive. “Glybera is a treatment for a rare condition that causes pancreatitis. It costs $1.3 million for a single patient's full course of treatment” (Schellekens et al., 2017). Researchers and scientists are looking for other solutions to bring down the cost of personalized or precision medicine. The clinical trials and commercialization process is simply not designed for specialized or personalized medicine. The data collection process (through clinical trials) and the drug manufacturing and distribution process ultimately make specialized medication virtually unaffordable.

Paying for Digital Therapeutics

Payers looking at digital therapeutics are examining their potential to improve outcomes and efficiency of healthcare. However, there are challenges measuring and providing evidence for promised outcomes.

> **“**Private health insurers, for example, will want to know that covering a new therapy will offer clear improvement in quality outcomes. If it can lead to better management of conditions, help control adverse events of unmanaged chronic conditions, close gaps in care, and so on, then they will consider paying for it. The problem is proving measurable and material outcomes that are clearly tied to the new approach and can be captured by the insurer in an adequate time frame. Some of the chronic diseases targeted by digital-therapeutics companies fester for years before requiring costly treatment.” (Joyce, 2018)

In addition, because chronic diseases are long-term and are often diagnosed many years after onset of the first symptoms, payers are struggling with how to reimburse these preventative measures when the return may be captured by a competing organization. (Joyce, 2018)

> “The incentive for a payor to invest in any therapy to prevent diabetes, let alone a relatively new digital one, when the return is likely to be captured by another organization, could be low. Employer health plans or single-payor systems might be better targets for companies offering

> digital therapies. Employers have a larger net in which to capture savings, as their incentives include protecting against productivity loss, which is influenced by absenteeism and employee morale. Meanwhile, single-payor systems, such as government schemes that provide insurance for life, absorb the long-term risks with patients and have an incentive to pay for therapies that might mitigate them." (Joyce, 2018)

In addition, with much of the opportunity for digital therapeutics in the chronic health space, the amount of time required to collect sufficient clinical evidence may also prove costly.

There are significant hurdles and barriers to be considered to innovating for both pharma and digital therapeutic companies. With payors eager to reduce costs of care, they may be incentivized to find alternative approaches to clinical approval for digital therapeutics, which could create a significant threat to the pharmaceutical industry.

1.1.3 Care Delivery

Physicians and Patients

Physicians are seeking tools to provide their patients with better care and are grappling with new technologies, yet there are challenges with consistencies between providers. Providers are looking for multi-modal treatment options that extend beyond pharmacological products in some cases, but there might barriers to insurance coverage. However, providers are eager to leverage tools to share best practices and to generate real world evidence for their clinics. They're looking for more opportunities to leverage technology in a meaningful way to address issues as they arise. Patients and Physicians have the opportunity to gain significantly if there are additional, expanded treatment options. With the shift to more value-based models of care, physicians'

services might increasingly rely on outcomes delivered. In this case they will be looking for opportunities to create and monitor impact more closely.

Physicians act as an exposure point in the healthcare system. It is here that the tensions emerge and play out where it matters most — in the delivery of care.

> "[Physicians interviewed] also said that the direct relationship between a doctor and a patient, including close supervision, would make it easier to diagnose safety issues as they arise" (Schellekens et al., 2017).

For this reason, it is important to look at how healthcare providers interact with the broader system to understand the motivations and constraints that will impact their ability to consider pharmacological alternatives in the future.

Digital Tools Orientation to Providers

Digital Therapeutics offer physicians an opportunity to be closer to their patient, and potentially deliver truly personalized care. However, while the potential for digital therapeutics is recognized, physicians exist in a system which incentivizes the use of pharmaceutical products over multi-modal approaches to care. The reason for this may be that digital therapies require additional education, analysis and insight generation.

> "Believers in the power of digital therapeutics think that one day prescriptions for apps will be as widespread as they are for pills. But for apps to be widely adopted, they will have to be oriented as much to the provider as to the patient. Many digital therapies currently require changes to provider processes. For example, if an app tracks dosage and patient-reported symptoms, a provider is usually expected to do something with the data produced. The data requires analysis, and analysis requires time. Where capacity is constrained, physicians can regard additional data as more of a nuisance than an aid." (Joyce, 2018)

In addition to this, some digital therapeutics do not actually require a great deal of clinical intervention. These types of tools would essentially mean making themselves obsolete in certain cases.

> "Where general practice is private, or in public payor systems that contract to private providers, physicians might have less interest in shifting demand elsewhere or in recommending digital tools—such as Sleepio, a Big Health app that targets insomnia using cognitive behavioral therapy—that might disintermediate them. As Hames says, "Behavioral interventions can be very, very low clinical risk, and deliberately open up a new care pathway of delivery mechanisms that don't necessarily require a doctor or health professional, and that instead can rely upon self-referral." (Joyce, 2018)

This creates a tension for physicians who might be looking for alternatives to pharmaceutical products but at the same time would like to maintain relevancy and regular contact with their patients.

Lack of Alignment Between Providers

> DNA testing has become increasingly useful in the detection and treatment of various conditions, including cancer, intellectual developmental delays, birth defects, and diseases of unknown origin, and the cost of genetic analyses has dropped even as the speed with which their results are delivered has risen. Nevertheless, for most people, genetic medicine is not yet delivering customized care. ("The Problem With Precision Medicine", 2015)

Innovations in medicine and early steps forward in medical innovation have been made by genomics companies like Illumina and 23 & Me that are working on creating databases of genetic data. In the emerging provider ecosystem, there is a distribution of ownership that includes biotech, technology, pharma, and other non-traditional players, including digital healthcare providers. These new providers of healthcare are distributed across the system and forging new models of care - in the rush for innovation these companies occasionally do not consult physicians in development of technology. These technologies are sold to physicians and

care practices as an opportunity to drive better outcomes in care. (Graber, 2015) The challenge is that while technologies that collect this data have the ability to play a functional role in diagnostics, there is little standardization to ensure consistency from company to company. This can be confusing for healthcare providers, who do not have the time or resources to analyze these differences and make an educated assessment of their value. (Graber, 2015)

At the same time physician education is falling behind the capabilities offered by technology companies. This is best exemplified in new capabilities in gene testing. "As scientists continue to draw connections between DNA data and health outcomes, the problem of interpretability continues to grow. Many doctors are simply not qualified to make sense of genetic tests, or to communicate the results accurately to their patients." (Graber, 2015)

In the field of genetic testing, too few physicians are educated to understand and apply genetics technology. (Graber, 2015) Genomics companies are attempting to fill the education gap by providing physician education themselves, which is seen as inherently biased and sometimes creates contradictions between companies. In many cases, these companies may not be subject to the same oversight as pharmacological companies, so they may tend to push infallibility of their products without sufficient evidence of their effectiveness in creating better diagnostic outcomes.

> The director of financial operations at a 500-plus bed institution said he sees physician recruitment as a first, essential step in preparing to deliver precision medicine. "You've got to have doctors who can specialize in it before you can really even get the patients in. You can say, 'Hey, we want to focus in on [precision medicine].' That's great, but until you have the physicians, that's the key. So, for now, our focus is recruiting the right physicians and getting them the tools they need to be successful. (Graber, 2015)

Still, physicians recognize the value that increased data (in this case genomics data) could add to their practice and improve their ability to apply precision medicine, and they are eager to engage. "In this race to offer more value, they are jumping the gun, in my opinion…." (Graber, 2015)

Physician Action Bias

One challenge with increasing the data available to make clinical decisions, and one that will continue to be a challenge as digital tools proliferate. With the introduction of new technologies there has been an increase in physicians' ability to detect abnormalities, but this hasn't had a direct positive impact on health outcomes.

> Virtually every family in the country, the research indicates, has been subject to over-testing and overtreatment in one form or another. The costs appear to take thousands of dollars out of the paychecks of every household each year. Researchers have come to refer to financial as well as physical "toxicities" of inappropriate care—including reduced spending on food, clothing, education, and shelter. Millions of people are receiving drugs that aren't helping them, operations that aren't going to make them better, and scans and tests that do nothing beneficial for them, and often cause harm." (Gawande, 2015)

This trend may continue as more data is available, leading to more diagnoses of diseases and even more impetus to take action as a result of an increase in diagnostic testing. This is important to watch as any efficiency or value that is created by digital tool proliferation will rely on appropriate use (rather than overconsumption) of new tools. The system is set up in a way that incentivizes specialists to perform their craft. In addition to that, physicians are typically paid on a per-service basis rather than overall health outcomes.

> H. Gilbert Welch, a Dartmouth Medical School professor, is an expert on overdiagnosis, and in his excellent new book, *Less Medicine, More Health*, he explains the phenomenon

> this way: we've assumed, he says, that cancers are all like rabbits that you want to catch before they escape the barnyard pen. But some are more like birds—the most aggressive cancers have already taken flight before you can discover them, which is why some people still die from cancer, despite early detection. And lots are more like turtles. They aren't going anywhere. Removing them won't make any difference. (Gawande, 2015)

1.1.4 The Data Ecosystem

Tech, or tech enabled Health players

> The virtual monopoly that medical centers like Mount Sinai now exercise over patient data will be smashed, and researchers will finally have the masses of genetic data that the medical breakthroughs of the future require. "Can we do better for human well-being if information is more broadly accessible, where you're leveraging the mindshare of the entire planet to evolve the models of disease?" Schadt asks. "Absolutely." This is medicine as math, not guesswork, and every disease—even stage 4 cancer—might one day be druggable. (Mark Warren, Wired Magazine, October 2016)

A foundational requirement to create the capacity for digital therapeutics is the ability to track, store, and analyze data to generate personalized insights into patient health. We are currently living in a moment rich in information, with the ability to collect data from wearable, implantable, and ingestible devices, digital diaries and a plethora of data streams available from other sources. However, there are still significant hurdles to collecting and storing data in a way that is meaningful for providers and researchers to deliver on the promise of precision medicine.

Achieving Differentiation From the Wellbeing Market

Digital therapeutics companies are tasked with the challenge of establishing themselves as differentiated from the wellbeing market in the minds of consumers and providers.

> "Indeed, some apps have fallen foul of regulators because of unsubstantiated claims about clinical benefits, helping instill doubts about digital therapeutics in the minds of consumers and healthcare professionals alike. As Peter Hames, CEO of Big Health, a digital medicine company, says, "We are in what I would consider the 'quack medicine' era of digital medicine

> and digital therapeutics, where there's a huge morass of solutions with incredible variance in quality—and there isn't yet an established set of criteria." (Joyce, 2018)

However there is significant opportunity to disrupt and innovate, once differentiation is established and approved.

> "For instance, the US Food and Drug Administration (FDA) recently approved a mobile application to help treat alcohol, marijuana, and cocaine addiction, citing clinical trials that showed 40 percent of patients using the app abstained for a three-month period, compared with 17.6 percent of those who used standard therapy alone[1](see sidebar "What is the value of digital therapeutics?").(Joyce, 2018)

If this trend continues, it is likely to create disruption for pharma if they do not develop strategies to keep pace with the rate of technological innovation.

Data Infrastructure is Fractured – Protocol and Real-World Evidence

> With this digital infrastructure in place, Schadt envisions a future in which more and more patients share not only their genomes but also medical and lifestyle information collected by monitoring devices like glucometers, blood-pressure trackers, and inhalers. The hope is that, ultimately, these increasingly sophisticated, increasingly patient-friendly tests will be so comprehensive that a patient's microbiome can be regularly sequenced, their RNA frequently examined, and their blood cells constantly monitored for signs of trouble. (Warren, 2016)

The infrastructure required to facilitate digital therapeutics includes biobanks, secure data storage, a means for physicians to access the data in real time, and an affordable means to extract it from patients. Electronic medical records are an essential starting point, which, as they currently stand in the U.S. and Canada, pose significant challenges to integrating data via Application Program Interface (APIs) as a result of HIPAA compliance and the cost of investment in technical infrastructure.

In order to prepare providers to truly absorb the capabilities that health data may offer, healthcare organizations will need to implement Learning Health Systems (LHSs), and a means by which patients and can collect, own, and share their data. A LHS is a networked data infrastructure system that exists at and across sites that allow administrators, providers and patients to collect, store and analyze data.

Learning systems are nearly ubiquitous across industries. "The capability to share data – and harness its potential to generate knowledge rapidly and inform decisions – can have transformative effects on complex systems that produce goods and provide services." (Friedman et al., 2014) Healthcare systems in US and abroad have not yet transitioned through this transformation. "The LHS as a vision for an integrated health system "… in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and healthcare." (Friedman et al., 2014) The base value of an LHS is to figure out what works best and to provide that knowledge to all major stakeholders in the healthcare value chain—clinicians, public health professionals, patients, and other stakeholders—to create feedback loops. This will have the added impact of creating a level of standardization in infrastructure that is critical to create data that may have clinical use cases. "… second, there is a lack of standardization of the collection, storage and analysis of large amounts of genetic, serological, histological and population data to enable patient stratification in clinical practice." (Schellekens et al., 2017) Learning Health Systems enable physicians with "knowing what works, understanding why it works, learning for whom it works, and applying that knowledge to address patient needs…" (Friedman et al., 2014).

Further physicians, researchers and administrators face challenges with technological system integration to make the data actionable, insightful and easily integrated into existing EMR.

> Providers who outsource aspects of their precision medicine initiatives, such as using outside genomic sequencing or lab support, sometimes struggle more with data integration than providers who establish a supporting technology infrastructure in-house. That is because when physical samples are sent to an outside lab for processing, the report is often sent back to the provider as a PDF attachment. PDF attachments cannot be entered into EMRs as data points. Nor can they be integrated with clinical decision support tools. (Graber, 2015)

In order for the data to be truly valuable we must first have the technology in place to facilitate data sharing between patients and their providers and between providers to ensure continuity of care and accuracy of diagnosis.

Data Security & Ownership

> The problem is getting these exabytes of genetic data. Turns out you can't just walk up to people, millions of them, and say, "Your data, please." You must first persuade them that you'll only do good things with it and won't let it fall into the wrong hands. (We do like our privacy.) You must then convince the medical centers and genetic companies that collect this data that, rather than hoard it for their own profit. (Warren, 2016)

Of paramount concern to the facilitation of precision medicine is the need to ensure the security of patient data. This is of critical concern especially when considering highly sensitive health information such as genetic data. At the moment, patients are rightfully wary of sharing information with health providers, let alone researchers.

New entrants in the health space are beginning to contribute to the process of data creation. These new entrants include consumer technology data capturing companies like FitBit and Apple Health, specialized consumer products like 23 & Me, and larger genetic sequencing companies like Illumina.

Genetic research companies that are working on creating vast amounts of genetic data, like Illumina, produce research and sell their findings to customers such as pharmaceutical companies, hospitals, and researchers. They, along with other biotechnology companies also use their findings to create a variety of products and services that may be marketed and sold directly to health consumers. Some is used to create direct-to-consumer products, like Illumina's spin-off company, Grail, which is working on developing an at-home cancer testing kit.

This industry is developing more rapidly than the average consumer can keep pace with. While the sharing of this data is critical to advancing digital therapeutics, it is also imperative that industry regulators protect patients by giving them ownership of their personal data making consumers more active stakeholders in the ecosystem so as not to repeat the mistakes of the pharmaceutical industry.

With the existing barriers facing the pharmaceutical industry in addition and the evident increasing capability of digital therapeutics, it is clear that pharma must adjust their organizational strategies to remain resilient in the future.

1.2.0 Where is there evidence of the future?

1.2.1 Discovery

Pharma Innovation

> We are graduating from the century of the molecule to the century of the system. It's how the neurons connect and form networks that creates consciousness and behavior, and it's creates the care we want.
>
> — Atul Gawand

Stratified Medicine

In breast and lung cancer care there is a great deal of research that is helping scientists understand how genetic factors play into treatment compatibility. The science is still, however, incredibly imprecise; genetic markers may give practitioners a better idea of how to treat a patient but they still have a limited number of tools (drugs) to treat disease. However, without understanding the patient's unique genetic composition and how genetic receptors play into the efficacy of a treatment, physicians are not yet able to create treatments that are truly personalized. A more appropriate term for the way that medicine is being practised today may be stratified medicine, and this is still only true for certain conditions.

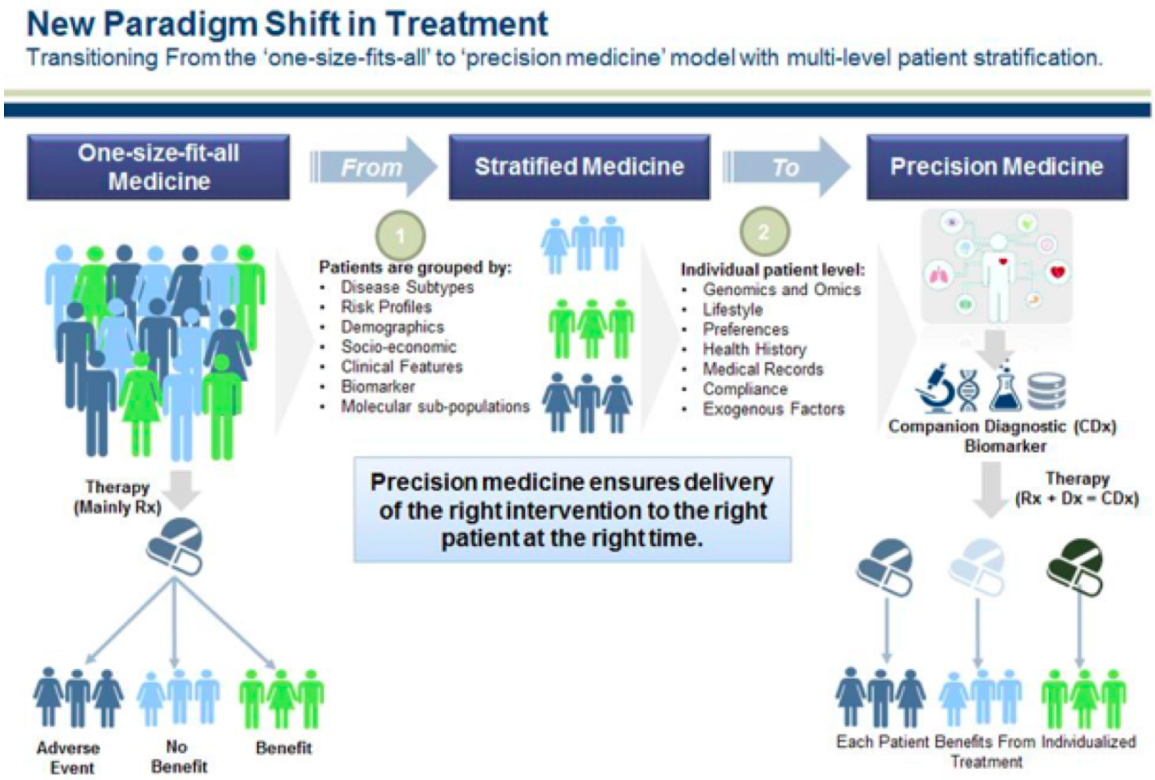

Figure 5 – New Paradigm Shift in Treatment (Das, 2017)

While stratified medicine is bringing providers closer to the ability to choose the most appropriate treatment plan for patients, it does not necessarily exist on the same continuum as truly personalized medicine. Stratified medicine relies on the logic of statistical significance based on isolated genetic factors, whereas precision medicine takes an integrated approach at diagnostics and treatment.

> "As a recent article in *Nature* noted, an estimated 90% of the conventional and top-selling blockbuster medicines only work for 30% to 50% of patients. What is even worse is the side effects and adverse reactions caused by these imprecise medications, accounting for 30% of acute hospital admissions every year." (Das, 2017)

Challenges in efficacy create additional costs in the healthcare system as many patients have to continually try new treatment options as a result of adverse events or lack of efficacy.

Researchers are continuing to look for ways to develop and commercialize new treatments that are more effective for patients. However, there are forces within the healthcare system that are hampering progress and may prevent innovations in precision medicine.

In order to remain resilient, pharmaceutical companies will have to continue to drive research into increasingly rare conditions and specialized molecules. Some researchers believe major policy changes will be necessary to ensure that pharmaceutical companies continue to innovate rather than simply swap assets and seek strategic loopholes to generate profits.

> If revenues can only be sustained by exploiting the legislative loopholes, companies willing to invest in the development of medicine will face a serious dilemma on a long-term scale. Without proper policy intervention, the rise in patent challenges will not only shorten the effective market life, but also contribute to the dearth of high-risk and high-necessity drugs. (Song and Han, 2016)

With the loss of revenues from molecules coming off patent and the majority of the low hanging fruit having already been developed, it is likely that pharma will be forced to consider strategic alternatives that may include some push toward precision medicine, and "niche busters."

> The "low hanging fruits" in drug development have been picked to a large extent (Williams 2011) and it is necessary to protect their revenue stream by measures other than unjustifiably abusing the intellectual property right at the expense of competition and public welfare (Glasgow 2001). Therefore, pharmaceutical companies are encouraged to focus on specialty drugs with low substitution potential by creating the so-called "niche busters" (Dolgin 2010; Kakkar and Dahiya 2014). (Song and Han, 2016)

Further, it is critical that innovations continue to occur beyond medication as more payers are switching to value based models that require pharma to substantiate real world outcomes over the long term to prove that real value and efficiency is being created by keeping patients healthy. For many diseases, this requires doctors to find a balance for the patients between lifestyle management and medication.

> In future, most medicines will likely be paid for on the basis of the results they deliver and pharmaceutical companies need to pursue the path of "profiting together" instead of "profiting alone" by moving into health management space and to go beyond medicine (pwc 2009). (Song and Han, 2016)

Pharma Leveraging Digital Technologies

In addition to attempting to innovate in the realm of precision and personalized medicines, Pharma is looking to digital technologies to increase the efficacy of their existing products. Sensors and digital pills can be supplementary to a pill by encouraging adherence and generating helpful patient insights.

> "This is extremely important because if you're looking you might have noticed silicon and software are the technologies that are transforming pretty much any industry that's out there. We have an opportunity now for the pharmaceutical industry to embrace those kinds of tools, to build them into their drug products and create a whole new window of opportunity for innovation that leverages the entire library of drugs that already have been discovered. And that is probably one of the most important opportunities in 100 years." (Joyce, 2018)

This is an area of opportunity for pharma to innovate and increase efficacy without radically disrupting their product base, however if these insights or technologies do not add significant value for patients and providers, they may not deliver on the value promised.

1.2.2 Payers, Access and Commercialization

Government/Hospitals and Insurance Companies

"Truth in science can be defined as the working hypothesis best suited to open the way to the next better one." Konrad Lorenz

> According to OECD predictions, exceeding budgets on health spending remains an issue for OECD countries. Maintaining today's healthcare systems and funding future medical advances will be difficult without major reforms. Public expenditure on health and long-term care in OECD countries is set to increase from around 6 percent of GDP today to almost 9 percent in 2030 and 14 percent by 2060. (The Medical Futurist, 2018)

The n-of-1 approach to medicine is the process by which a physician can determine the impact of treatment decisions on a single patient, share the results with other physicians, and then create a meta-synthesis of the data to determine efficacy and results of the process. (Lillie, 2011)

With more widespread access to digital tools like wearable, implantable, and ingestible devices that can passively record patient data, it may soon be easier to facilitate n-of-1 trials that produce reliable, easily shareable results. The FDA and other regulatory bodies are in support of the n-of-1 approach, but the challenges of designing and facilitating these trials remains a persistent barrier.

> American Health Regulators, the Food and Drug Administration and National Health Insurance have tried to encourage the use of "n-of-1" trials despite the fact that these have been disparaged as merely anecdotal, and despite pharmaceutical companies positing that they are excessively expensive to run. However, proponents believe that n-of-1 trials can create greater efficiencies in the healthcare system by obviating the long-term costs of administering inappropriate treatments and interventions. (Kravitz et al., 2014)

In Schork's paper "Personalized Medicine: Time For One-Person Trials" he states that "if enough data are collected over a sufficiently long time, and appropriate control interventions are

used, the trial participant can be confidently identified as a responder or non responder to a treatment. Aggregated results of many N-of-1 trials (all carried out in the same way) will offer information about how to better treat subsets of the population or even the population at large." (Schork, 2015)

Schork cites the following ways that the clinical trial process could begin to initiate n-of-1 trials:

1) Exploit the diversity of health-monitoring devices

2) Identify new health monitoring devices and identifying appropriate disease biomarkers, such as tumor DNA circulating in the bloodstream.

3) Engender a cultural shift in regulatory agencies, pharmaceutical companies and at the clinic level. (Schork, 2015)

Bedside Pharmacy

> In terms of healthcare economics as a whole, the main contributor to soaring costs is innovation in a market that is driven by what is offered, rather than by medical need. There is no reason to expect this dynamic to change, despite the advent of precision medicine. If economics are driven by fee-for- service rather than by medical need, there is no reason why existing models of precision medicine would alter cost-effectiveness." (Schellekens et al., 2017)

Given the constraints and challenges facing the pharmaceutical industry and healthcare providers in making precision medicine a reality, leading thinkers are looking to uncover ways to "retool the development and product of drugs so that they are as close as possible to the patient." (Schellekens et al., 2017) Advocates of this approach argue that if "a treatment occurs in the

same legal entity as the production of a drug, no restrictive, expensive and time-consuming marketing authorization would be necessary" (Schellekens et al., 2017). This would mean that providers would have to have legal recognition as both providers and manufacturers. Bedside Pharmacy, also known as magistral production, would create an opportunity for certain types of drugs that have smaller markets to be more available for reasonable cost, while being well suited as a platform to develop new drugs.

> "The expertise for producing drugs should no longer be the sole domain of industry; indeed, many people with expertise in drug R&D are being dismissed by larger drug companies increasingly focused on clinical development and marketing. Perhaps such individuals could now be coopted to support magistral drug development in academic medical centers." (Schellekens et al., 2017)

Incentivizing Preventative care

Payers are increasingly looking toward technology that incentivizes preventative approaches toward care. There are insurance companies like HealthIQ that offer cheaper premiums to individuals that make healthy lifestyle choices. In addition, there is a recognition that more data may offer more clear avenues for people to receive improved insurance rates based on their lifestyle.

> Technologies that allow collecting and storing data and connecting systems make it possible to move from reactive care towards preventive and personalized care, and it will be more and more so in the future. The spread of electronic medical records, the connectivity of data systems and big data analytics help collect, store and analyze more and more health data. Moreover, piles of data will be augmented with information stemming from health sensors, wearables, and trackers – which enable data collection about lifestyle choices. (The Medical Futurist, 2018)

There is a large incentive for insurance companies to continue to create offerings like this for their customers as it decreases their costs and acts as a value-add for healthy living individuals.

Bypassing Biological Trials

For pharmaceutical products that have large sets of data available, researchers will soon be able to simulate the drug's responsiveness through data analysis. If this is to be a viable alternative to clinical trials, this could radically disrupt the drug discovery process. Eventually this could mean matching individualized data with drug data to determine likely results and outcomes, reducing the cost of clinical trials and providing researchers with real time feedback on how to modify, augment and innovate for optimal outcomes. (Kurtzman, 2017).

Researchers are also experimenting with microchips that "recapitulate the microarchitecture and functions of living human organs" that will allow researchers to simulate a biological response to drugs. At the moment these are aimed at replacing the animal testing phase of a molecule, but eventually it could replace more advanced stages of the trials process. This again may lead to lower costs for clinical trials, which could reduce the cost for pharmaceutical innovation and make it more affordable for pharma to pursue "niche busters" and personalized medicines.

3D Printed Drugs

Facilitating truly personalized medicine may require a retooling of the drug manufacturing process. 3D printing technology innovations may eventually enable reproduction of single molecule drugs that are customized for patients.

> Additionally, a doctor or a pharmacist would be able to use each patient's individual information — such as age, race, and gender — to produce their optimal medication dose, rather than relying on a standard set of dosages. 3D printing may also allow pills to be printed in a complex construct of layers, using a combination of drugs to treat multiple ailments at once. The idea is to give patients one single pill that offers treatment for everything they need. (Borukhovich, 2018)

These 3D printed drugs may enable new mechanisms of action that are currently not possible with mass production techniques. The implications for this are wide and varied and would create a new supply chain that would extend manufacturing into new arenas such as pharmacies and hospitals, and eventually homes requiring education and resources to manage this new dimension of drug delivery.

> Drug release profiles explain how a drug is broken down when taken by the patient. Designing and printing drugs firsthand make it much easier to understand their release profiles. 3D printing makes it possible to print personalized drugs that facilitate targeted and controlled drug release by printing a binder onto a matrix powder bed in layers. (Borukhovich, 2018)

3D printing would eliminate the need for animal testing by allowing researchers to test drugs on imitation human tissue and increase the manufacturers ability to iterate on drug design quickly. While the new capabilities and implications that may be facilitated by 3D printing are still very much in the discovery phase, pharmaceutical companies like GSK are committed to exploring the technology's new potential. (Goulding, 2018)

1.2.3 The Data Ecosystem

Disruption from Non-traditional Players

It is currently challenging for players outside the pharma or biotech space to invest in and develop products, simply because of the cost of testing and validating products through the clinical trial process. With the emergence of digital tools such as wearables, it is becoming easier for non-traditional players to collect sufficient data to prove the efficacy and safety of their medical interventions.

In the race to develop more cures and accelerate research, the clinical trial process plays a crucial role. As more treatment types emerge and data devices become more easily accessible, there may be an opportunity to disrupt the way clinical trials are run, allowing other players to prove their drugs' efficacy and gain market traction as physicians prescribe those drugs.

As more data becomes available by clinically approved devices, genetics companies, health platforms and other sources, doctors may be able to prescribe non-molecule based treatments with proven health outcomes, including digital medicines and lifestyle changes, to achieve targeted results. Only once this barrier is broken will it be possible for truly personalized medicine to be practised.

Companies like Evidation Health are finding ways to generate clinical data for tools designed to prevent illness or create behaviour change to gain clinical approval.

At the same time, a Swedish nuclear physicist was able to generate enough data to gain clinical approval to have a birth control app approved as a contraceptive (Berglund, 2017). It is as effective as the birth control pill but uses only algorithms to modulate behaviour.

Due to regulatory hurdles, many companies are more likely to work towards providing digital tools that support wellness before trying to prove their clinical value. For this reason, there are many tools available, including 23 & Me, which focuses on providing its customers with data to help them identify conditions they may develop at some point in the future. As capability continues to grow, the applicability of these tools in clinical settings is likely to increase as well.

1.2.4 Care

Prevention Strategies in China

> **“**With nearly a fifth of the world’s population in China, there’s plenty of data out there, but little is collected or organized in a way that can be analyzed. This has made the Chinese government focus on accelerating the roll-out of the disease-based standard clinical data repository across a range of therapy areas.” (Ho, 2017)

The Chinese government is working to prove the viability and impact of prevention strategies. Their approach relies heavily on digital therapies and devices. (Ho, 2017) As a result of undersupply of healthcare workers, overcrowding of some of the country's most sophisticated hospitals, and poor access to healthcare, healthcare costs in China are becoming unmanageable. The Chinese government is launching an initiative to move the country away from a disease-centered approach to care and move towards one that they are calling “big health” which aims to “deliver a full suite of health services that cover the entire care continuum with an emphasis on health management and chronic disease management.” With 62% of the Chinese population surveyed believing that Healthcare Professionals (HCPs) should focus on prevention, there is broad public support to push this movement forward. The goal is to have three, well established, digital national databases that incorporate health information, health profiles, and medical records by 2020. The Chinese government is also looking to smart devices and wearables to continuously collect health and contextual data with the intention of reducing readmissions, and facilitating more rapid emergency response and more immediate care to “avoid deterioration or adverse events, such as stroke or falls.” (Ho, 2017)

The Emerging Patient Archetype – The Empowered Patient

In a future where devices to track and collect personal health data are readily available, a new kind of patient archetype is set to emerge. The patient of the future that is empowered with their own data and education may shift the orientation of the patient-physician relationship.

Evidence of this is seen in emerging cases of patients that are leading the treatment or diagnosis of their conditions. A particular instance of this occurred with Dr. David Fajgenbaum, a former medical school student who developed symptoms of a rare disease. Unable to rely on routine treatment plans or medications, he was treated by a team of specialists who sought to uncover the mysteries and potential treatments for his condition. (Thomas, 2017)

In Dr. Fajgenbaum's case, he related to other doctors as consultants, and took full ownership of his condition, and became the primary expert of his condition. (Thomas, 2017) A data-fueled patient-centric system may operate in the future, where digital therapeutics make up a portion of a patient's treatment plan may increase incidences of patients leading care. Creating more opportunity for self-management and self-learning may create less reliance on traditional pharmaceuticals and decrease the impact of pharmaceutical marketing efforts.

2.0.0 Third Horizon

The Third Horizon expresses imagined futures and emerging changes. It highlights the transformative shifts from the present, exploring a broad range of future possibilities that could emerge. This section surfaces questions underlying cultural assumptions.

2.1.0 What's the hopeful future?

> It does little good to forecast the future of semiconductors or energy, or the future of the family (even one's own family), if the forecast springs from the premise that everything else will remain unchanged. For nothing will remain unchanged. The future is fluid, not frozen. It is constructed by our shifting and changing daily decisions, and each event influences all others. Alvin Toffler, The Third Wave

---

> "If we combine all these emerging technologies, if we focus them and make sure that the connections are made, then the possibility of discovering new cures, the possibility of applying medicines more efficiently and effectively so that the success rates are higher, so that there's less waste in the system ... the possibilities are boundless." — former U.S. President Barack Obama

> "You have to create a system where you have the patients' permission to follow them throughout their lifetimes so that you can define the populations for whom a particular technology or treatment is beneficial." — William S. Dalton, Ph.D., M.D. CEO, M2Gen, Director, DeBartolo Family Personalized Medicine Institute at Moffitt Cancer Center

The future is created by our collective conceptions of how it might look; our goals and conceptions of how far we can push the future forward. In order to gain some understanding of future trajectory, this section presents viewpoints on the future as expressed by some of the world's influencers in technology, innovation, and medical science.

CEOs Discuss The Future of Health Care (Robert Reiss, Forbes Magazine, July 24, 2017)

Robert Reiss: What word codifies the potential future of healthcare?

Sandra Fenwick: Precision medicine. I think we are on the cusp of some of the greatest opportunities for transformation in diagnosis, treatment and disease prevention. Now we are able to literally go into the disease-causing gene, modify it and either change the course of that disease or cure it. This is game changing!

Paul Kusserow: Personalization. Personalized care planning when combined with behavioral economic principles drives engagement. When you look at it a lot of issues in health care, they are actually behaviorally driven, which means they are potentially preventable. I think it's 80 percent of all health care could be cured or avoided if people changed their behaviors and habits. Once people are responsible for and own their care management and compliance, they can positively impact their own health.

Brandon Carter: Customization. Data and digital platforms can match products and services to customer needs. For example, health care customer relationships can start to look like banking relationships where customers can swipe their card and health care companies will know if the customer has made a healthy choice. Just as banks incentivize their customers to use their cards for cashback or rewards on purchases, this technology could be used at supermarkets, restaurants, and health facilities to enable healthcare companies to create incentives for customers to live healthier.

We are at a point in time where we are beginning to see the edge of the next horizon in health care. This, for many, means curing, preventing and managing the majority of physiological diseases. We seem to be in the midst of a societal movement that extends beyond the traditional parameters of the medical field to leverage our current technology, ability to collect data and quantify the body towards the goal of generating breakthrough knowledge that will enable us reach this goal, but we're not there yet. What remains to be seen is how much of the value of these discoveries is realized and how we're likely to access these technologies in the future. However, the push towards this holy grail will continue to guide us towards this goal.

In a lecture at University of California, San Francisco, Mark Zuckerberg asked "Can we cure, prevent or manage all disease by the end of this century?" His question was apt, in that it articulated the aspirations of visionaries, and this sense that it is not out of the realm of possibility that we might do so (Letzter, 2016).

The goal of the future of medicine, specifically Precision Medicine, is to create the possibility for patients to receive "the right drug, at the right time, for the right patient." The vision is that more diseases will be prevented and managed through lifestyle and social indicators, and for more complex diseases that will require a pharmacological response, there will the capability to personalize and customize treatment options that would optimize outcomes and minimize side-effects.

2.1.1 Discovery

Providers With Time to Provide Care

Precise treatments that take into account the individual's context and lived history require not only a means to collect data but also a reliable means to analyze and interpret that data.

> With this digital infrastructure in place, Schadt envisions a future in which more and more patients share not only their genomes but also medical and lifestyle information collected by monitoring devices like glucometers, blood-pressure trackers, and inhalers. The hope is that, ultimately, these increasingly sophisticated, increasingly patient-friendly tests will be so comprehensive that a patient's microbiome can be regularly sequenced, their RNA frequently examined, and their blood cells constantly monitored for signs of trouble. Mark Warren, Wired Magazine, October 2016

This can be done by individuals, professional and family caregivers, or physicians in this analysis. For the time being, the best representatives we have to play this role are medically trained professionals, or providers who have some education. In order to allow them to capitalize on the findings, the system must change in such a way that gives providers more time to spend interpreting the results and translating these to better care for patients. The depths of these insights may allow physicians not only to improve health outcomes for today but also make way for the possibility that we can prevent diseases from developing in future generations as well.

2.1.2 Payers, Access and Commercialization

Equity

One of the major concerns with advancing precision medicine is the level of gross inequities it could cause. While the possibilities are inspiring on an individual level, there is concern that not

everyone will have access because of higher costs of individualized treatments before the production of such treatments reach an economy of scale that makes them more readily available.

> We have single gene tests, which are covered. But it's still very hard to realize that reimbursement," Moeckel said. The hospitals regularly have to negotiate patients' coverage on their behalf. Oftentimes, tests will be bundled into existing packages so there's no option for direct or additional reimbursement. Juliet Preston, MedCity News, May 2017

Leading thinkers like Moeckel are already trying to get ahead of this trend by facilitating necessary public support for public solutions — mandatory health insurance, government support programs, etc. — and innovation approaches to disseminating the benefits of new discoveries to marginalized populations.

> Precision medicine's aim is not to optimize the health of one individual. It seeks to systematically shift the entire medical practice and improve outcomes on a population-wide scale. One by one. Whether socioeconomic factors are a part of this new paradigm, or simply a barrier to its implementation, there's no getting around their existence. Which is why we need organizations like Dignity Health to realize the precision medicine dream — in its entirety. Juliet Preston, MedCity News, May 2017

This focus on creating equity around the world — especially in the United States — is a unified vision, and perhaps even an imperative. Former President Barack Obama expressed the importance of this after launching the Precision Medicine initiative in 2016: "Democracy can't function if you have 20% - 30% of the population living longer than anyone else." He went on to discuss why investment in supportive public infrastructure was critical to meet this goal.

2.1.3 Data Ecosystem

Privacy & Openness

One of the defining factors that will shape the future is how data is shared, owned and protected. One hope for the future is that new technologies like blockchain will provide long-term security to patients who are willing to volunteer their information for public use. While many people currently share private information openly with technology companies in exchange for access, neither company policies nor user expectations are clear. Many companies are building profit models built on an expectation that users will share private information in exchange for access; consumers should be empowered to control how their data is used.

While data-based healthcare offers many opportunities for patients to become more active participants in their healthcare — with giant monoliths like Illumina already dominating the genetic data market — we're at risk of repeating mistakes of systems-past that favour corporate monopolies that minimize the rights of patients. This is especially hazardous in the healthcare environment where access may be perceived to be critical to survival.

In order to facilitate precision medicine in a way that is accessible and equitable, it is critical that data is owned by individuals and that there is safe and secure means by which they can share that data anonymously. It requires that organizations remain collaborative in sharing data and that payers find ways to provide equal access.

2.1.4 Care

Creating Opportunities for Collaborative Problem Solving

"The only time that a physician and physicist get together is when a physicist gets sick."
Malcolm Gladwell

Priscilla Chan and Mark Zuckerberg have launched the Chan Zuckerberg foundation with the lofty goal of eradicating all disease within this century (Letzter, 2016).

The three objectives of the foundation's initiative are:

- To foster collaboration between teams of scientists and labs across multiple universities over long periods of time.
- To focus on developing tools that are geared toward eradicating diseases rather than simply treating them.
- To improve and expand scientific funding writ large.

There is a recognition of three major challenges in their objectives:

1. the need for improved approach to funding and commercialization;
2. the need for increased efficacy of drugs; and
3. the need for more collaborative decision making and problem solving within medicine.

As new, non-traditional providers disrupt the healthcare ecosystem, bringing with them the philosophy and ethos that dominates the technology sector of failing fast, empowering consumers and creating human centered experiences there may be changes to the way that healthcare problems are solved. It is the need for collaborative approaches to solving problems

that may start to dominate the practise of decision-making in healthcare. This is critical; we seem to be at a moment in time where there is great need and great potential. Yet, this will be dependent on the ability of major stakeholders in the health ecosystem to collaborate, share knowledge and create novel approaches to solving some of the greatest challenges facing healthcare today.

2.2.0 What's worth keeping from the present?

With the diversification of healthcare options – it is critical that there remain mediators built into the system and that patient rights are protected and evolved to include broader definitions of data.

2.2.1 Protecting Primary Care

> I noticed other patterns in Bordone's interactions with her patients. For one thing, they almost always left feeling better. They had been touched and scrutinized; a conversation took place. Even the naming of lesions—"nevus," "keratosis"—was an emollient: there was something deeply reassuring about the process. The woman who'd had the skin exam left looking fresh and unburdened, her anxiety exfoliated. ("A.I. vs M.D.", 2017)

It is critical that as the organization of healthcare teams begins to shift, providers continue to provide patients with a single point of contact. This has two benefits: on the one hand, it ensures high quality service to patients; and on the other, it keeps physicians in touch with real world evidence.

> The chain of discovery can begin in the clinic. If more and more clinical practice were relegated to increasingly opaque learning machines, if the daily, spontaneous intimacy between implicit and explicit forms of knowledge—knowing how, knowing that, knowing why—began to fade, is it possible that we'd get better at doing what we do but

> less able to reconceive what we ought to be doing, to think outside the algorithmic black box?. ("A.I. vs M.D.", 2017)

If physicians are removed from aspects of the health continuum, it would be more challenging for them to assess broader pattern recognition. Smaller symptoms of seemingly simple ailments could actually add up to more complex health challenges that physicians are experts in interpreting.

> A deep-learning system doesn't have any explanatory power," as Hinton put it flatly. A black box cannot investigate cause. Indeed, he said, "the more powerful the deep-learning system becomes, the more opaque it can become. As more features are extracted, the diagnosis becomes increasingly accurate. Why these features were extracted out of millions of other features, however, remains an unanswerable question. The algorithm can solve a case. It cannot build a case. ("A.I. vs M.D.", 2017)

2.2.2 Data Transparency & Ownership

There is a growing movement to shift the balance of data ownership to individuals over organizations. This exists at the tension of making data pools increasingly transparent and open to encourage research and insight development. However, there is always a risk of over-regulation of data, which could put insight development in peril.

> A balance must be struck between an individual's desire for privacy and their desire for good evidence to drive healthcare, which may sometimes be in conflict. Opportunities for research on EPR and public health medical datasets have already demonstrated impressive results in generating new evidence (2); however, new computer science approaches analyzing real-time Big Data streams generated by social media and increasingly popular tracking/wearable devices have re-charted the data ownership landscape. (Kostkova et al., 2016)

Increased security and advanced thinking around the regulation of data could have a significant impact on the way data is integrated and leveraged in healthcare for the purposes for precision medicine in its ideal form.

The potential of opening healthcare data and sharing big datasets is enormous – but the challenges and barriers to achieve this goal are enormous. As transparent access to Big Data is the key challenge for healthcare research on clinical and population research datasets, policymakers, and scientific and business communities should embrace the underlying challenges of a political and legal nature. (Kostkova et al., 2016)

3.0.0 Second Horizon:

The Second Horizon provides an opportunity to look at both the past and the future – in it, designers may consider possible solutions, recommendations, and areas for further research that would help bridge the gap. In this section, designers may begin to grapple with areas for innovation and the potential trade-offs that may have to be managed in order to solve problems highlighted in the first horizon.

3.1.0 How to Bridge the Gap

Moving to a healthcare system in which precision medicine is possible is a massive undertaking. Key aspects of the healthcare system must evolve in order to facilitate the possibility of delivering the right treatment, at the right time, for the right patient. Especially prevalent is the need to rethink the design and focus on a healthcare system that currently places a large focus on pharmaceutical products that are limited in their ability to act as effective 'cures' to diseases as a result of barriers in the pharmaceutical innovation process.

This report examined the ways in which precision medicine is being inhibited by existing and entrenched systems related to the regulation and practice of producing and distributing pharmaceuticals. Specifically, this study looked at pharmaceutical products which are a major contributor to the increasing cost of healthcare. This section will hypothesize potential solutions

and strategies to facilitate the next generation of medicine, which moves away from an industrialized approach to one that is individualized.

With rising healthcare costs, an aging population and mass inefficiencies, it has become evident that a change needs to occur. For most major stakeholders that are concerned with revolutionizing healthcare, there is a recognition that reducing inefficiencies and improving quality of life lie in the ability to create treatments that are more effective and personalized to an individual's health context and preventing illness before it starts. Both prevention and personalization require improved ability to understand health implications and improved health management on an individual level. Fortunately, we are at a moment in time that offers an abundance of new technologies and scientific advancement that could have a major impact on the way that treatments and the delivery of those treatments are improved. Facilitating these treatments will require a multipronged, long-term investment in a unified vision of precision medicine and the investment in the technologies, capabilities and processes to ensure that this is happening at every level in an equitable way.

To better compare the research findings, a 2x2 matrix was created to demonstrate the differences in how differing visions of the future may drive different trajectories across the continuum of possibilities. The purpose of the matrix is to highlight the extremes that might exist at either end - in reality, at any given point in time, multiple 'futures' coexist across different geographies, political environments and institutions.

There will likely be a cross-section of the possibilities highlighted in the matrix that exist at one point in time, however, where this becomes useful is identifying how dominating stakeholders might operate in order to ensure their continued survival, and where this may cannibalize resources away from other efforts at investment. For stakeholders outside of pharma, this may reveal opportunities for policy shifts, technology investment etc. In fact, this might reveal that the pharmaceutical industry may not be best poised to lead the movement towards precision medicine.

Specifically, this will look at two critical tensions which have emerged from the research, individualization versus collectivism and pharmacological versus diversity in treatments.

Critical Tensions

Individualization*:* The individualization of society and resultantly, of healthcare, has been guiding an increasingly accepted view that individuals are responsible for their own health. New technologies such as wearable devices, while helpful to track individual fitness, diet and other behavioral aspects of health, are an example of a shifting of responsibility from the collective to the individual.

> In short, "neoliberalism" is not simply a name for pro-market policies, or for the compromises with finance capitalism made by failing social democratic parties. It is a name for a premise that, quietly, has come to regulate all we practice and believe: that competition is the only legitimate organizing principle for human activity. (Metcalf, 2018)

Pharmaceutical companies operate at a juncture in healthcare that is inherently collective and yet also a beneficiary of individualistic approach to medicine. If individualism continues to guide the

development of our system it may eventually provide pharma with an opportunity to bypass government all together and sell directly to health consumers.

> Thirty years on, and it can fairly be said that Hayek's victory is unrivalled. We live in a paradise built by his Big Idea. The more closely the world can be made to resemble an ideal market governed only by perfect competition, the more law-like and "scientific" human behaviour, in the aggregate, becomes. Every day we ourselves – no one has to tell us to anymore! – strive to become more perfectly like scattered, discrete, anonymous buyers and sellers; and every day we treat the residual desire to be something more than a consumer as nostalgia, or elitism. (Metcalf, 2018)

Collectivism: A collective approach towards healthcare is one that values and structures systems that facilitate collaborative approaches towards public health, that highlights the interconnectivity and social nature of health. A collective approach requires a central governing body (like government) to coordinate and regulate strategies and health systems. Examples of this can be seen in China, where the state government is focusing efforts on more preventative measures by encouraging the use of digital tools to help manage lifestyle disease factors and care for chronic diseases.

Pharmacological Carel: The last 50 years have seen increasingly close ties between the medical industry and pharma. Moving into the future, the ways in which those ties are either endorsed or opposed by public policy will impact the way that innovations in precision medicine come to life.

> Over time, this casual alliance has been reinforced with such complex and often invisible bonds that, in Dr. Brody's title metaphor, medicine and pharma are now "hooked" like two pieces of Velcro, tethered by a million barbs and as dependent on each other as any addicts are on their substance of choice.

The ways in which this relationship progresses will determine the way that precision medicine is shaped and delivered in the decades to come.

> All this mutual back-scratching would be fine if patients' interests were indeed being served. But ample data indicates quite the reverse. Patients, after all, are the ones who pay for expensive drugs when cheaper would do as well, and the ones who swallow dangerous drugs nudged to market by their manufacturers.

***Diversity of Care**:* A more diverse approach to disease management would involve collaboration amongst payers, providers and patients to endorse and educate on the use of a diversity of tools to support health, including holistic, natural, device-based treatments for disease and disease management.

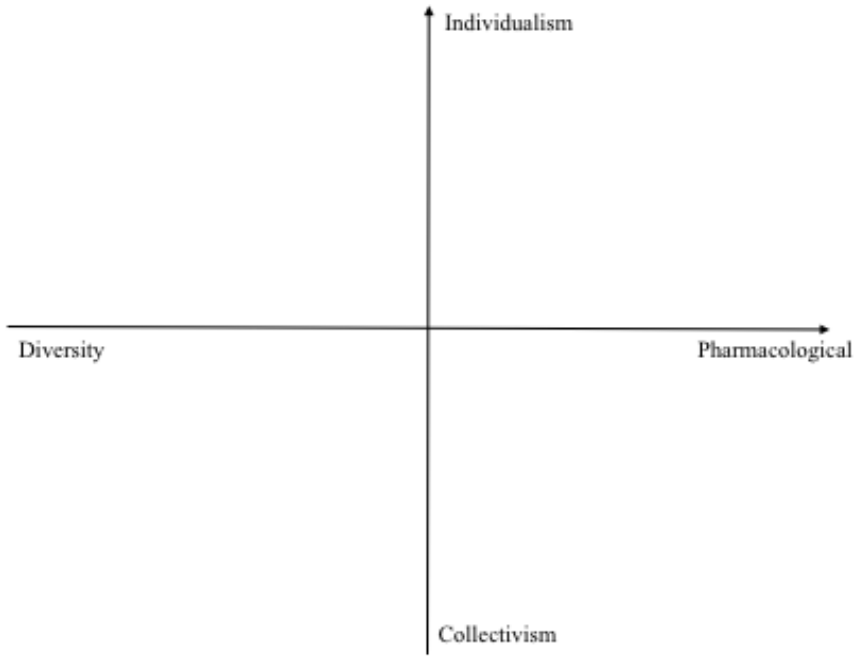

Figure 8 – 2x2 Matrix – Lindsay Roxon

Scenario Quadrant Characteristics

1 - Individualism/Pharmacological

- Neoliberal values dominate
- Dominated by self-management of disease
- Pay for performance models push risk on physicians and patients, which decreases ease of access and equity, decreases physician profits
- Regulations around access (to limit cost & find efficiency)
- Precision medicine lives mostly as increasingly stratified medicine + cost of drugs becomes more expensive
- Winner takes all + monopolies of data & treatments
- Innovation is driven by the need to find efficiencies in the existing system. A focus on developing cheaper routes to commercialize pharmaceuticals.
- Clinical Trials are increasingly simulated as data available increases and capability of machine learning increases
- Reliance on tech to solve efficiency woes, but not necessarily to create solutions or improve the quality of treatment
- Pharma extends its value chain into hospitals to increase capacity for genetic testing to secure market for gene therapies and other, expensive niche products.
- Patient empowerment rhetoric (neo-liberalization of healthcare) is very strong.

Richard spent the morning arranging his shoe collection. He had arranged them by colour and brand in his very large shoe closet. He has been living with cancer for 20 years, he thought often about how much different things would be if he had been diagnosed 10 years earlier. When he

was diagnosed he was immediately tested by physicians and prescribed a cocktail of medications that were customized for his genetic profile. It wasn't perfect though and they said that it would extend his life by 5 – 15 years -- quite the range, but it seemed to be working. It was expensive, but thankfully he had premium insurance through his employer, AI Services Inc.. He barely saw a doctor now - his vitals were tracked in real time and analyzed by a lab remotely – where, he wasn't sure – but he paid a lot for the service.

Since the improvement of drug simulation process and a shortening of the patent protection to 10 years from 20 years, there seemed to be new innovations all the time. There were products marketed to treat, prevent, augment, improve and generally optimize your biological condition. Frankly, no one knew if they even needed the drugs but they were hard to deny when they were marketed as completely customized to optimize with your own individual genome. He had heard that the science was still undecided about what the collective effect of this was, or how reliable biomarkers are as an indicator for certain diseases but, hey it seemed to be keeping him alive. He felt that if they were available it was his responsibility to take care of his health. He consulted a variety of services to verify, cross reference, assess his treatment options, his current health. Taking care of his health was paramount to everything else, it wasn't just him, this seemed to be the case for all of his friends. Sipping his morning coffee, the cup started vibrating to remind him to eat and take his prescription medication before starting his day.

Signals:

1. Human Organs on Chips
2. Genetic Testing at Hospitals

2 - Collectivism/ Pharmacological

- Pharma is incentivized by payers and regulation to focus R&D on preventative measures
- Over the counter, offloading of low complexity diseases to device and over the counter treatments.
- High policy regulation/databanks become ubiquitous and become combined funding initiatives between pharma and government to ensure that treatments are optimized.
- Many mergers between pharma & technology companies, a broader scope and role of Life Sciences companies.
- Value chain in hospitals is funded by pharma
- Mergers across industry -- retail and pharma etc.
- Quality of care improves overall but still missed opportunities for innovation
- International collaboration is incentivized to create more awareness of global health initiatives.
- Pharma continues to fund medical science in place of cash-strapped government.

The new democratic government has spent years forging collaborative partnerships with pharmaceutical companies. Sharon, a government relations representative, absolutely loves her job. She collaborates with government to set targets for R&D for her company. Since the new regulations were put in place that measure real time impact to public health through widely worn wearable devices and mobile phones, it is critical that AbbVie work closely with government to make sure that R&D is targeted and endorsed by government.

Sometimes, she gets frustrated by the pressure to compete with international markets on innovation simply for political reasons, but innovation is innovation, and at least she knows she's moving the needle somehow. China has been leading in preventative healthcare, so they've been getting a lot of pressure to develop products with the promise of preventing the development of disease – counteracting all the negative impact of lifestyle, low quality food and exposure to chemicals – the trouble is that China is staying ahead because they're able to encourage lifestyle changes, not just market drugs but she knows that they're doing more harm than good so day in and day out she pushes to create more collaboration, more innovation and work closer and closer with government. She's excited to see what the future holds!

Signals:

1. DePuy Synthes Acquires Tissue Regeneration System's 3D Printing Technologies to Treat Bone Defects
2. Pioneering Data-Sharing Network Created to Accelerate Cancer Precision Medicine Development

3 - Individualism/ Diversity

- Bedside pharmacy becomes popular and there is a reorganization of drug production value chain
- Reorganization and distribution of power of providers as more direct to consumer options become available.
- Non-traditional players play a disruptive role by driving efficiencies and innovation from outside the bounds of the conventional healthcare system.

- Digital solutions that offer alternatives to pharmaceutical products are clinically approved and endorsed.
- Deregulation to allow for new entrants, new providers in hopes to lower cost of care.
- Patients work in a mix and match system, trying to have needs covered, need for much oversight and consulting by intermediaries which is not available to everyone.
- Possibility that unregulated emerging therapies cause harm as well as good

Things have been challenging for Millie recently. She hadn't worked in 15 years and since her husband lost his job they've had to be very conscious about the time and money that they spend on healthcare. He with diabetes and she with chronic pain, health is constantly top of mind. Looking back over the last decade, things have changed so much. The technology companies had doubled down on health innovations and had put pressure on insurance companies to begin to offer reimbursement for digital and holistic devices.

Wearables and machine learning had made it possible, and affordable for these companies to collect clinical evidence to substantiate reimbursement and it changed everything. Except now the only problem was that no one knew what worked best – technology often operated outside of the physicians knowledge and every company claimed to have the best product. It was a fulltime job to weigh all the options and decide on the most affordable treatment plan – thankfully, she had the time. She was happy to have all the options, but still sometimes yearned for simpler days and less options when she could trust her doctor to make those decisions for her.

Signals:

1. Aetna & CVS Merger
2. Natural Cycles gains clinical approval in Europe

4 - Collectivism/Diversity

- Connected care, social pressure, next generation "Big Health" approach
- Digital tools become ubiquitous and highly encouraged by public health officials and providers
- Collaboration between different stakeholders is incentivized and encouraged
- State plays a larger role in healthcare delivery
- The biohacking movement gains legitimacy as tools to track, measure and share results of self-experimentation grow.
- Diminished Pharma role has potential to reduce costs to system as a whole, but rising tech players may have a balancing effect

Anna checked all of her monitoring devices to make sure they were all functioning and that her levels were sound, and then triple checked. She was going to be consulted by Amazon's health representative tomorrow and she wanted to be ready. The more that she was able to prove that she had been following the regime that they had given her (customized for her genetic profile) the bigger the discount she and her family would receive on their purchases over the next six months. As an employee and manager she had exclusive access to anonymously trade her data for health discounts – provided that she was following the regime. Every month Amazon ran an

employee contest for extra discounts – usually as part of company research initiatives. She always participated. Beyond the incentives she loved being part of process of developing a new treatment that would change lives! Amazon had already developed a cancer drug recently moved to the open market. Very exciting!

Growing up, she couldn't have imagined being so diligent with her health, but now it was second nature. The kids participated too, although they were more motivated by the graphics and characters that their devices used to engage kids in staying healthy. She felt lucky – Amazon's stats were out performing all other HMOs, mostly because everyone was always encouraging each other and checking out each other progress. It felt like being health responsible was helping everyone, not just her own family.

Signals:

1. "Big Health" in China

Summary of Findings:

Stakeholder Group	**Incentive/Priorities**	**Risk**	**Opportunity**
Discovery – Pharma and risk-adapted corporate players	As for-profit entities, pharma is incentivized to remain profitable and retain market control. In order to do this, they work to ensure exclusivity and access of their products, they attempt to secure and elongate profits from existing assets. Pharma is faced with the tension of balancing the cost of	Losing market share to digital therapeutics and other emerging players that have the ability to bypass the costly innovation barriers, iterate more quickly and capitalize on existing competencies in the digital space.	De-risk R&D by finding efficiencies in the clinical trials through the use of digital tools and technologies. These include computer simulated trials, testing. Improve the efficacy of current pharmaceutical products through the use of digital sensors to ensure adherence.

	innovation with potential for profitable outcomes, which acts as a barrier to innovation and reinforces the need to protect assets.		Invest in and partner with digital natives to further the efficacy and reach of digital therapeutics.
Access – Government and Insurance Companies	Government is interested in decreasing public expenditure on healthcare via improved health outcomes and affordable therapeutics. Private payers are similarly incentivized to improve health outcomes and efficiencies to increase profitability and lower payout costs. However, they face less risk as they're able to pass through costs to the broader system.	Underregulating emerging players at the expense of public safety and decreasing healthcare efficiency. Overregulating emerging players at the expense of stifling innovation. Maintaining status quo, an overreliance on pharmaceutical innovation at the expense of realizing efficiencies and impact of alternatives like digital therapeutics.	Working across industries to achieve optimal results. Funding innovators outside of the pharmaceutical space. Providing pathways for digital therapeutics and other alternatives.
Data Ecosystem – Technology Companies	Technology companies are interested in clearing regulatory hurdles for digital therapeutics and in the meantime demonstrating potential use-cases for digital therapeutics to gain credibility, iterate to improve product quality and begin to attract investors and generate profit.	Failing to prove clinical use-cases, loss of investment and public trust in digital therapeutics. Failing to provide pathways to affordable, scalable means access.	Alternatives to private health insurance, disruptive players in health insurance that endorse the use of digital therapeutics or other alternative therapies.
Care – Patients and Physicians	Patients and physicians are principally concerned with improving health outcomes and increasing the availability of affordable efficacious options.	Limited access to pharmacological alternatives. Lack of access to truly individualized medicines that are more effective, less costly	Provide patients with greater agency, education and access to digital therapeutics and alternatives that offer the opportunity to take a

		and with fewer side-effects. Physicians risk displacement by digital therapies that bypass the physician. Risk being replaced by professionals with alternative training/education capable of solving or addressing patient's health challenges.	more empowered role in individual care. Increase research and physician training on integrated, holistic, therapies that incorporate digital therapeutics as well as other alternatives. Decouple the notion of treatment with traditional pharmaceutical products.

Table 1 – Summary of Findings – Lindsay Roxon

Strategic Priorities

Discovery - Pharmaceutical Companies and Risk-Adapted Corporate Players

1. Work to move beyond strictly the manufacturing and producing of pharmaceutical products to marketing, strategy and revenues models based on healthcare outcomes.
2. Work with government, providers and researchers to generate more cross-functional problem solving and goal creation.
3. Continue to invest in new approaches to manufacturing and distribution of products to one that would support more personalized treatments – 3D printing, bedside pharmacy.

4. Pharma to design business models for the future that poise them as a facilitator of science versus an innovator.

Access- Government and Insurance Companies

1. Expedite approval pathways for non-pharmaceutical based products to gain appropriate data for reimbursement.
2. Develop a roadmap to supporting the digitization of hospitals, clinics and providers offices to create not only an integrated EMR, but also Learning Health Systems.
3. Establish collaborative relationships with providers, medical educators and health administrators to roadmap evolution of digital health and especially the changing nature of provider roles – assessing possibility, educational requirements, and system roadblocks.

Data Ecosystem – Technology Companies and Emerging Players

1. Develop partnerships and means to collaborate with providers to ensure clinical relevancy.
2. Coordinate or create a governance body to create standardization across the industry to increase credibility and reliability of digital therapeutics.

Care – Patients and Physicians

1. Conceptualize and test models for care that support chronic disease patients and test the capability of digital therapeutics to assist this process.
2. Funding for medical practitioners to codify and educate other physicians.

Conclusion

There are innovations emerging from every direction that have a potential application to improve medical treatment and push Precision Medicine forward. This requires corporations entering the healthcare space to regard their role critically. In a capitalist society that has long prioritized economic growth over individual or ecological wellbeing, it will be important to look at healthcare businesses through a lens that is distinct from both the public and private sectors. Executives and policymakers may need to look at the successes and limitations of pharmaceutical companies. Is it time to ask the question, is wellbeing a right or a privilege? And what is an acceptable baseline? Going into the future, this may become an increasingly important question as new treatment possibilities emerge.

Innovation beyond pharma is poised to massively disrupt healthcare in the coming decades. As consumers, care providers and technologists get smarter about creating effective approaches to treat health conditions that are customized to patients needs and the cost of clinically validating these approaches decreases, there is potential for physicians' and patients' tool box to broaden significantly. A resilient and socially conscious strategy for pharma may be to participate in the active disruption of their core product, leveraging existing resources to become a facilitator of science and innovation broadly. Perhaps, acting as manufacturers, facilitators and investors to

enable bottom up innovation (from citizen and HMO level) and act as stewards of collaboration in medical science.

Policy makers, Health Administrators, payers should focus efforts and resources on clearing the pathways for innovation and adoption for players outside of pharma in order to allow physicians a broader toolkit to treat patients. This includes creating pathways for reimbursement for holistic care approaches, digital tools for health and natural remedies to incentivize innovation outside of pharma. By expanding the use of digital tools and greater collaboration between clinical validation organizations that create pathways for clinical approval for nonpharmacological treatments.

In order to support this disruption it is critical that policy makers continue to build data infrastructure to support innovation at the clinic level. This means improving the EMR systems and equipping hospitals with Learning Health Systems that allow them to develop Real World Evidence to define and share best practises for individual disease states.

True innovation may lie in the very complicated and complex terrain of creating open data networks, allowing open access and providing independent funding for scientists that work outside the realm of pharmacological research. Ultimately, creating a system where more bottom up innovation and collaboration is supported, with power distributed across major players in the healthcare. In addition, it is important that collaboration continue to be encouraged across geographies and between specialties for knowledge sharing and interdisciplinary problem solving.

Next Steps

As a next step, it may be useful to more closely examine the use-cases for digital therapeutics including how they may work in a clinical setting. It would be worthwhile to more deeply understand the incentive structures around physicians and some of the risks and incentives involved in adopting a practise that is focus on a wider range of therapeutics. A potential outcome of this study might be understanding how the role of provider/physician should adapt for the next generation of medicine. As part of this study, it would be useful to understand which physician tasks are best and most likely to be displaced by technology in the coming years, and how physicians should be educated or upskilled to adapt and continue to push medicine forward rather than be incentivized to practise and promote the status quo.

Limitations of this study

This study was based exclusively on secondary research – it would have benefited from primary research and discussion with representatives of each stakeholder group to validate the ideas in the report. This study was intentionally broad, to provide an overview of some of the changes that may come to pass in the coming decades – this is also a limitation and there is a great amount of complexity within each of the major pillars that is discussed only at a high-level.

Works Cited

A.I. vs M.D. (2017). The New Yorker. Retrieved from https://www.newyorker.com/magazine/2017/04/03/ai-versus-md

Akinboro, Oladimeji, Linda Williams, and Daniel Pomerantz. "N-Of-1 (Single-Patient) Trials For Statin-Related Myalgia". Annals of Internal Medicine 161.7 (2014): 531. Web.

Aronson, Samuel J., and Heidi L. Rehm. "Building The Foundation For Genomics In Precision Medicine". Nature 526.7573 (2015): 336-342. Web. 25 June 2017.

Biankin, A., Piantadosi, S., & Hollingsworth, S. (2015). Patient-centric trials for therapeutic development in precision oncology. Nature, 526(7573), 361-370. http://dx.doi.org/10.1038/nature15819

Big health' and the future of medicine in China. (2017). World Economic Forum. Retrieved 26 December 2017, from https://www.weforum.org/agenda/2017/06/big-health-future-medicine-china/

Braun, W. (2002). Systems Archetypes.

Borukhovich E. (2018). How 3D printing will change the pharmaceutical world forever. The Next Web. Retrieved 9, February, 2018, from https://thenextweb.com/insider/2016/03/29/3d-printing-changes-pharmaceutical-world-forever/

Cdc.gov. (2018). *Chronic Disease Overview | Publications | Chronic Disease Prevention and Health Promotion | CDC*. [online] Available at: https://www.cdc.gov/chronicdisease/overview/index.htm [Accessed 6 May 2018].

Collins, Francis S., and Harold Varmus. "A New Initiative On Precision Medicine". New England Journal of Medicine 372.9 (2015): 793-795. Web. 25 June 2017.

Das, Reenita. "Drug Development Industry Bets Big on Precision Medicine: 5 Top Trends Shaping Future Care Delivery". Forbes 2017. Web. 13 June 2017.

Definition of Differential Diagnosis (2018) MedicineNet. Retrieved 22 February 2019, from http://www.medicinenet.com/script/main/art.asp?articlekey=2991

Dupre, Lola. "The Cure For Cancer Is Data—Mountains Of Data". WIRED. N.p., 2016. Web. 13 June 2017.

Fightchronicdisease.org. (2018). [online] Available at: https://www.fightchronicdisease.org/sites/default/files/docs/GrowingCrisisofChronicDiseaseintheUSfactsheet_81009.pdf [Accessed 6 May 2018].

Food and Drug Administration. Paving The Way For Personalized Medicine FDA'S Role In A New Era Of Medical Product Development. 2013. Print.

Friedman, C. et al. "Toward A Science Of Learning Systems: A Research Agenda For The High-Functioning Learning Health System". Journal of the American Medical Informatics Association (2014): n. pag. Web. 13 June 2017.

Gartman, Heather. "What "Precision Medicine" Means For Rare Diseases". Pharmexec.com. N.p., 2017. Web. 25 June 2017.

Graber, Cynthia. The Problem With Precision Medicine. (2015)..The New Yorker. Retrieved from https://www.newyorker.com/tech/elements/problem-precision-medicine

Goulding, C. (2018). The R&D Aspects of 3D Printing Pharmaceuticals. 3DPrint.com | The Voice of 3D Printing / Additive Manufacturing. Retrieved 11 February 2018, from http://3dprint.com/182400/rd-3d-printing-pharmaceuticals/

America's Epidemic of Unnecessary Care. (2015). The New Yorker, [online] (May 11, 2015 issue). Available at: http://www.newyorker.com/magazine/2015/05/11/overkill-atul-gawande [Accessed 25 Jun. 2017].

Hodson, Richard. "Precision Medicine". Nature 537.7619 (2016): S49-S49. Web. 25 June 2017.

Hodgson, A., & Midgley, G. (2015). Bringing Foresight Into Systems Thinking - A Three Horizons Approach.

Hood, L., & Rowen, L. (2013). The human genome project: big science transforms biology and medicine. Genome Medicine, 5(9), 79. http://dx.doi.org/10.1186/gm483

How Drugs are Developed and Approved. (2017). Fda.gov. Retrieved 23 December 2017, from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/

Juengst, E., Flatt, M. and Settersten, R. (2012). Personalized Genomic Medicine and the Rhetoric of Empowerment. Hastings Center Report, 42(5), pp.34-40.

Khan Academy, Lawrence, H. (2011). Healthcare system overview | Health care system | Health & Medicine. Presentation, Stanford Medical School.

Kostkova, P., Brewer, H., de Lusignan, S., Fottrell, E., Goldacre, B., & Hart, G. et al. (2016). Who Owns the Data? Open Data for Healthcare. Frontiers In Public Health, 4. http://dx.doi.org/10.3389/fpubh.2016.00007

Kurtzman, L. (2017). Big-Data Analysis Points Toward New Drug Discovery Method. UC San Francisco. Retrieved 24 December 2017, from https://www.ucsf.edu/news/2017/07/407696/big-data-analysis-points-toward-new-drug-discovery-method

Kravitz RL, Duan N, eds, and the DEcIDE Methods Center N-of-1 Guidance Panel (Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S). Design and Implementation of N-of-1 Trials: A User's Guide. AHRQ Publication No. 13(14)-EHC122-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/N- 1-Trials.cfm.

Letzter, R. (2016). *Here's what's behind Mark Zuckerberg and Priscilla Chan's $3 billion plan to cure all disease*. [online] Business Insider. Available at: http://www.businessinsider.com/mark-zuckerberg-cure-all-disease-explained-2016-9 [Accessed 9 May 2018].

Lillie, Elizabeth O et al. "The N-Of-1 Clinical Trial: The Ultimate Strategy For Individualizing Medicine?". Personalized Medicine 8.2 (2011): 161-173. Web.

Metcalf, S. (2018). *Neoliberalism: the idea that swallowed the world*. *the Guardian*. Retrieved 22 January 2018, from https://www.theguardian.com/news/2017/aug/18/neoliberalism-the-idea-that-changed-the-world

Nordling, Linda. "How The Genomics Revolution Could Finally Help Africa". Nature544.7648 (2017): 20-22. Web.

Pharmaceutical company. (2017). ScienceDaily. Retrieved 13 December 2017, from https://www.sciencedaily.com/terms/pharmaceutical_company.htm

Preventive Medicine - American College of Preventive Medicine. (2017). Acpm.org. Retrieved 25 December 2017, from http://www.acpm.org/page/preventivemedicine

Providers identify top three precision medicine challenges. (2017). Healthcare IT News. Retrieved 23 December 2017, from http://www.healthcareitnews.com/news/providers-identify-top-three-precision-medicine-challenges

Rare Diseases Foundation - The Ryan Foundation. (2018). Ryanfoundation.org. Retrieved 9 January 2018, from http://ryanfoundation.org/home

"Rare Diseases | Precision Medicine At Columbia University". Precisionmedicine.columbia.edu. N.p., 2017. Web. 25 June 2017.

Schellekens, Huub et al. "Making Individualized Drugs A Reality". Nature Biotechnology (2017): n. pag. Web.

Schork, Nicholas J. "Personalized Medicine: Time For One-Person Trials". Nature 520.7549 (2015): 609-611. Web.

Sheingold, B., & Hahn, J. (2014). The history of healthcare quality: The first 100 years 1860–1960. International Journal Of Africa Nursing Sciences, 1, 18-22. http://dx.doi.org/10.1016/j.ijans.2014.05.002

Shultz, Dr. Wendy. "Three Horizons Bootcamp: A 'Blowing The Cobwebs Off Your Mind' Event". 2013. Presentation.

Song, Chie Hoon, and Jeung-Whan Han. "Patent Cliff And Strategic Switch: Exploring Strategic Design Possibilities In The Pharmaceutical Industry". SpringerPlus 5.1 (2016): n. pag. Web.

Spiga, Ottavia et al. "Aprecisekure: An Approach Of Precision Medicine In A Rare Disease". BMC Medical Informatics and Decision Making 17.1 (2017): n. pag. Web. 25 June 2017.

Staff, I. (2018). Blockbuster Drug. Investopedia. Retrieved 18 January 2018, from https://www.investopedia.com/terms/b/blockbuster-drug.asp

Strimbu, K., & Tavel, J. (2010). What are biomarkers?. Current Opinion In HIV And AIDS, 5(6), 463-466. http://dx.doi.org/10.1097/coh.0b013e32833ed177

Thomas, K. (2017). His Doctors Were Stumped. Then He Took Over. *The New York Times*, pp.https://www.nytimes.com/2017/02/04/business/his-doctors-were-stumped-then-he-took-over.html.

Timeline of a Pharmaceutical Drug Development-From an Idea to The Market - Scientifist. (2017). Scientifist. Retrieved 21 December 2017, from http://scientifist.com/timeline-pharmaceutical-drug-development-idea-market/

Tyrol, Kate;. "How We Understand Medicine". TechnoScience as if People Mattered. N.p., 2017. Web. 13 June 2017.

Walsh, R. (2010). A history of the pharmaceutical industry. Pharmaphorum. Retrieved 9 January 2018, from https://pharmaphorum.com/articles/a_history_of_the_pharmaceutical_industry/

"White House Precision Medicine Initiative". The White House. N.p., 2017. Web. 13 June 2017.

Visionforesightstrategy.wordpress.com. (2018). *Verge: a General Practice Framework for Futures Work*. [online] Available at: https://visionforesightstrategy.wordpress.com/2014/09/15/verge-a-general-practice-framework-for-futures-work/ [Accessed 6 May 2018].

Appendix A

Literature Review

This review will present the academic literature that was referenced in the process of writing this paper. Each source will be reviewed and will include commentary on how the knowledge contributed to the overall development of the paper.

This review is organized to represent the order in which I constructed my understanding of the topic through the existing literature. Each source will be covered in a summary that will address: what was learned, why the lessons are important, and how they apply to the project.

Ultimately, this literature review was conducted to inform my analysis, using the Three Horizons tool to shed light on structural barriers and enablers to making precision medicine a reality.

Understanding the origins of the current system

One of my first major questions in setting out on this journey was how our healthcare system had evolved to favour our current, interventional approach with medicine rather than a preventative or holistic approach to healing. My very broad and earnest questions were: how did our healthcare system evolve to become what it is? Why do we have the incentives in place that we do? How are these structural foundations still relevant today? Where are we seeing the

breakdown of this system? What might need to change to usher in the next generation of medical science?

The idea of a *healthcare system* is a relatively new concept. In Brenda Helen Sheingold's paper, "The History of Healthcare Quality," she discusses the origin of the modern conception of healthcare as coming about as a result of a series of unrelated events, converging at different points in time to create the foundations of not only the American healthcare system, but systems around the world simultaneously. Through the discussion of "key tipping points" as a result of scientists, politicians and other changemakers, the modern healthcare system was conceived. A section of her paper focuses on the advent of pharmaceuticals in the late 1800s with the introduction of vaccines and penicillin — one of the first blockbuster drugs.

Her paper, which focuses on the concept of quality of care and tracking measurable outcomes to improve care outcomes, mentions changes in industry and their impact on the conceptualization of quality in care. She cites Henry Ford's Six Sigma approach and personal philosophy — "we are charged with discovering the best way of doing everything" — as a key influence on the approach and values that guided the early development of the healthcare system. Similarly today, we can track the zeitgeist on individualization and personalization across industries, including healthcare.

Personalization as a movement is not solely restricted to healthcare. Perhaps as a backlash to mass production and globalization, where "same-same" had become the new normal, everything from technology to approaches to education and consumer brands have been exploring the value associated with personalization. It seems that society at large is riding the wave of the

personalization trend that is focused on reorienting our definition of quality to one that focuses on value brought to the individual and realized outcomes rather than a product or service existing for its own sake.

Conducting this research gave me insight into not only the origins of the system, but also some of the cultural beliefs that have led to some of the existing roles in the healthcare systems and some cultural beliefs that reinforce these roles. This was critical to providing the same structural framework for what might be important to include in the First Horizon's "Evidence of the Future," in that healthcare is as much a part of social and values trends as other consumer product industries.

Basics in Health Economics

In David Cohn's book *Sick: The Untold Story of America's Health Care Crisis and the People that Pay the Price*, he discusses the origins of the healthcare system in the United States. It was only in the 1920s that doctors and other caregivers learned enough about illness that they were able to make a significant difference in health outcomes for their patients. It was at this point that doctors began to charge more than patients could afford. It was this initial gap that created an opportunity for health insurers to develop, starting initially as nonprofit insurers based at a single hospital — Baylor Hospital in Dallas. Eventually this caught on, and nonprofit insurance became more widespread. Taking this as a signal for market opportunity, commercial insurance companies entered the arena. All the while, medical advancement was accelerating and with it, costs. Employers began to compete for talent by offering competitive health insurance packages,

and providers in turn were able to increase their rates. This trend continued to the point where health care costs are virtually unsustainable and even employers are beginning to cut reimbursements for care accessed.

These learnings were important to understand as they create the cultural and economic foundations that underpin the healthcare system. In the United States, the healthcare industry was founded with a sound belief that each individual should receive equal access to care; however the involvement of commercial insurance has created tensions in the system that have led to grave inequities. It is critical to understand that the double-edged sword of this dynamic has also meant a healthcare industry that, despite its inefficiencies, is able to scale as a result of the profit it generates in order to continue to accelerate and create more specialized cures, which in turn creates more burdensome costs that are unsustainable.

This is essential to understand as one of the key considerations in the implementation of any new treatment is its financial sustainability. We'll look into the challenges of scalability from a health economics point of view when looking at rare diseases and the FDA approach to personalized medicine. While personalized medicine has the potential to create efficiencies, it is critical that there is a financial model in place that can facilitate discovery for individuals. As we've seen in the past, without consideration of the emerging changes, the potential of personalized medicines may only be realized by individuals who can afford them, further exacerbating the inequalities already driven by the healthcare system.

Precision Medicine

In Richard Hodson's paper "Precision Medicine" he explains that the "underlying concept of precision medicine, in which healthcare is individually tailored on the basis of a person's genes, lifestyle and environment is not new: transfusion patients have been matched with donors according to blood type for more than a century. But advances in genetics, and the growing availability of health data, present an opportunity to make precise personalized patient care a clinical reality" (Hodson, 2017).

This is important, as it explains why precision medicine has become so entangled with genetics-based healthcare. The reason for this is not that precision medicine is only based on genetic profiling, but rather that it is one of the areas of personalized data for which there is significant research and an evidence-based approach to tailor care through biomarkers.

The paper explains that the since the first "human genome was sequenced in 2001," the cost for technology for genome sequencing is finally decreasing and availability of genome sequencing technology (particularly to diagnose rare disorders) is becoming more common.

The paper clearly states that "Precision Medicine is powered by patient data. The health records and genetic codes of patients and healthy volunteers are vital, and help people influence their own health care and the direction of research. Securing participants' trust is crucial to the success of large-scale programmes such as the US National Institutes of Health's precision medicine Initiative."

In Francis Collins and Harold Varmus' article "A New Initiative on Precision Medicine" the authors address former President Barack Obama's decision to launch the precision medicine

Initiative. “Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier”(President Obama, 2015).

This paper clearly outlines some of the near- and long-term agendas for precision medicine. In the near-term it will be focused on cancers and then expanding to the broader range of health and disease. They identify that precision medicine has recently been made possible because new science is now within our reach, including “advances in basic research, including molecular biology, genomics, and bioinformatics. Furthermore, the initiative taps into converging trends of increased connectivity through social media and mobile devices, and Americans’ growing desire to be active partners in medical research.”

Beyond the ways in which precision medicine may be applied to oncology, the paper discusses some of the changes that need to happen at the system level in order to facilitate precision medicine. “Achieving the goals of precision medicine will also require advancing the nation’s regulatory frameworks. To unleash the power of people to participate in research in innovative ways, the NIH is working with the Department of Health and Human Services to bring the Common Rule, a decades-old rule originally designed to protect research participants, more in line with the participants’ desire to be active partners in modern science.”

The paper describes that in order to help speed discovery, the FDA is working with the scientific community to make sure its oversight of genomic technology supports innovation. It expresses its desire for this to eventually be collaborative with other health systems around the world.

The key finding here is that there is quite a bit of confusion around the term precision medicine, with many using the term to describe medicines that have been designed to target genetic profiles. In fact, precision medicine is much broader and includes (as stated by former President Barack Obama) the use of tools from fields such as bioinformatics and molecular biology. This distinction is important to understand because the way that we think about and introduce precision medicine will differ depending on how those leading its charge understand the term. That perspective will inform policy, clinical trial design, and ultimately other structural aspects of the healthcare system that have been designed around mass medicines.

Inefficiencies of Care and the Clinical Trial

"Millions of Americans get tests, drugs, and operations that won't make them better, may cause harm, and cost billions." — Atul Gawande (surgeon and public health researcher)

After reading Nicholas Schork's article "Imprecision Medicine." which opens with a powerful comment, the importance and expansiveness of the emerging capabilities to collect, synthesize data as a result of monitoring devices, machine learning and Artificial Intelligence (A.I.) became apparent. "Every day, millions of people are taking medications that will not help them. The top ten highest-grossing drugs in the United States help between 1 in 25 and 1 in 4 of the people who take them. For some drugs, such as statins — routinely used to lower cholesterol — as few as 1 in 50 may benefit. There are even drugs that are harmful to certain ethnic groups because of the bias towards white Western participants in classical clinical trials." (Schork, 2015) He argues that there is a need to rethink the way pharmaceutical products are developed and prescribed in order to address the inefficiencies that are created when prescribing the wrong drug. She believes that in order to push forward the precision medicine movement, the healthcare system

needs to facilitate a means for N-of-1, or trials that a trial where a single patient constitutes the entire trial, or individual trials) approach to testing, validating and commercializing medicines.

She states that while physicians have always done this in an ad hoc way, few clinicians or researchers have formalized the approach into well-designed trials, "usually a handful of measurements are taken, and only during treatment."

She states simply that "if enough data are collected over a sufficiently long time, and appropriate control interventions are used, the trial participant can be confidently identified as a responder or non responder to a treatment. Aggregated results of many N-of-1 trials (all carried out in the same way) will offer information about how to better treat subsets of the population or even the population at large" (Schork, 2015).

She goes on to identify a few possibilities to see this process come to life. This includes:

1) Exploiting the diversity of health-monitoring devices

2) Identifying new ones and identifying appropriate disease biomarkers, such as tumour DNA circulating in the bloodstream.

3) A cultural shift in regulatory agencies, pharmaceutical companies, and at the clinic level.

She goes on to discuss how researchers will often run post-trial analyses to try to identify why certain patients don't perform well in clinical trials. In these post-trial analyses, researchers will

try to match results with chromosomal or genetic profiles to try to determine a correlation between performance and the individual profiles of a certain patient.

> Conventional phase III trials involve thousands of people. The intervention being tested is often given at random to one group while another group receives a sham treatment, such as a sugar pill or the standard treatment that physicians would give such patients. Because scant data are collected on factors such as genetics, lifestyles and diets, the results of these trials often indicate the need for yet another study to validate the effectiveness of the intervention among the apparent responders and to establish the underlying mechanisms. (Schork, 2015)

Schork's article made it clear that, according to her, the key to integrating more holistic measures to determine the effectiveness of a drug lay in the ability to track and integrate data in a more thoughtful way — essentially a technology and design challenge.

He points out that there are challenges in N-of-1 trials beyond logistics. For example, in creating studies to measure a population-based response to something, it may be difficult to control variables, since an effective N-of-1 trial would require repeated and efficiently measured results. The added complication is that it is not always clear what to measure, in certain conditions where a biomarker hasn't been identified or a condition presents in an idiosyncratic way in different patients.

He cites rare diseases as a proxy for observing the effectiveness of N-of-1 trials. He also indicates that although N-of-1 trials are more costly in certain cases, they tend to actually reduce cost over time because treatments are more effective.

He also cites the need to create an understanding of individual or personal thresholds for uncovering diseases. "For instance, US physicians generally view levels of a blood protein called

CA125 greater than 30 or 35 as an indication of ovarian cancer. However, a level of 20 or 25 may be a cause for concern if the person's average CA125 levels hovered around 10 or 15 over the previous year." (Schork, 2015)

He discusses some of the barriers to making clinical trials a reality, including cultural changes at regulatory agencies, with physicians and researchers moving away from classical clinical trials. She suggests new profit models for pharmaceutical companies that let them move away from drugs that can be used by thousand or millions of people. He proposes reducing the cost of genetic sequencing and funding more research on effective biomarkers, monitoring devices, study designs, and analysis methods. Her report seems to indicate that while N-of-1 trials are not likely to solve all the challenges in the healthcare system, they are "a key component will be transforming everyday clinical care into solid N-of-1 trials."

His paper was important in that it outlines one of the key challenges and opportunities in precision medicine with respect to the way drugs are trialled and approved. He references rare diseases, the need for data tools and infrastructure, while also stating that N-of-1 trials could and should be made a part of regular clinical practice.

A follow up paper co-authored by Schork, Lillie, Patay, Diamant, Issell and Topol, "The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?" reinforces this perspective. This paper reviews the "history, motivation and design of n-of-1 trials and emphasizes the great utility of modern wireless medical monitoring devices in their execution." It ultimately argues that n-of-1 trials "demand serious attention among the health research and clinical care communities given the contemporary focus on individualized medicine."

He mentions that, at the moment only 10% of labels for FDA-approved drugs contain pharmacogenomic information and that the "FDA is actively involved in creating a streamlined review approach to diagnostic companion tests with therapeutics where n-of-1 trials could play a role in facilitating the approval process." However, she notes that these approaches, while a step forward, are not truly individualized but rather simply a stratification of patients into subgroups. She goes on to discuss different approaches to trial design and data analysis for trials.

The ability to leverage wireless medical devices make n-of-1 trials a practical possibility in a way that was not feasible in the past. They argue that in order to enable successful trials, the patient experience must be completely seamless to allow for the accurate measurement of relevant clinical end points. "Remote clinical phenotyping and wireless devices have enormous potential in this light." As discussed in Smriti Sakher's project *The Walled Gardens of Care,* many health monitoring devices have not yet proven to be reliable in clinical settings, and until they are, they cannot facilitate n-of-1 trials.

The authors cite the following barriers to be overcome in order to facilitate n-of-1 trials: a nationwide agenda in individualized medicine; appropriate training for physicians; early phase trials; leveraging medical records; treatment repositioning; and clinical equipoise.

Patient Empowerment: Rallying Cry or Passing the Buck?

Another perspective on personalized medicine is offered in the paper "Personalized Genomic Medicine and the Rhetoric of Empowerment,"(Juengst, Flatt and Settersten, 2012). The authors

argue that personalized medicine may offer an opportunity for medical breakthrough, but warn that the patient empowerment rhetoric may be overstating the benefits to patients. It goes on to insist that the benefits and challenges to patients in a system that is highly individualistic need to be carefully weighed. The paper cites three groups of stakeholders that are "heavily invested in empowerment rhetoric":

1) direct-to-consumer genomic scanning companies and the "early adopters of their services

2) the leaders of genomic medicine programs at premier biomedical research and health care institutions

3) genomic medicine's government sponsors and advocacy groups

The authors warn that while there are many positives that can come of this movement, "the shift should prompt concern within the personalized genomic medicine movement because it may increase pressure on patients to comply with physicians' recommendations." They go on to say that what is "even more worrisome is that individuals who are unable to become a "health-creating person" or who do not make the "right" health choices are easily "marked out as irresponsible and hence unfit to be self-governing citizens."

This paper offered a perspective into some of the challenges of personalized medicine. While this project won't be focusing on the patient point of view, it is still critical to represent some of the challenges that physicians may face in the near- and long-term future as the benefits of precision medicine come to bear. Similarly, it becomes an issue for which we need to design when retooling the healthcare system to make personalized medicine possible.

In the paper "Patent Cliff And Strategic Switch: Exploring Strategic Design Possibilities In The Pharmaceutical Industry" (Song and Han, 2016), the authors detail some of the major challenges that pharmaceutical companies currently face as it becomes more and more difficult to create blockbuster drugs. Other authors state that the "low hanging fruits" in drug development have been picked to a large extent (Williams, 2011) and it is necessary to protect the pharmaceutical company's revenue stream by measures other than unjustifiably abusing the intellectual property right at the expense of competition and public welfare (Glasgow, 2001). Therefore, pharmaceutical companies are encouraged to focus on specialty drugs with low substitution potential by creating "niche busters"or drugs that target rare and low incidences diseases. (Dolgin 2010; Kakkar and Dahiya, 2014). This is important as it may provide some indication on the willingness of pharmaceutical companies to begin to innovate in more niche markets that could eventually lead to more personalized drugs, if the environmental conditions (regulatory and reimbursement) are favourable.

In the paper "Design and Implementation of N-of-1 Trials: A User's Guide" (Kravitz et al., 2014), the authors provided a detailed guide to understand the history of n-of-1 trials, their utility, and the possibilities that they present to the healthcare system. According to the paper, "N-of-1 trials are a specific form of randomized or balanced designs characterized by periodic switching from active treatment to placebo or between active treatments ("withdrawal-reversal" designs). N-of-1 trials were introduced to clinicians by Hogben and Sim as early as 1953, but it took 30 years for the movement to find an effective evangelist in the person of Gordon Guyatt at McMaster University."

The paper goes on to say that the success of an n-of-1 trial is highly dependent on the commitment and collaboration of both the clinician and the patient. The authors point out that n-of-1 trials are "particularly suited to chronic conditions," meaning that in our current environment of rising healthcare costs and increased chronic disease, the savings to the healthcare system could be substantial. The paper goes on to detail how clinicians can run these trials. This was interesting as it is indicative of the high reliance on primary caregivers and other clinicians in running trials, which is a significant change from the current model that relies on a highly hierarchical approach to recruit and compensate study leads.

The paper outlines a number of opportunities and challenges. The authors indicate that n-of-1 trials are helpful in identifying "ineffective therapies, thus reducing polypharmacy, minimizing adverse effects, and conserving health care resources." The paper underscores that there is a possibility that patients may become more engaged in their own care, which is associated with better outcomes. The third opportunity presented by the paper is that n-of-1 trials can blur the boundaries between clinical practice and clinical research, making research more like practice and practise more like research, which would increase relevance and generalizability of results, and increase opportunities for creating clinical evidence.

The barriers identified by the paper include the need for Learning Healthcare Systems (LHS) or intelligent data infrastructure to collect and store data, the need for research ethics boards to approve the validity of an n-of-1 approach, and the need for some automation of clinical data to make analysis more accessible for patients and physicians.

In Chapter 3 of the paper, The Design and Implementation of n-of-1 trials, "The Financing of an n-of-1 Approach" (Kravitz et al., 2014), the authors discuss some of the challenges that may be faced when they are put into practise.

> Despite their many potential benefits, n-of-1 trials have not become part of mainstream clinical medicine, and to our knowledge have never been a covered benefit in any insurance plan (private or government run) in the United States or Canada. A 2010 systematic review found 108 unique trial protocols from the years 1986 to 2010; the vast majority had authors from Canada (35%), Europe (26%), or the United States (22%). N-of-1 trial services have been run almost exclusively by academic centers with little reach into community practice in the United States; somewhat broader reach has been achieved in Australia. (Kravitz et al., 2014)

The article concludes by indicating that the reimbursement or financing for n-of-1 trials will be largely dependent on the ability of technology companies to facilitate an accurate and reliable way to collect, store, and analyze data. Once these systems are in place it will be more cost-effective to run and easier to scale.

Beyond recognizing some of the technical barriers, the paper recommends more engagement with physicians to run n-of-1 trials in identifying patients and analyzing results.

Understanding the Data Environment

From readings in understanding how we might make trialing of drugs possible at the clinician level, it became obvious that a lack of digital infrastructure and reliable monitoring devices makes such trialing difficult.. In order to further understand the gaps and the possibilities, research was conducted to get a sense of the optimal data infrastructure ecosystem.

In "Toward A Science Of Learning Systems: A Research Agenda For The High-Functioning Learning Health System" (Friedman et al., 2014) the authors detail the anatomy of a Learning Health System, which would provide the "capability to share data, and harness its potential to generate knowledge rapidly and inform decisions, can have transformative effects that improve health. The infrastructure to achieve this goal at scale — marrying technology, process and policy — is commonly referred to as the Learning Health System." (Friedman et al., 2014)

The paper goes on to mention that LHS would provide health care workers — from administrators to physicians — an opportunity to study the system itself and improve. "There is a growing recognition of the US healthcare system's inability to routinely study its own behaviour; an LHS would provide such capability, and would significantly address many of the current challenges faced by the system." The paper goes on to explain that developing effective LHS will require complex processes of stakeholder engagement. "From these developments, it is evident that achievement of a national-scale LHS will not be the work of a single organization, stakeholder group, or governmental entity. Rather, it is anticipated that the LHS will require active participation of and cooperation among multiple and diverse stakeholders, nationwide and ultimately globally."

Regulation of Personalized Approaches to Medicine

In a paper written by the U.S. Food and Drug Administration, the authors outline the ways in which the FDA will facilitate personalized medicine.

"For well over a decade, personalized medicine has changed the FDA while the FDA, in turn, has changed personalized medicine"(citation, date)

The FDA has a long history with personalized medicine beginning in the 1980s with the characterization of molecular characteristics of disease that led to personalized therapeutics.

> Shortly following the announcement of the completion of the human genome project, each of the FDA's medical product centers — the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation And Research, the Center for Devices and Radiological Health - as well as the national Center for Toxicological Research, took steps to begin to put into place regulatory process policies and infrastructure to meet challenges. (Food and Drug Administration, 2013)

The FDA's approach is mostly comprised of developing committees and expertise around Personalized Medicine within the organization. The FDA has been actively working on streamlining processes for devices to be approved since the practise of precision medicine will often require devices working together.

They are also working to speed the development of new therapeutics by "developing regulatory science standards, reference libraries, research methods and tools that are needed for integrating genetic and other biomarker information into drug and device development and clinical decision making. These include: Biomarker Qualification Program, MicroArray and Sequencing Quality

Control Project, Genomic Reference Library for Evaluating Whole Genome Sequencing Platforms (to streamline approach and determine value on an individual level), Virtual Physiological Patient (incorporating computational model into clinical practise), High-Performance Integrated Virtual Environment for Next-Generation Sequencing Analysis Infrastructure (cloud for storage of extra-large data), Development of High Resolution Human Leukocyte Antigen Typing (Database), Development of Molecular Tools to Facilitate Blood Group Typing (Database), Clinical Trial Designs and Methodologies.

The paper outlines the following challenges: Limited understanding of the intrinsic biology of disease, Common conditions involving multiple genes/biomarkers, an outdated disease classification system, lack of infrastructure, clinical implementation of new diagnostics, investment uncertainties, and access to personalized therapeutics.

The Role of Pharmacy

In the paper "Making Individualized Drugs a Reality" (Schellekens et al., 2017), the authors argue that while precision medicine is the aspiration, it may be a challenge to bring the aspirational visual into reality as a result of regulatory hurdles. The authors argue that the challenges are not so much in the regulatory environment but rather in how medication is manufactured.

> The starting point of personalized medicine can be traced to the completion of the Human Genome Project, which sequenced almost the entire human genome, in 2001. Since then however, only a limited number of personalized pharmaceutical treatments have reached patients. Technical issues like the lack of validated genetic tests and biomarkers to predict

> patient responses are often cited as reason for the disappointingly slow rollout of precision medicines.(Schellekens et al., 2017)

The author, however, argues that the current pharmaceutical model is unsuitable for creating precision medicines, since it takes about three years "from the time a company submits a new drug application to the FDA or EMA before it reaches patients." This is inherently unsuitable for an individualized product that is in demand at the moment.

As the approval process is currently structured, precisely the same product must be used during preclinical and clinical development (although experimentation with dosage is encouraged), and the marketed product must also be the same formulation. Any change in the product or in the way it is used requires all the testing to be repeated, adding years to the process.

The paper introduces the concept of "bedside pharmaceuticals" as a way to solve these challenges. "When production and treatment are under the responsibility of the same institute, no marketing authorization is needed. This approach bypasses the pharmaceutical industry."

Drug production at that small level is common practice in the pharmaceutical industry during the discovery and early development phase of biopharmaceuticals — meaning the technology is available for production in hospital pharmacies.

> In terms of healthcare economics as a whole, the main contributor to soaring costs is innovation in a market that is driven by what is offered, rather than by medical need. There is no reason to expect this dynamic to change, despite the advent of precision medicine. If economics are driven by fee-for-service rather than by medical need, there is no reason why existing models of precision medicine would alter cost-effectiveness. (Schellekens et al., 2017)