Precision Medicine:
An Action Plan for California

Precision medicine – which encompasses our ability to harness all available data and technology tools at our disposal to prevent and treat human illness and improve human health – is a tremendous opportunity.

Map of Scientific Connections
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The Precision Medicine Advisory Committee created this report based on countless discussions, expert presentations, public forums, and review of peer-reviewed literature. The committee would like to extend gratitude to a number of people who informed their thinking for this report.

A special thank you to:
Attendees at the public forums
Amy Tong
Calum MacRae
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Claudia Williams
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Letter to the Governor

December 26, 2018

The Honorable Edmund G. Brown Jr. Governor of California

Dear Governor Brown:

On behalf of the entire Precision Medicine Advisory Committee, we are pleased to submit this report entitled, “Precision Medicine: An Action Plan for California,” for your consideration as requested in your letter dated October 27, 2017.

We want to commend your leadership in establishing this committee, creating funding for California to advance precision medicine, and working with the Legislature’s leadership and incoming Governor-elect Newsom to position California to be a leader in the future of healthcare. The committee brought together perspectives from a variety of institutions and stakeholders, making it clear that the promise of precision medicine in California can only be realized through partners working collaboratively together, sharing knowledge and expertise across institutions.

Since the committee was appointed, we have held a total of six meetings (three in-person, three virtually) over a 13-month period, and consulted with more than two dozen experts in the various subfields of precision medicine. We also hosted two forums for public input.

As noted in this report, we are in the early stages of moving toward a precision medicine-based healthcare system in California and across the nation. Our report makes several recommendations to accelerate the transition from our current system of care to precision medicine, focusing on near-term practical actions the state and others can take.

Below we address each of the issues that you raised in your letter:

1. Barriers to using big data and better data. How can we make it easier and more likely for patients, providers and researchers to use the most relevant data for prevention, management and treatment of diseases?

> We believe that much better integration of various data sources is possible (including the social, economic, and environmental data) and beneficial, and can be activated through state leadership. We recommend exploring the feasibility of a California Patient Record that gives all Californians the ability to access their complete health record, with ability to contribute their own data and share their record with any provider or researcher. We also recommend protections for patients when they do share that data. We believe this will be important in making precision medicine a reality for all Californians.

2. Timely impact on care and outcomes. How can we understand and measure whether a “precision medicine” approach to care is being used at the right time, by the right health care providers and having an impact on patient outcomes?

> We believe that in order to understand precision medicine’s impacts, we must begin with a pilot that integrates the various components needed for precision medicine (e.g., technology tools, data integration and sharing, research and clinical partnership, patient-centered care) within a defined population. Piloting a precision medicine model of care for a high-needs population would serve the dual purposes of not only understanding precision medicine’s impact on patient outcomes, but also whether precision medicine can be a cost-effective model and reduce health disparities. The recommendations made by the committee include several possible pilots.

3. Access and education. Who can access precision medicine-based care? How will patients and providers learn about this?

> Without implementing more structured changes in our healthcare education and training programs, the vast majority of patients will not benefit from precision medicine. Currently, precision medicine exists to some degree in disease specific areas, e.g., a cancer patient whose tumor is sequenced, which leads to a tailored treatment plan with sophisticated technology-enhanced monitoring. But few are able to experience the comprehensive capabilities of precision medicine, as detailed in our patient and researcher profiles, which are included in this report. We highlight several opportunities to improve the education and training of professionals, noting that universities, licensing boards, accreditation councils and the Legislature will be important partners in making these changes.

4. Areas for biggest impact. Are there certain diseases where precision medicine can make an immediate or near-term impact?

> Precision medicine is most often discussed in the area of cancer. Advances in genomic medicine have led to significant improvements in the identification and treatment of some types of cancers. It is important to underscore, however, precision medicine's potential in many disease areas apart from cancer. Diabetes, depression, Alzheimer's disease, and environmental impacts on health, such as climate change, represent some of the unique opportunities for big impact in California and beyond. In fact, demonstration projects already supported by California focus on diseases and conditions such as multiple sclerosis, traumatic brain injury and heart disease. These precision medicine projects may soon illustrate the changes that are necessary to achieve positive, significant near-term impacts in diseases and conditions apart from cancer.

5. Future of precision medicine. How will precision medicine-based care be sustainable? Should people be prepared to spend more or less money on healthcare?

> We address the potential cost issues of implementing precision medicine in chapter six of the report. It is highly likely that precision medicine will result in increased health care spending—at least for some period of time. Careful attention must be paid to understanding the evidence base for new treatments and therapies. At the same time, we must redouble our efforts to contain current spending that does not lead to better health outcomes. Precision medicine-based care can only be sustained by eliminating ineffective or less effective care. This, however, will take time. We recommend continued work through the development of pilots, and the appointment of a commission to delve more deeply into cost issues.

On behalf of the entire precision medicine advisory committee, we want to express our gratitude for catalyzing this effort to help frame the future of precision medicine, which is poised to change the future of healthcare. We believe the state has a significant opportunity to be a leader for the country and the entire world, and demonstrate how precision medicine can be responsibly and sustainably delivered to millions of Californians. Our time to act is now.

Sincerely,

The Precision Medicine Advisory Committee

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TABLE OF CONTENTS

Executive Summary

In 2017, Governor Edmund G. Brown Jr. announced the formation of a precision medicine advisory committee to provide concrete recommendations for actions to improve health and healthcare through precision medicine.

To define precision medicine, or precision health as some call it, is to describe a future ideal state of healthcare, in which people are viewed as individuals whose health is impacted by many factors, from where they live and work, to the food they access, whether and where they can exercise, what their genetic risks are, to how they are treated based on those risks or on the molecular basis of a disease they have developed. It envisions a system of healthcare that is highly coordinated and technologically sophisticated, in which patients, providers, and researchers alike can access the best research trials and findings and the best data and tools to drive decision-making, and in which providers offer the care and communication necessary to address how people live and the challenges they face. Driven in large part by advances in technology and the increasing availability and granularity of data, precision medicine is predicated on the belief that through these advances and new tools at our disposal, we will be able to prevent and treat human illness and improve human health in ways that were not possible before. While these capabilities will only grow in the future, we are still far from optimally integrating all we know. Our culture, structures, financing and laws reflect the healthcare system of the 20th century, not the healthcare of tomorrow.

How we move from our current healthcare system to a precision medicine system is the challenge we face. As members of the precision medicine advisory committee, we believe we are at a crossroads. As precision medicine becomes a reality, we can offer it to those who can afford it, exacerbating current health disparities in the process; or we can think carefully about how to deliver precision medicine for all—particularly to individuals and communities who need it the most. We can chase how others in the world develop and implement precision medicine, primarily as a race to be first in biomedical and genomic discovery; or we can lead the world in demonstrating how precision medicine should be responsibly and sustainably delivered.

This report attempts to describe the changing landscape of the healthcare world we know, how we would like the landscape to evolve with precision medicine, and some initial steps California and its partners can collectively take to reach our goal of precision medicine for all, sustainably and responsibly delivered. The report is organized into seven chapters, each of which includes a set of recommendations (which are also listed collectively following the executive summary).

The introduction highlights precision medicine as a paradigm shift towards a “learning healthcare system” and details the state’s $53 million investment in the California Initiative to Advance Precision Medicine (CIAPM), as well as the committee’s charge for this report. International investments (in the billions), various definitions for precision medicine (more than a half dozen), and patient and researcher profiles (comparing current and future states of fictional narratives) are also contained within this first chapter.

The second chapter examines key issues surrounding data—from data sources to storage, infrastructure, security, and sharing. Among the key points are: 1) how electronic health records (EHRs) have proliferated, thanks to federal financial incentives, and how EHRs can form the foundation for new insights and more equitable research; 2) how data outside the EHR have become ubiquitous, from clinical trials to consumer generated tools and devices, like smartphones, activity trackers, and sensors; 3) how data related to social determinants of health (SDOH), such as air and water quality, access to transportation, healthy foods, early childhood development and education, and prevalence of crime and violence, are already accessible. The challenge for all of these datasets is how to make them appropriately accessible and interoperable in order to be useful in new ways, and to incentivize their use. Other issues highlighted in this chapter include the dramatic increase in the amount of data that we generate and must store; the move to cloud-based storage and

computing and the trust framework that must be developed between all users of these data, including patients; the need to develop standards for assessing data quality and promote the creation of data security plans to mitigate the growing cybersecurity risks.

Chapter three focuses on the necessity of greater patient-partnerships in the research and care environments. As discussed in chapter two, many more patient and consumer-oriented tools, devices, and websites make it easier to engage patients in both research and healthcare, but many still experience multiple barriers to becoming more active participants, such as the inability to access all of their data and records, and misalignment between patients' life goals and clinical outcome goals. Mounting evidence demonstrates that when patients and healthcare consumers have more access to their medical data, they are more engaged in their care and can make better decisions about treatments and health behaviors (behavior change being an important aspect of many treatment plans). This in turn yields better outcomes and lower healthcare costs. Community trust, greater transparency and communication in research, removing barriers to participating in research and access to one's full EHR, increased focus on SDOH, authentic patient engagement, and patient experience are all discussed in this chapter.

The fourth chapter delves into the changes we need in our education and training systems to enable the delivery of precision medicine, which relies on data to optimize the delivery of patient-centric care. A new education model must emphasize training practitioners in using vast quantities of data from multiple sources and working in nontraditional multidisciplinary teams, including data scientists, researchers, genetic counselors, patients, and community stakeholders. Training practitioners to address health equity issues is also seen as key, as is preparing them for adaptability as new technologies emerge and fostering the empowerment of community members as equal partners. The chapter notes that California is a leader in training physicians, nurses, and allied health professionals, and also leads in data science, engineering and biotechnology. It makes clear the opportunity for California to lead in the transformation of training across the career spectrum (from doctors to nurse practitioners (NPs), to behavioral health specialists, genetic counselors, data scientists and allied health professionals), and throughout career paths (from high school through college, professional schooling and continuing education classes), including retraining of the current workforce and development of interest in earlier years of training, in order to enable the delivery of precision medicine.

Chapter five surveys the significant scope of regulatory issues that are part of the precision medicine landscape, but focuses most of its attention on use and potential misuse of genomic and other new types of identifying data, as well as the challenges for oversight and regulation of new genetic tests. The chapter provides a technical discussion on the current federal approach to regulation and laboratory developed tests (LDTs), and offers thoughts about where regulation may go in the future. This chapter highlights the need to reexamine our current laws related to genetic and other information to balance consumer protection and innovation in this rapidly changing environment.

Chapter six reviews economic issues within precision medicine. Prominent in this chapter is the problem of current healthcare spending—on track to grow to almost 20 percent of gross domestic product by 2026, or $5.7 trillion at the national level, and to nearly $550 billion by 2022 in California alone. Unlike other sectors in which new technologies or business models are seen to drive gains in productivity and efficiency, new technologies and therapies in healthcare are generally viewed as having additive costs, which makes precision medicine an expensive proposition if not approached thoughtfully with a goal toward eliminating less effective treatment modalities concurrent with precision medicine's advance. This chapter also highlights the necessity of tackling health disparities and integrating social and environmental factors into precision medicine approaches in order to make precision medicine not only more equitable, but more workable from a financial perspective. The chapter discusses the concept of implementing value-based precision medicine that carefully applies standards of evidence for treatments and therapies, acknowledging that the standards of evidence are changing with the new knowledge we are acquiring about an individual's unique characteristics down to the molecular level. Finally, a discussion about the precision medicine

economy in California and our competitiveness on the world stage of biomedical and genomic discovery closes the chapter.

Noteworthy are the brief profiles of projects funded by California, which are scattered throughout the report. If they prove to be successful, they can help promote the practice of precision medicine for specific disease areas.

Finally, the report closes, in chapter seven, with an overarching message that continued state investment in precision health and medicine is needed, and continuing the work identified in the report, through establishment of a council, will help inform future funding and policy decisions for precision medicine. For precision medicine to thrive in California it goes beyond any one institution, it is about all of the different stakeholders, similar to the composition of this committee, working together to achieve a bold vision of ushering in the next generation of medicine.

Summary of Policy Recommendations

The chart below includes all of the policy recommendations in this report by chapter. The top portion of the graph demonstrates the cross-cutting relationship with other workgroup discussions and policy recommendations.

Policy Recommendations	Data	Californians as Partners	Education & Workforce	Regulation	Finance
Data in the context of precision medicine					
The Governor's Office of Planning and Research (OPR) should create a public-private working group to establish standards for social determinants of health (SDOH) data collection and examine the feasibility to require health systems to gather and regularly report on the SDOH.	✓	✓	✓		✓
The Legislature should require vendors operating in California to provide application programming interfaces to allow health systems to provide broader patient access to comprehensive electronic health record data.	✓	✓			✓
OPR should convene public and private precision health and medicine stakeholders to create cross-institution data-sharing guidance.	✓	✓			
California's Office of Statewide Health Planning and Development (OSPHD) should incorporate principals of interoperability and enhanced data collection as they build the Health Care Cost Transparency Database.	✓				✓
Californians as Partners in Care and Research					
Through legislation and incentives, California should reduce barriers for patients to obtain and share their data and correct errors in their EHRs.	✓	✓			
As recommended in the Data in the Context of Precision Medicine chapter, which would have OSHPD incorporate principals of interoperability and enhanced data collection in the Health Care Cost Transparency Database, the committee recommends the database incorporate patient registry data for a cohesive and connected system.	✓	✓			
OPR should name a public-private working group to study the feasibility of a California Patient Record. This can include looking at different types of incentives that enable the patient	✓	✓			

Policy Recommendations	Data	Californians as Partners	Education & Workforce	Regulation	Finance
and providers to contribute to and have immediate access to medical records in order to serve patient care delivery needs first, and can be expanded upon to provide unique access to research participants and data.					
OPR should work with public and private partners and academic research intuitions across California to develop a model consent framework and education toolkit, and explore incentives for adoption. This group should coordinate with the group established to work on data sharing.		✓	✓		
The Governor's Office should work with its federal partners, which fund the majority of research, to promote participant-centered study design.		✓			
The University of California in partnership with other health systems should create programs to promote an understanding of and access to research participation.		✓	✓		
Education and Workforce					
The committee recommends that California colleges and universities develop interdisciplinary health informatics and precision medicine training programs that integrate the expertise available in healthcare, engineering, biomedical sciences, social and environmental sciences (focused on ethical issues, social policy, SDOH), and data sciences.	✓		✓		
The committee recommends that the Legislature invest in the development of additional masters programs in Genetic Counseling to meet future workforce needs.			✓		✓
The committee recommends that academic programs in California institute new admissions requirements for medical, nursing, and physician assistant training that include courses in data science (in place of prior requirements for mathematics/calculus) and in social sciences that are relevant to understanding the SDOH.	✓		✓		
The committee recommends that California's 72 graduate medical education-sponsoring institutions work with the Accreditation Council for Graduate Medical Education to design and implement novel residency and fellowship programs in clinical informatics, genomic medicine, and bioengineering.	✓		✓		

Policy Recommendations	Data	Californians as Partners	Education & Workforce	Regulation	Finance
The committee recommends that the California Medical Licensing Board and CME California invest in a curriculum of continuing medical education (CME) courses that would expose physicians to the disciplines of precision medicine.			✓		
The committee recommends that the UC Biomedical, Research, Acceleration, Integration and Development consortia develop educational programs for research participants and establish partnerships with community-based organizations to train and disseminate information using evidence-based models.		✓	✓		
Regulatory Challenges					
Enact legislation to further strengthen the California Genetic Information Nondiscrimination Act provisions to ensure that it prevents the unauthorized use of genetic information to influence employment decisions, or affect access to health, life, long-term-care, and disability insurance.		✓		✓	
Direct precision medicine staff at the state level to participate in a federal standards working group to improve laboratory developed tests (LDTs).				✓	✓
The Governor's Office should appoint a committee to conduct a study of the feasibility to implement a model for conducting 3rd party review for LDTs and direct-to-consumer tests.				✓	✓
Finance and Cost Models					
OPR in collaboration with the California Governor's Office of Business and Economic Development should establish a research consortium of business leaders (both entrepreneurs and technology leaders), patients, academics, healthcare practitioners, and payers to develop a pilot that integrates social, environmental, behavioral, and medical data and healthcare delivery, leverages available technology tools, and evaluates outcomes and cost-effectiveness of a precision medicine approach to care.	✓	✓	✓		✓
State agencies should institute programs and policies that position the state as the leader in value-based transformation for both traditional and precision medicine.	✓				✓

Policy Recommendations	Data	Californians as Partners	Education & Workforce	Regulation	Finance
Healthcare system leaders should actively build on existing efforts and partner with existing organizations.			✓		✓
The Governor should appoint a commission or workgroup of public and private academics and practitioners to develop a consensus economic model for healthcare.			✓		✓
Overarching Considerations and Conclusion					
Continue to invest in precision health and medicine.	✓	✓	✓	✓	✓
Establish an Economic and Cost Model Council to continue the work identified in this report and inform future funding and policy decisions for precision medicine.	✓	✓	✓	✓	✓
Invest in broad disease areas.	✓	✓	✓	✓	✓

Chapter 1: Introduction

A third wave of healthcare is coming. It includes the mass digitization of health and research data, the accessibility of genome sequencing, the rise of consumer health tracking tools, wearable devices, and artificial intelligence (AI). Collectively, an age where personalized, predictive, preventive, participatory, transparent, data driven, consumer-inclusive, equitable, industry-aligned, technology-enhanced healthcare is now possible. However, this future has not yet fully arrived.

The Internet started simply with a handful of two-dimensional digital connections. Later, it exploded to change forever the way information is accessed, communication exchanged, and business transacted. We believe we are standing at the edge of a similar juncture of transformational change. ***Precision medicine—which encompasses our ability to harness all available data and technology tools at our disposal to prevent and treat human illness and improve human health—is a tremendous opportunity.***

At stake are the lives and health of our citizens as well as the trillions of dollars the U.S. spends on healthcare each year. And so is our country's and state's preeminence in healthcare research and discovery. Many countries are competing with us by investing billions of dollars in the race to discover and capitalize on new genomic and biomedical therapies.

This next wave of healthcare is not without significant peril. Like the Internet itself, new modes of information and communication will bring new opportunities, but also new risks in the areas of personal privacy and cybersecurity. Moreover, still not fully understood is how AI will accelerate our capacity to identify effective therapies and cures, or how the healthcare workforce will need to adapt. It remains unclear how laws and policies may need to adapt to manage this future.

Such issues are myriad and wide-ranging. This report of the Governor's Precision Medicine Advisory Committee is a first step in identifying the landscape and a few major areas of opportunity from a systemic view, with the understanding that many efforts, and often the most near-term effective ones, are local in nature. Regardless of where the locus of action or change may occur, this committee believes that precision medicine will touch the lives of all Californians and Americans in the near future—and we collectively have a responsibility to shape that future with a cohesive vision that can lead the way.

What is Precision Medicine? And Why Now?

Precision medicine is the future of medicine today. Medicine has seen many advances over the centuries, each advance yielding a new understanding of disease, its causes, and treatment. For instance, the microscope was invented during the renaissance and the practice of "humorism," a belief system adopted by the Greeks and Romans that based disease on a system of four bodily fluids, was gradually replaced with germ theory, greatly improving treatments for infectious disease.

Akin to the microscope, data and technology can offer new insight into health and disease. ***Precision medicine (also known as precision health, which we will use interchangeably in this report) is defined as an approach that aims to use advanced computing tools to aggregate, integrate, and analyze vast amounts of data from research, clinical, personal, environmental, and population health settings, to better understand health and disease, and to develop and deliver more precise diagnostics, therapeutics, and prevention measures.***

This committee views precision medicine broadly, encompassing molecular, clinical, and population level domains, yielding knowledge that can be applied to improve and maintain health and treat disease. While precision medicine is sometimes viewed as interchangeable with 'genomic medicine' or 'personalized medicine', the committee asserts that the intention is not to limit the discussion to genomic applications and the promise of new therapeutics. The committee's intent, given the substantial evidence over the last several decades on the importance of social, environmental, and

economic factors (also known as the SDOH), **is to consider *all* data and applications that are relevant to health.** In fact, the committee views precision medicine as an opportunity to understand more fully how all of these factors affect health and disease and to design more tailored treatments to meet patients "where they are," with an aim of better outcomes as well as to provide more precise prevention.

Precision Medicine Definitions

California's Definition: Precision Medicine is an approach that "aims to use advanced computing tools to aggregate, integrate and analyze vast amounts of data from research, clinical, personal, environmental, and population health settings, to better understand health and disease, and to develop and deliver more precise diagnostics, therapeutics, and prevention measures."

UK NHS Definition: "Precision (or personalized) medicine is defined as the application of emergent technologies to better manage patients' health and to target therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease. Used properly, precision medicine should both improve patient outcomes and deliver benefits to the health service - including reducing the cost of ineffective treatment and multiple tests" (1).

Precision Medicine Initiative: "An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (2).

Centers for Disease Control: "Precision medicine, sometimes called personalized medicine, is an approach for protecting health and treating disease that takes into account a person's genes, behaviors, and environment. Interventions are tailored to individuals or groups, rather than using a one-size-fits-all approach in which everyone receives the same care" (3).

Institute for Precision Medicine, University of Pittsburgh: "Precision Medicine is a medical approach that proposes to prevent and treat disease based upon a person's unique genetic makeup and their lifestyle habits" (4).

University of California, San Francisco: "Precision medicine is the use of advanced computing tools to aggregate, integrate and analyze vast amounts of data from basic science, clinical, personal, environmental, and population health settings, to better understand biological processes and define disease mechanisms, and to develop and deliver more precise diagnostics, therapeutics, and prevention measures. Everyone, including patients, can contribute their own data to this dynamic network" (5).

University of California, Los Angeles: Uses the concept of "precision health": "Precision health takes into account differences in people's genes, environments and lifestyles and formulates treatment and prevention strategies based on patients' unique backgrounds and conditions" (6).

Stanford University: Stanford also prefers the concept of "precision health": "The vision would be to go beyond Precision Medicine: instead of a frantic race to cure disease after the fact, we can increasingly focus on preventing disease before it strikes. By focusing on health and wellness, we can also have a meaningful impact in reducing healthcare costs…we call this idea Precision Health, where we focus on helping individuals thrive based on all the factors that are unique to their lives, from their genetics to their environment" (7).

A Paradigm Shift Towards a “Learning Healthcare System”

Precision medicine is also shifting the paradigm around discovery. Traditional biomedical research was conducted with a clear delineation between the laboratory and the patient care setting. Clinical trials were conducted, patients were consented for a specific study question, and then, after months or years of monitoring for specific health measures, analysis was done to see if the medication or intervention was effective. The gold standard methodology was a large-scale randomized control trial.

Although this model still exists, the paradigm is now adapting. Along with the advent of and increased access to EHRs, there is a movement to leverage the traditionally siloed information within those health records. Rather than creating large cohorts pursuing the answer to one specific research question, the movement is to have a “learning healthcare system” that allows for many types of queries on multiple types of data and patients at various times points and uses new knowledge to improve clinical care. For instance, in type 2 diabetes, one might ask how do patients respond to the common treatment option metformin versus metformin and insulin? Ultimately, the goal is to find out what works and why the same treatments work differently in subsets of the population. Furthermore, what various treatment protocols are used in medical practice and how do people follow them? The answers to these types of questions are now possible to identify with increasingly interoperable EHRs.

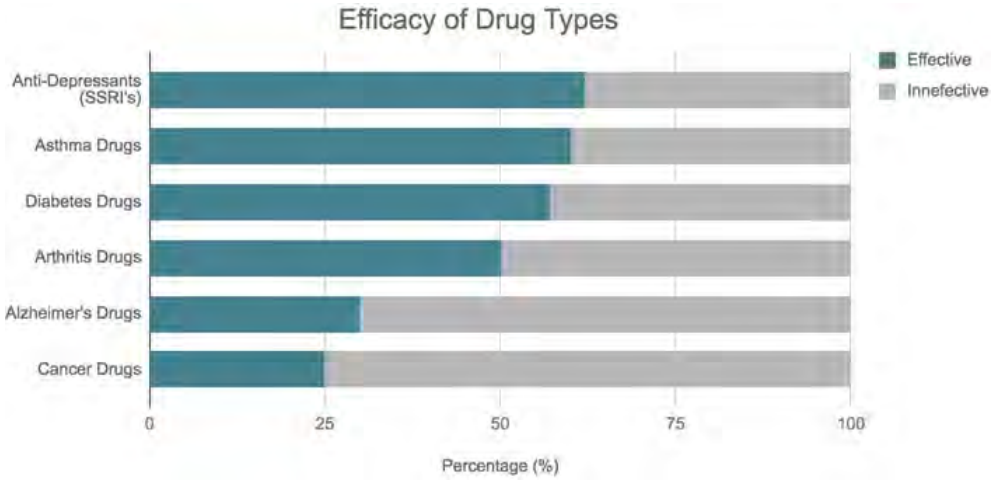


Figure 1: Efficacy of drug types. Drug treatments work differently in subsets of the population. Data Source: Spear B, Heath-Chiozzi M, Huff J. Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, pages 201-204

Many cohorts are also now being created with the potential to answer multiple questions in tandem, rather than the traditional research model whereby one variable or research question can be tackled at a time. As an example, President Obama under the Precision Medicine Initiative (PMI) started the All of Us Research Program in FY2016 (8). The National Institutes of Health (NIH) received $130 million from Congress to build a large-scale cohort of one million participants. This cohort will allow queries and investigation across a spectrum of diseases and incorporates data from environmental exposures, genetics, mobile health and the EHR (9). Other countries have also started to create cohorts such as this, and medical systems such as Kaiser Permanente and Geisinger Health System are increasingly looking to their health system data to use clinical information to understand subgroups of patients and answer questions that inform clinical care (10).

California’s Opportunity as an Emerging Leader in Precision Medicine

California has all the components needed to usher in this next frontier in medicine. California is home to bold entrepreneurs, world-class academic centers, leading health systems, and the epicenter of venture capital investment for the nation. California’s preeminence in biotechnology and advanced computation—two domains that are bringing rapid change and economic growth—creates a unique opportunity for the state to lead the intersection of these fields and transform the healthcare ecosystem.

In April 2015, with $3 million, California launched a unique investment in a strategic precision medicine program, which has grown to $53 million in state funding over the last several years. Several million was also contributed by the private sector. The statutory guidance for this program established CIAPM in OPR. CIAPM is a partnership between the state, the University of California, and other public and private entities. Its aim is to help build infrastructure and assemble the resources necessary to support precision medicine efforts in the state. The majority of funding supports patient-focused demonstration projects and key activities aimed at fostering collaborations and advancing precision medicine.

The demonstration projects have been vital to creating new partnerships. The state is currently funding eight demonstration projects in precision medicine impacting age groups from children to the elderly, and across the spectrum of disease, from prevention to treatment. The disease areas span cancer, multiple sclerosis, infectious disease, and heart disease, and range from predicting (and preventing) cardiac events to using data from brain images to detect brain bleeds more quickly in computed tomography scans with AI. These projects are already having an impact (11), and importantly are also providing insight into some of the challenges and opportunities to allow precision medicine to thrive. However, a supportive policy landscape is critical to truly advance this emerging field.

International Precision Medicine Efforts

A number of countries have launched precision medicine initiatives, which have included significant investments in genomics and large-scale collection and analysis of health data.

In 2012, the UK government began the 100,000 Genomes Project, a program to sequence the whole genomes of National Health Service patients with a focus on rare and infectious diseases and some common types of cancer (12). In 2018, the UK government further committed £210 million to the precision medicine challenge. This initiative aims to improve data use for diagnosis and precision medicine, and will fund the development of diagnostic tools for patient stratification and the application of AI to the analysis of medical imagery (13). In 2016, meanwhile, the French government launched a national plan for precision medicine, Genomic Medicine 2025, and committed €670 million in public funding to the goal of sequencing 235,000 genomes each year by 2020 (14). These various initiatives seek to promote the development of national genomics sectors and to place Britain and France among global leaders in precision medicine (15). They also provide a framework for integrating genomic sequencing into routine clinical practice and supporting the collection and integration of clinical and genomic data in national databases.

The Chinese government, in turn, launched its precision medicine initiative in 2016. This initiative is a 15-year project with $9.2 billion in funding that aims to sequence 100 million human genomes by 2030 and establish China as a global leader in genomics research (16,17). The Chinese government is also developing a centralized and integrated data platform for precision medicine and supports additional precision medicine projects, including research to employ data analytics and machine learning to improve diagnosis (18). Furthermore, Chinese companies, like iCarbonX, have begun to collect data on patients' genetics, environment, and behavior and apply AI in order to determine which healthcare treatments are likely to be effective for particular individuals (17).

In contrast to those countries that have created high-profile, nationwide precision medicine research initiatives, Canada has supported small-scale and regional precision medicine projects. Genome Canada, a non-profit, government funded organization responsible for developing the Canadian national strategy for supporting research in genomics, awarded more than Can$160 million in early 2018 to 15 regional and specialized precision medicine genomic initiatives (19). In addition, the Canadian Institutes of Health Research (CIHR) have invested almost Can$180 million since 2010 in personalized health research. The creation of predictive analytic models that can stratify patients by outcome and risk is a priority area for the CIHR (20). Currently funded projects include the development of predictive modeling to determine which patients will benefit from particular spinal surgeries (21). Genome Canada announced a national initiative for the clinical implementation of precision medicine in 2018. This initiative will begin with a pilot program to sequence samples from rare disease patients and their families, develop best practices for sharing data, establish clinical sites, and achieve regulatory approval and accreditation (22).

Precision Medicine Advisory Committee

As an important step to advance California's future as a leader in precision medicine, Governor Brown announced this committee on October 5, 2017. This group was tasked with providing concrete recommendations no later than December 2018 on actions to both improve health and healthcare through precision medicine. The committee was not restricted to thinking solely about state policy, but had the ability to examine potential policy actions across federal, state, local, public, private, or private nonprofit sectors.

The Governor's specifically tasked the committee to consider:

- Barriers to using big data and better data. How can we make it easier and more likely for patients, providers, and researchers to use the most relevant data for prevention, management, and treatment of diseases?
- Timely impact on care and outcomes. How can we understand and measure whether a "precision medicine" approach to care is being used at the right time, by the right healthcare providers, and having an impact on patient outcomes?
- Access and education. Who can access precision medicine-based care? How will patients and providers learn about this?
- Areas for biggest impact. Are there certain diseases where precision medicine can make an immediate or near-term impact?
- Future of precision medicine. How will precision medicine-based care be sustainable? Should people be prepared to spend more or less money on healthcare?

Committee Composition

To consider the complex areas and intersections of precision medicine and represent diverse perspectives and expertise from these various stakeholder groups, the Governor appointed a committee with expert members representing a broad range of relevant perspectives. (Appendix 1)

Figure 2: At committee meetings a variety of experts in biotechnology, patient engagement, academia, finance, health disparities, and more, came together to discuss precision medicine.

Vision

At the initial meeting, the committee members created a vision statement based on the committee tasks and committee values to guide them through the year of deliberation, conversation, research, and ultimately recommendations. The committee also identified guiding principles that included:

- Keep in mind the state definition of precision medicine, which also includes precision health:

> "Precision medicine aims to use advanced computing tools to aggregate, integrate and analyze vast amounts of data from research, clinical, personal, environmental and population health settings, to better understand diseases and develop and deliver more precise diagnostics, therapeutics, and prevention measures."

- Deliver recommendations that are flexible, fitting a rapidly changing ecosystem.
- Put patients and health improvement or improved health outcomes at the center of all discussions.
- Consider implications for health equity in all recommendations.
- Acknowledge the truly interdisciplinary nature of precision medicine and take into account different perspectives and potential consequences or impact of recommendations on diverse communities.
- Consider the different levels (international, federal, state, private industry, etc.) at which policy recommendations could be enacted for each topic of discussion, and how recommendations will impact the entire ecosystem.
- Consider economic impacts for policy recommendations.
- Consider emerging science and technology opportunities for precision medicine.
- Recognize the translational science needed to achieve precision medicine: cross-fertilization between basic biomedical sciences and clinical research & data.
- Identify the short-term, medium-term, and long-term societal and health value for patients.

Precision Medicine Advisory Committee Vision Statement

PMAC will provide recommendations that will enable California to establish itself as a national leader in the shift in healthcare towards precision medicine and health, through the creation of statewide policies that will enable all centers in California to provide the best prevention, diagnosis, and care with cutting-edge technology that improves health outcomes and lowers healthcare costs by 2025.

Committee Process and Organization of the Report

The committee held a total of six meetings (three in-person and three virtually) to gather information from experts, stakeholders, and the public. Based on the tasks and early conversations, five key areas of focus were selected for further research and deliberation that also informed the meeting agendas. These areas included: 1) data in the context of precision medicine; 2) Californians as partners in care and research; 3) education and workforce; 4) regulatory challenges; and 5) finance and cost models. The committee formed workgroups to focus on each of these topics and to develop specific recommendations. The output of the committee workgroups is presented in detail with background information and recommendations in the following chapters. Additionally, this report includes a section on cross-cutting themes with overarching recommendations.

A Timely Opportunity

Precision medicine is not unique to California, it is a worldwide movement and California can and should be at the forefront. Other countries are investing. Patients are waiting. The time for collective action is now.

Our Future Health and Precision Medicine Approaches

Researcher's Quest to Improve Health

Today's Situation

Jorge, a scientific researcher, needed data from a large group of people—including not only patients with the rare disease he was researching, but also a comparison group of people not diagnosed with that disease. He planned to use machine learning to identify new biomarkers for the disease by comparing the two groups. Unfortunately, assembling the participants and data was expensive and required months of effort. First, Jorge had to recruit people with the disease, which was not something he was experienced in doing. This required outreach to interest groups and specialist physicians around the state, as well as advertising on social media. Then, respondents had to be screened to see if they fit the study criteria, which was a time-consuming process. For the non-disease cohort, Jorge also had to negotiate with a variety of data "owners" who either wanted large access fees or expressed concerns about whether their institutional review boards (IRBs) would allow this use of the data.

Once his study was under way, Jorge experienced considerable drop-off in participation; patients told his team the protocol was too burdensome.

Our Future

Jorge signs in to the online researcher toolkit and starts the process of setting up a small trial. He defines the parameters of the cohort he would like to recruit and sees that 9,078 Californians meet his criteria. Before he can recruit them, he needs to get patient input to inform the development of his protocol. The tool describes what's needed for a structured explanation, applies a standard set of patient feedback questions developed by patient feedback experts, then lets him define additional questions. The tool then invites some of recruited patients to provide feedback through their California Patient Records. Jorge adjusts his protocol based on the feedback, and then sets up his study invitation.

The tool offers him some hints about best communication practices that tend to result in higher enrollment. It also asks him to specify some details, such as which of a standard set of study risks are involved, and whether there are any additional risks not covered in the template. Jorge does not have the resources to do extensive marketing, so he is grateful that he can check a box and include some pre-made frequently asked questions about medical research. When he's ready, Jorge sends off his invitation. The tool does rolling recruitment (sending invitations in batches until the enrollment target is met) to avoid overburdening patients with too many invitations.

Through the course of his study, access to medical records lets him see when anything clinically important happens outside of study visits, such as when a participant has gone to the emergency room. Jorge also uses the California Patient Record as a portal for communication with his participants. At the end of the study, he is able to use the portal to make publications available to participants.

Better Disease Management

Today's Situation

When Karen was diagnosed with multiple sclerosis (MS), she faced a hard choice: Should she start a disease-modifying drug right away to delay nerve damage, or wait until her symptoms got worse, since the drug would eventually lose its effectiveness? Once she decided to start treatment, Karen's doctor suggested the most common first-line therapy. A month later, Karen switched drugs because of substantial side effects. Her second therapy was more tolerable, but Karen's fatigue and mobility issues seemed to increase rapidly over the next year. Worsening depression and anxiety, combined with the increased physical symptoms, led to more hospital and doctor visits, an inability to work, and a couple of additional prescriptions to manage her mental health. Karen finally switched to a third MS treatment option, which appeared to slow her progression.

Although Karen gradually adapted to managing her condition, circumstances sometimes took her by surprise, such as when a heat wave exacerbated her MS symptoms and sent her to the emergency room. While at the hospital, Karen experienced a dangerous drug interaction because her EHR did not reflect the other drugs prescribed by her psychiatrist. After that episode, Karen realized she was better informed about her overall health than any of her individual healthcare providers. Unfortunately, only one of her care team had a patient portal, which reflected only part of her record and offered her no way to correct outdated information.

Our Future

When imaging shows that Karen has MS, her healthcare provider orders a precision diagnostic test to identify exactly what subtype of MS Karen has. She has a subtype that is likely to progress rapidly, so her doctor suggests she start a specific disease-modifying drug right away. Karen's genetic results show two therapies are likely to work well, but one is likely to cause severe side effects. Once she starts therapy, Karen's fatigue and mobility issues improve. She remains largely stable for the next three years. Although her symptoms don't increase, a precision monitoring test detects an increase in disease activity. Karen and her care team decide to switch to a new, more targeted drug. Although her MS continues to progress, Karen is able to keep working (and avoiding major mood disorders) for several years.

As a Californian, Karen has access to her unified California Patient Record. When she eventually begins seeing a psychiatrist, Karen grants him access to view and update her record, so he can see her complete history and enter new prescriptions. A regular digital reminder encourages Karen to update any medications, health issues, or social history her providers might not know about.

Karen's care providers also encourage her to use a wearable device and to log her good and bad days online. A disease management application alerts Karen to important correlations: her mood symptoms are better when she walks at least 5,000 steps, her mobility symptoms are worse when she gets less than 7 hours of sleep, and her fatigue and mental fog are much worse when the temperature exceeds 73 F. Based on her sleep and the weather forecast, the application notifies Karen of days when she might want to manage her energy or environment.

Patient-centered Research

Today's Situation

When Uday was diagnosed with a rare cancer, he was told that his best bet was to participate in a clinical trial. He wasn't certain what this meant. Would he get the real treatment? Was it safe? The trial clinic was not close to his home; it would be a two-hour drive each way. Having his care fully covered was appealing, but the commute would be expensive and time-consuming.

Uday eventually joined the trial as his best chance to get better. The enrollment process was cumbersome. The protocol was burdensome too; it seemed to Uday that some of the check-ins could have been done over the phone or at his local lab, but this was not an option. However, Uday's cancer responded so well that it was worth it. He assumed he was receiving the trial therapy, which was intended to be a long-term maintenance drug.

A year later, when the trial was over, Uday was dismayed to realize he would not have ongoing access to the drug, which was not yet approved for use outside of trials. Uday did not even know how the trial had gone: Would the drug be approved? How long would it take? What could he do in the meantime to stop his cancer from returning?

Our Future

When Uday first set up his access for his California Patient Record, the system asks him to confirm that his primary care physician, other members of the care team, and any emergency medical staff can access his records as needed for treatment. It also explains that his medical data can help researchers prevent and treat disease. The California Patient Record then walks him through a brief, clear consent process that explains the risks and some example uses, then asks which kinds of data he is willing to share, and whether he wants to be notified when his data have been used in a study.

Later, Uday gets notified about a study suitable for him. The benefits and risks seem clear, and it looks like only a couple of office visits are needed. He goes through the online consent process and enrolls, then gets the first study questionnaire, which he can also complete online. As the study progresses, Uday gets the occasional progress update from the researchers and study coordinator through his California Patient Record, so he feels like part of the team. He continues to do online check-ins. After office visits, Uday and his regular doctor can see the blood tests and scan results in his record. Although Uday does not know if he is in the placebo arm of the study, his cancer is moving toward remission.

At the end of the study, Uday is informed that he was on the trial drug and is offered the chance to continue it, provided he continues to share data about his experiences. He agrees. When the results are published, Uday gets a notice that includes a short summary of the findings, as well as a link to the original publication, which he can access without having to pay for access to the journal in which it appeared.

Chapter 2: Data in the Context of Precision Medicine

Introduction

The data workgroup was tasked with critically examining the many data issues inherent in precision medicine—from the types of data sources available, to how data is collected and stored, to how it is kept secure and ultimately accessed and used. This group recognizes that California is in a unique position to drive smart data policies, which will move the field of precision medicine forward. An environment that encourages broad and open data sharing and balances patient and participant protections will be critical to these efforts, as will interoperability between existing systems and newly created data streams.

Key Issues

Data Sources

Technology allows us to collect more data than ever before. Data resides within health systems but many other types of novel data can now be captured, creating new opportunities, but also new challenges.

Healthcare and life science data reside within the EHR. The data continue to grow, and if harnessed appropriately, can serve as an accelerant for precision medicine. EHR data include patient visits, medical claims and billing, radiology reports, pathology reports, and laboratory data (although often these data are not digitized).

California Spotlight:
Data Harmonization in the California Kids Cancer Comparison (CKCC) Project
Funded by California

The California Kids Cancer Comparison (CKCC) project, led by researchers and physicians at the University of California, Santa Cruz (UCSC) in collaboration with partners across the state of California, exemplifies the need to harmonize data to advance biomedical research and ultimately improve clinical care. The project aims to improve upon the less than 10% success rate that UC Medical Centers have in using genetic analysis to identify new therapies for the 500 California children with cancer that lack or fail to respond to standard therapies each year. CKCC's approach is to compare an individual's tumor DNA and RNA sequences with a database of thousands of other peoples' tumor sequences. These computational analyses can inspire scientific hypothesis generation and help identify targeted treatments that are less toxic and more effective than state-of-the-art therapies. While the project team aims to at least double the number of children that can benefit from a targeted cancer treatment, the approach can also potentially be scaled and applied to improve treatments for other genetic diseases and for all 176,000 Californians diagnosed with cancer each year (11).

In addition to EHR data, there are vast amounts of data from clinical trials, research, consumer sensors such as Fitbits, patient-generated data, direct to consumer genetic data such as from companies like 23andMe, environmental sources, and other passive data collection sources such as from a smartphone or digital watch. Although all of these data are being created, they often sit within different silos—companies, health systems, individual storage, or academic centers. If the data are accessible, it is often still challenging to use it since frequently it is not in a standard format or accompanied by metadata (a full description of the data) to fully compare and use the data.

Occasionally these data are generated within the traditional clinical context; however, more data elements are coming from outside of this arena. The ability to collect and aggregate these diverse sets of information is maturing. As such, both the cadence (from episodic to continuous) as well as the amount (from several gigabytes to several terabytes) of data being captured is evolving rapidly. As the data grow, there is tremendous potential to use all of the data as input for algorithms and AI allowing for more real-time understanding and intervention. The working group identified several data elements that are expanding at a particularly rapid rate but two specific opportunities for California-specific precision medicine applications include the sheer number of EHR records and the ability to integrate SDOH into precision medicine analyses.

Electronic Health Record Data

Due to the Health Information Technology for Economic and Clinical Health (HITECH) Act, which was part of the federal economic stimulus package in 2009, funding has been provided to stimulate the broad integration of EHRs into care settings. Specifically, if EHRs are implemented and used in accordance with “meaningful use,” which is a set of reporting criteria indicating the use of certified EHR software technology in a manner predetermined to be meaningful, then providers can be eligible to receive funding. Additionally, the California Health Information Partnerships and Services Organization (CalHIPSO) received a $31 million grant to achieve a series of aims: provide education, outreach, and technical assistance to primary care providers as they are adopting EHRs. On a hospital level, as of 2016, over 95% of eligible and critical access hospitals were found to demonstrate meaningful use of certified health IT through CMS EHR incentive programs (23). California is now on par with this national average, and continued efforts are warranted as technology and standards evolve.

Although the primary impetus for EHR implementation has been clinical care, data collection via the EHR has also allowed for a new wave of clinical investigation, ranging from punctuated, cross-sectional studies embedded in an individual hospital system to long-term, multisite evaluations on dispersed groups of patients. These datasets can result in large sample sizes, cost-effective approaches to research, and more findings (24). In an analysis that compared survival rates among patients across several cancer trials to those in a general cancer population, the researchers found that event rates in the trials were not representative of those in the broader group (25). This study highlights how data that comes from the real world, such as data captured in the EHR, could assist with understanding health and disease in a comprehensive fashion and ensure that precision medicine truly reflects the population. It also emphasizes the value of broad data sharing, whether from the EHR or a clinical trial.

With a population of over 39 million people, California has greater than 13 million emergency department visits, 3 million hospital admissions, and numerous outpatient encounters annually (26). The opportunity exists to harness data from these events to improve precision medicine, and efforts are underway. An early example is the University of California Research eXchange (UC ReX), formed in 2011, which includes more than 15 million patient records derived from EHR and administrative sources across the University of California medical centers in Davis, Irvine, Los Angeles, San Diego, and San Francisco. The UC ReX data explorer includes deidentified (no patient or institutional identifiable data) information on: demographics (age, ethnicity, gender, language, marital status, race, religion); diagnosis codes; procedures codes; laboratory values; medications; visit details (length of stay, visit type); and vital signs. UC ReX is an early example of the capacity of

academic medical centers to harmonize clinical data and has led to a number of specific quality improvements across the sites. Efforts such as this one, that include an even broader swath of California, could continue to place the state at the forefront of precision medicine by having access to large data sets that combine data in unique ways.

California has made recent strides to gather and make available more data related to the financing of healthcare, keeping in line with other states. In 2018, the state Legislature passed a law to "establish a system to collect information regarding the cost of health care. Health care data is reported and collected through many disparate systems. Creating a process to aggregate this data will provide greater transparency regarding health care costs, and the information may be used to inform policy decisions regarding the provision of quality health care, reduce disparities, and reduce health care costs" (27). This legislation will create the Health Care Cost Transparency Database that is now underway and will be set up by July 1, 2023. This database will be important to combine with healthcare service data to monitor clinical efficacy and health outcomes to fully understand reimbursement of precision medicine approaches. Given that this is a cross-cutting theme, further discussion is also reflected in the Californians as Partners in Care and Research Chapter as well as the Finance and Cost Models Chapter.

Social Determinants of Health Data

Not only is California a large state with access to many records, the population is also very ethnically and racially diverse. Data shows that health disparities disproportionately impact communities of color and California has made addressing health disparities a key priority (28). Addressing health disparities and achieving greater health equity cannot be done without factoring in the SDOH (29).

The World Health Organization defines the SDOH as the conditions in which we live, learn, work, and play (30). More specifically, the California Office of Health Equity and Let's Get Healthy California suggests: "These conditions include a broad range of socioeconomic and environmental factors, such as air and water quality, the quality of the built environment (e.g., housing quality; land use; transportation access and availability; street, park, and playground safety; workplace safety; etc.), opportunities for employment, income, early childhood development and education, access to healthy foods, health insurance coverage and access to healthcare services, safety from crime and violence, culturally and linguistically appropriate services in all sectors, protection against institutionalized forms of racism and discrimination, and public and private policies and programs that prioritize individual and community health in all actions" (31).

Hospital Innovation, Leveraging Analysis of Housing Data to Improve Health Outcomes

Cincinnati Children's Hospital collects comprehensive data about community conditions in order to improve health outcomes. Cincinnati Children's serves Ohio's Hamilton County, which is characterized by substantial income and health disparities; between 2009 and 2011 children from low-income neighborhoods were 88 times more likely to be admitted for emergency treatment for asthma than students from affluent communities. In the face of such disparities, the hospital began to track admission rates for conditions by neighborhood and identified "hot spots" where incidence of disease was particularly high. It found that high rates of asthma were the product of poor quality housing and partnered with the Cincinnati Health Department and Legal Aid to identify, on the basis of hospital admission records, housing units in need of inspection and improvement. Cincinnati Children's continues to collect and deploy data to address the underlying conditions that are responsible for disease and poor health outcomes. The hospital has taken a comparable approach to injury data to map and gauge neighborhood violence. The director of the hospital's Community Health Initiative summarizes this data-driven approach, "With pattern recognition and good surveillance, you can up pick up patterns about social problems and contribute to the community solving them" (32).

California already collects significant amounts of data through city, county, regional, and statewide programs; transit data, environmental health data such as air quality, housing and homeless data, crime statistics, education outcomes, etc. Collecting data on the SDOH in a systematic, interoperable way would make it far more accessible and enable a precision approach to care. Currently this is not done, but it is possible if a common standard is implemented with a vocabulary that allows for comparison. Many of the major medical groups have encouraged collection of this type of data, including the American Academy of Pediatrics (33), the American Academy of Family Physicians (34), and many others. Likewise, many groups have started to develop toolkits (35, 36). Although tool kits are a start, they do not allow for interoperability nor do they allow for scalability across systems or more comprehensive research. No consistent standards or terminology exist across the SDOH. National groups such as the National Academy of Medicine have brought together expert working groups to look at potential standards, but they have still not widely been implemented (37). Likewise, other groups such as the National Quality Forum have examined the potential of integrating these types of factors into performance measures (38).

Data Storage, Infrastructure, and Security

It is estimated that, on average, a given patient currently has generated several gigabytes of health data, with the primarily driver being imaging. In contrast, a raw human genome sequence can generate 2.5 terabytes. With the dramatic increase of these data, it is important to anticipate what systems will be needed to manage these data in order to unlock new, precise insights.

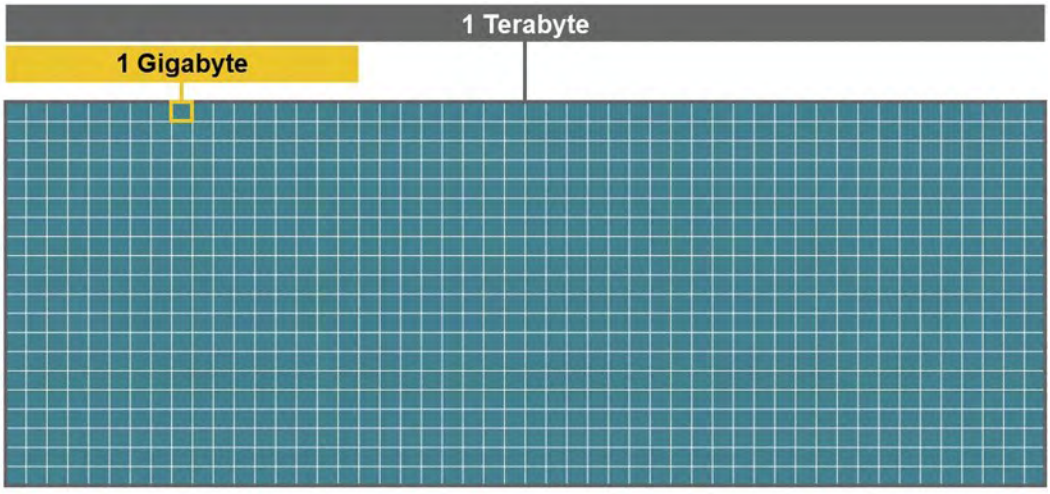


Figure 3: Data storage, infrastructure, and security systems will need to manage significantly more information as each patient increases from several gigabytes to a few terabytes of generated data

Fortunately, there have been improvements in infrastructure. In the early 2000s, data were held predominantly on one's own premises. These data sets were "siloed" preventing broad access and making analysis across datasets challenging. Productivity tools were built for individual and local usage. More recently, cloud-based systems have emerged, allowing for the use of a network of remote servers that can store, manage, and process data, and are instead hosted through the Internet versus a local server or personal computer. With the expansion of cloud-based and hybrid networks, distributed computing is now available providing better support for collaborative productivity tools. Trends show that health systems are increasingly migrating to software and cloud-based solutions to store and protect data (39).

At the national level, efforts are underway to understand how best to manage large amounts of medical data. The NIH Big Data to Knowledge (BD2K) initiative acknowledges that much of the data are not in the correct format (40). With this in mind, there has been a focus on a FAIR approach, which advocates that data should be: Findable, with unique identifiers and effectively labeled within

searchable resources; Accessible, with retrievable open systems and secure authentication and authorization; Interoperable, with the use of standardized vocabularies; and Reusable, with clear information about data-usage licenses and provenance.

As the volume of and access to biomedical data expand, California and the broader scientific community will need to continue to proactively manage a number of challenges and ensure that a trust framework is in place. First, cloud computing, while considered to be cost-effective in many applications, is a significant investment for large amounts of data and analysis. As biomedical data initiatives are contemplated, the storage and computing costs should be considered from the start. Second, the assessment of data quality is critical, and reliable data are a pre-requisite for meaningful analyses. Due to the diversity, breadth, and depth of biomedical data, assessing quality is no easy task, and California could help create the necessary standards. Additionally, health data need to be handled in a secure environment. These data can come from a variety of sources including traditional clinical trials, epidemiologic studies, molecular biobanks, patient reported outcomes, environmental-exposure records, and beyond. For precision medicine projects, data security plans will need to be developed that take into account the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Security Rule and National Institute of Standards and Technology (NIST) health-information security standards. New encryption techniques are also evolving in the field. Overall, there will continue to be a balance to promote broad biomedical discovery while factoring in the costs, quality, and security needed when assessing these data.

As the amount of electronic health data increase, so does the potential for new cybersecurity risks. Although digitizing data is helpful from an access standpoint, it can create new risks from a cybersecurity perspective (41). Healthcare has seen an increasing number of cyberattacks in the last several years impacting millions of people (42). In 2015, the attack on the Anthem health data compromised approximately 80 million health records (43). Stolen health data is valuable on the black market and can actually be worth substantially more to criminals than a social security number (44). There have been a few efforts recognizing the importance of cybersecurity in California. Recently the Governor's Office of Business and Economic Development (Go-Biz) and University of Southern California (USC) released a white paper, "Cybersecurity in Healthcare: How California Business can Lead" (45). This report provides many recommendations the state should take to maintain more secure medical technology and systems. Additionally, GoBiz and OPR through the California Advanced Supply Chain Analysis & Diversification Effort (CASCADE) released a report looking at the labor market to provide information about workforce and training needs to better prepare California for the new cybersecurity threats (46). As more devices (e.g., the Internet of things such as digital refrigerators, thermostats, and digital scales) or other digital devices (e.g., the smart phone) plug into EHRs, there is additional risk. However, with proper planning risks can be minimized and utility maximized for secure access and better use of data.

Data Science and Analysis

The emerging biomedical data need to be analyzed to have impact, and the field of data science is central to this effort. The NIH defines data science as "the interdisciplinary field of inquiry in which quantitative and analytical approaches, processes, and systems are developed and used to extract knowledge and insights from increasingly large and/or complex sets of data" (47). As such, data science will play a significant role going forward; however, it is worth noting that according to a 2016 survey, data scientists in different disciplines said they spend most of their work time (about 80%) collecting existing datasets and organizing the data. Thus, less than 20% of their time is available for activities such as mining data for patterns that lead to new discoveries. As tools continue to improve for data collection and organization, the aim is to further allow data scientists to contribute more robustly to the next generation of precision medicine efforts.

Training this next generation of data scientists will be critical, and California could develop new strategies to lead these educational initiatives. This is further discussed in the Education and Workforce Chapter. The field pulls from computer science, mathematics, statistics, and other

quantitative fields—all of which can be applied to biomedicine. Importantly, having strong grounding in relevant life sciences disciplines will be necessary for data scientists to optimally apply data science in healthcare. At the high school level, data science is gaining traction, and one report estimated that around 30 California high schools now offer data science classes for junior and senior students (48). Likewise, courses at institutions such as University of California, Berkeley are appealing broadly to undergraduates pursuing a wide range of fields (49). There is also recognition that a diverse group of researchers is needed to create the best tools and analytic methods. At the national level, the NIH BD2K Diversity Initiative is underway, and California could continue to build on these types of programs (50).

Now that new systems are available for the collection and organization of data, it is easier to perform traditional analyses on big data sets as well as use the latest AI, machine learning, and deep learning techniques to accelerate precision medicine. The Little Hoover Commission recently issued a report recognizing that AI is already changing society in major ways and now is a time for California to act and lead; the report also highlights the potential in areas such as healthcare (51). In one recent example, researchers from the University of California San Francisco, Stanford, University of Chicago Medicine, and Google collated deidentified EHR records from inpatient and outpatient encounters between 2009-2016 (52). The study included billions of data points, and it generated a representation of the raw EHR records using the new federal standard of Fast Healthcare Interoperability Resources (FHIR). The researchers demonstrated that deep learning methods accurately predicted multiple medical events, including in-hospital mortality and 30-day unplanned readmission, across the centers without using site-specific data harmonization. These models performed better than traditional approaches. Future studies that continue to explore these techniques will be of interest.

California Spotlight:
Artificial Intelligence (AI) for Imaging of Brain Emergencies
Funded by California

Every 28 seconds, an American suffers a catastrophic neurologic emergency, most commonly stroke or traumatic brain injury (TBI). Since the brain is susceptible to irreversible injury within minutes, immediate diagnosis, and treatment are essential. Unfortunately, expertise at the level of board-certified radiologists to accurately interpret CT head scans is not always available in a timely manner, especially in rural areas or busy trauma centers where many scans are happening at the same time. The delay and/or erroneous diagnosis can cost lives. UCSF has implemented AI “deep learning” image recognition technology to rapidly detect sites of bleeding in the CT head scan images. In detection of acute brain hemorrhages, the AI has achieved accuracy with parity to that of board-certified radiologists, and performance continues to improve. An industry partner is working to implement this AI system in the “cloud” so that CT scans can be uploaded for analysis worldwide. Looking forward, the goal is to expand the AI to predict outcomes of TBI and offer better treatment options (11).

California is home to three National Laboratories—Lawrence Berkeley National Lab, Lawrence Livermore National Lab, and Sandia Labs—all of which have access to supercomputing capabilities that do not exist in clinical settings or universities and could be used to accelerate advancement of precision medicine in California. One such example is highlighted by the collaboration between Lawrence Livermore National Laboratory (LLNL) and the American Heart Association. To accelerate drug discovery, the investigators plan to use the LLNL supercomputers to simulate precisely how drugs bind to target proteins. These predictions will be used to generate a number of potential therapies that ideally are more efficacious and safer than alternatives. The idea is to improve personal and population cardiovascular health by speeding up the pace at which drug-protein interactions are identified, prior to the assessment in a clinical trial. Going forward, broad analytic tools derived from a diverse set of disciplines may continue to have applications to biomedical research and precision medicine.

Data Sharing

Data sharing is an imperative in precision medicine. Not only is it essential to have quality data, data needs to be shared in order to generate the kind of analysis and insight that leads to scientific advancement (53). There have been several efforts to try to spur data sharing, but efforts continue to be fragmented. This fragmentation is a challenge to realizing the potential of precision medicine. A qualitative analysis published in Health Affairs examined data sharing lessons for precision medicine. The investigators looked at policy themes in data sharing agreements and found that many of the things for responsible data sharing also are considered barriers (54). Some themes such as autonomy, how participants consent to opt-in, have moved from the previously static form to include many more considerations. Although a potential barrier, there are new opportunities for innovation and more dynamic consent (55). Many of the other themes that emerged such as interoperability, attribution, and accountability highlight the need for ongoing policy conversation. There is a great need for public-private, cross-sector coordination, and innovation in this area. Many partners already exist and California is already working with the World Economic Forum on their international data sharing effort (56). Data sharing models will also be transformed over time and new examples, where participants are actually paid for sharing their data, are starting to emerge (57). These developments may be worth monitoring.

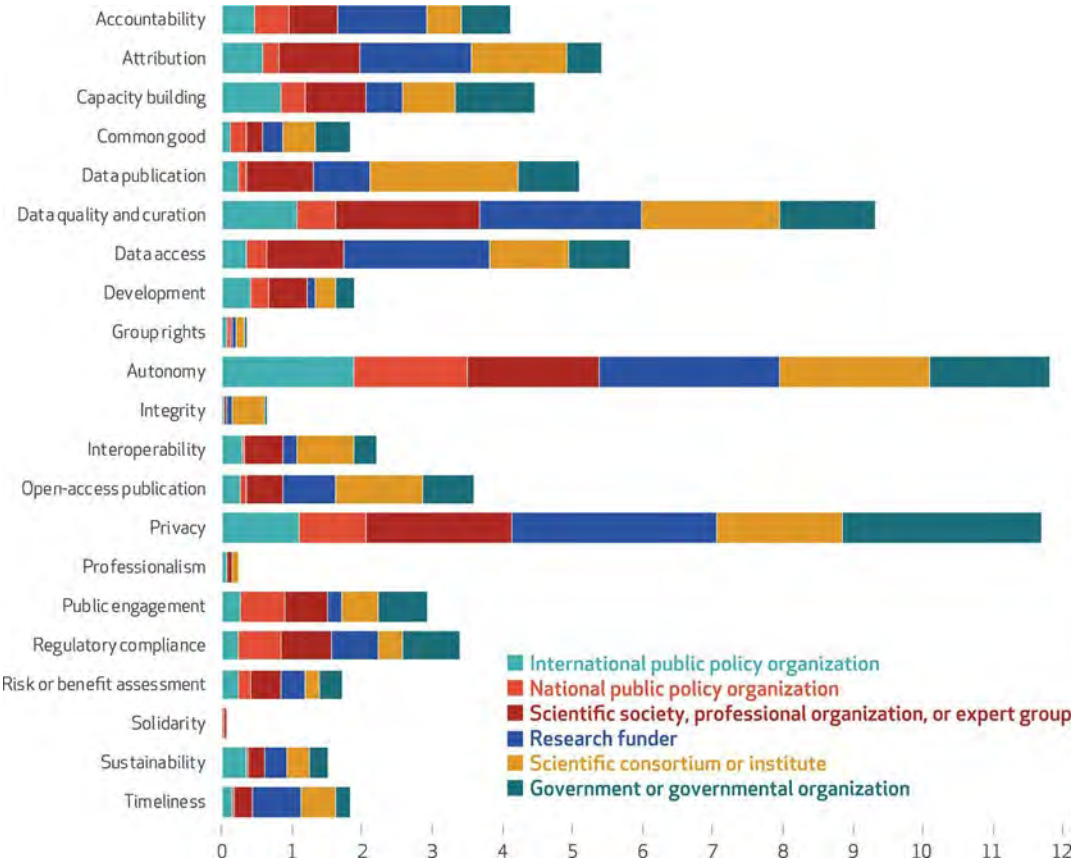


Figure 4: Frequency of References to the Policy Themes in Data Sharing Agreements by Organization Type. While data sharing and use remains a sensitive issue for many stakeholders, and there are many policy themes that emerge in data sharing agreements, there are many motivators that can drive successful data sharing in a safe, respectful manner.

Recommendations

The data landscape is broad with many different issues ranging from the availability of data sources, to how data is stored, to how it is shared. Although the policies in this area have often been

fragmented, there is a great opportunity to provide more alignment. The committee recognizes some things will be able to happen in the short-term, and other efforts will take a longer horizon. These recommendations incorporate many of these ideas.

1. OPR should create a public-private working group to establish standards for SDOH data collection and examine the feasibility of requiring health systems to gather and regularly report on the SDOH. Health systems routinely report elements of race, ethnicity, and age across various care settings, such as emergency rooms. While these are important patient demographics to capture, more data relevant to disease susceptibility and prevention could be obtained if more SDOH were routinely captured during healthcare encounters. There have already been several expert groups convened with several potential standards as reference, but California is uniquely positioned to work with partners to implement this. This would allow for increased research of the SDOH impact on health and disease and for more precise interventions, treatment, and likely prevention.

2. The Legislature should require vendors operating in California to provide Application Programming Interfaces (APIs) to allow health systems to provide broader patient access to comprehensive EHR data. This set of data, including radiology and pathology images and all clinical notes, are currently missing or extremely difficult for patients to obtain digitally from all health institutions in California. We recommend the state go beyond the requirements set forth in the 21st Century Cures Act, and require vendors to provide imaging and clinical notes (i.e. Open Notes) to patients through APIs so patients have greater access to their data.

3. OPR should convene public and private precision health and medicine stakeholders to create cross-institutional data-sharing guidance. As noted above, there is a fragmented policy landscape to support data sharing, cultural shifts need to occur to truly advance this field. It is not due to one specific issue, but many separate issues that need to be considered from multiple perspectives. Access to data is fundamental to advancing precision health and medicine.

4. California's Office of Statewide Health Planning and Development (OSPHD) should incorporate principals of interoperability and enhanced data collection as they build the Health Care Cost Transparency Database. The state should study the feasibility of setting up a tiered access system within the new database to include deidentified EHR data. A large deidentified database of EHR data could serve as: 1) a way to compare standard practices across California health institutions; 2) compliance with best practices and consensus guidelines; 3) an open way to estimate inappropriate care or medical errors; 4) resources to study the comparative effectiveness of drugs, devices, and procedures; 5) training for future machine learning methodologies; and 6) the potential to capture diseases similar to what would be captured in disease registries.

Concluding Thoughts About Precision Medicine and Data

Data are the fundamental inputs for precision health and medicine analysis and understanding. Analyses will ultimately feed back into the learning healthcare system to improve clinical care. When data from genes, proteins, environment, lifestyle, and behavior are evaluated at the same time, the findings will yield unparalleled insights.

Chapter 3: Californians as Partners in Care and Research

Introduction

The workgroup was tasked with: a) identifying barriers to participation in precision medicine research; b) promoting ways to empower both healthy Californians and patients to be partners in their healthcare, including having access to health information and providing tools to freely share their data; and c) ensuring protections for research participants. Note that although equitable access to precision medicine advances is a critical issue for patients, it is best addressed in the economic discussion later in this report.

Improving healthcare and outcomes requires greater integration of patient perspectives into care delivery and research (58). At a time when clinical trial participation is at a low point, the inclusion of women and underrepresented minorities in biomedical research is meager (59), and real-world data is increasingly easy to capture, the committee believes it is essential to view patients as partners not only in their own care, but also in medical research. This will require a cultural shift towards shared decision-making between patients and healthcare providers, along with the development of the critical infrastructure that is required to integrate real-world data into research trials, give patients more control over their own health data, and maximize data sharing among researchers.

In today's digital age, the Internet, mobile apps, and social media have emerged as important tools for engaging patients in clinical research (60). These tools offer patients many opportunities to participate in research trials with a significant reduction in burden on patients such as transit to extra appointments. Instead, through technology, healthy participants and patients can collect data remotely. These tools are increasingly integrated into clinical trial recruitment and protocol design. California can leverage its technology industry to significantly accelerate the pace of research in more cost-efficient and secure ways. Leveraging the state's undeniable strengths in both technology and healthcare will position California to become a driver of innovation within the precision medicine ecosystem.

Key Issues

Need for Patient-Centered Care

Healthcare is at an inflection point in terms of our collective understanding of health and disease. For far too long, the medical system has approached illness from a more formulaic perspective without accounting for the patient's experience. The health system and treatment plans often do not account for the patient experience or holistically address quality of life and/or longevity when patients are struggling with challenging health situations, like living with a chronic disease such as multiple sclerosis or undergoing cancer treatments. PatientsLikeMe (61), a patient social network and online medical research platform, conducts research and works with healthcare stakeholders to achieve better, more patient-centered outcomes and improve quality of life. In over 120 ethnographc interviews conducted by PatientsLikeMe, patients reported that they too often experience a healthcare system that tries to fix a disease, rather than really addressing the patient's experience of the illness and truly meeting their needs (62). When patients have a health problem, they experience multiple barriers to getting well, including:

- Months or years of trial-and-error to find the most tolerable and effective treatment. This is largely due to imprecise understandings of disease, particularly in mental health conditions and other chronic diseases.
- Insurance coverage rules may require that patients "fail" first-line therapies before others are covered; these are sensible rules at the population level, but can place tremendous suffering and cost burdens on individual patients.

- Patients' quality of life goals may not always align with clinical definitions of success, but providers have little time to understand each patient's preferred outcomes. Outcome-based incentives may punish providers who focus on the sickest patients or who prioritize quality of life over months of survival.
- Multifaceted health, access, and environment issues may mean the obvious medical intervention is not the most appropriate. Providers and public health organizations lack the tools to recognize and address non-medical root causes.
- Because patient health data exists in silos owned by provider organizations, patients and providers may not have access to complete and accurate data when and where they need it. In the view of patients, this can make the current practice of medicine anything but precise.

Given the tools and increased insight into health and disease, precision medicine offers tremendous opportunity to more fully engage healthy participants as well as patients to help address many of the barriers and challenges highlighted from the ethnographic study. Precision medicine offers the ability to understand and reduce individual risk for developing various health concerns. This can support better decision-making about where to focus prevention efforts. It is well recognized that behavior change is an important aspect of many treatment plans, and also one of the most difficult. Through increased data and real time feedback, there is the potential to support more individualized behavior change that is more suited to the individual rather than a generic education program. Additionally, rather than the trial and error of therapies that are often experienced, precision medicine approaches, based on biological drivers, should be able to provide earlier diagnosis, preventing months or years of provider visits and tests, and can lead to earlier treatment and prevention of complications. Not only is there a potential to provide an earlier diagnosis, there is great potential to predict, based on use of large data sets, which intervention is most likely to achieve the desired outcomes with the fewest side effects. This has the potential to save treatment costs as well as reduce suffering and complications.

However, for any of this to happen, healthy participants as well as patients will need to be authentically involved in patient care and research. There are still many barriers that prevent this from happening. Today, patients have many reasons not to participate in research, including a lack of awareness, concerns about health or privacy risks, burdensome study designs, and logistical and financial concerns. In a survey of almost 6,000 patients, 37% thought their care would be worse in a clinical trial (63). For many patients, especially those from underserved communities, there is a feeling of having been taken advantage of or simply forgotten once the study is over. This is particularly relevant when patients do not derive any immediate benefits and there is no follow-up or communication regarding study findings (64). Those patients who do share their data may be frustrated if they believe researchers do not share it widely to maximize the potential benefit.

California Spotlight:
NeuroSHARE: Precision Medicine for Multiple Sclerosis
Funded by California
Sutter Health and the University of California, San Francisco (UCSF) partnered to take precision medicine for multiple sclerosis (MS) from "the bench to the bedside." As research accelerates and medical knowledge grows, doctors and patients need to keep up. The neuroSHARE application ("app") was designed to combine the latest medical knowledge and data with input from patients, in a single place. Input for the app was informed by a patient-centered design approach that brought together patients, designers, clinicians, and researchers. The goal was to make it easy for doctors to use so they could provide the best and most precise care for those with MS. The app collects and combines the latest data in real time and displays it during the patient's appointment: comparing the patient's disease progression and treatment response to others with MS. The neuroSHARE app brings precision medicine to the patient, whether that is at a top-ranked medical center or a small rural clinic (11).

In a recent report from the National Institute on Minority Health and Health Disparities (NIMHD), data were gathered from listening sessions with a variety of participants across the country, including significant numbers from community-based organizations, to inform the NIH-wide minority health and health disparities strategic plan (65). Similar efforts to include patient perspectives have also informed the All of Us Research Program to ensure that all voices are heard and represented in community engagement strategies (66). Some key messages that have emerged from community stakeholders across these national platforms include the importance of obtaining and maintaining community trust, removing barriers from participating in precision medicine research, an increased focus on the SDOH, data ownership and security, and privacy protections for meaningful use of genetic information. A need for greater transparency and communication in research was also highlighted, as was the importance of community-based participatory research, which includes community members as equitable partners and collaborators throughout the research process (67). Not surprisingly, the value proposition also emerged as being critical for participation in precision medicine research: participants want to know studies will deliver value to them personally and to the research community more broadly.

Need for Improved Access to Data

There is mounting evidence demonstrating that when patients and healthcare consumers have more access to their medical data, they are more engaged in their care and can make better decisions about treatments and health behaviors (68–70). This, in turn, yields better outcomes and lower healthcare costs (71). Various federal initiatives have attempted to increase patient access to data, both through legislation (e.g., HIPAA) and online tools, such as health portals, the Veteran Affair's Blue Button program or mymedicare.gov access to claims data. However, these well-intended programs continue to have limitations. As noted in the Office of the National Coordinator for Health Information Technology Policy Brief entitled "Individuals' Access to their Own Health Information," (72) some patients as well as providers still remain unaware of the individuals' right to access. Moreover, HIPAA regulation requires providers to make data available within 30 days, which is often not a reasonable timeframe for making treatment decisions. Additional challenges include format and compatibility challenges in getting data out of EHRs and into a format that is readable and accessible to patients. Furthermore, when patients use personal health records not owned by HIPAA-covered entities, their privacy may be at risk.

A 2016 consumer survey by Accenture on patient engagement revealed that most patients surveyed wanted *full* access to their electronic medical record, whereas physicians only wanted them to have *limited* access (73). The majority of physicians, however, did agree that patients should have the ability to modify some of the data in their EHR including demographic information, personal medical history, current medications, new symptoms, adverse events, and when available, additional surveys about the SDOH. Consumers and physicians both agreed that wearable technology could also increase patient engagement. However, there are technical and privacy challenges that make it difficult to integrate these data into EHRs. Interoperability and timeliness concerns interfere with patients' ability to see their own data and share it with other providers in a timely fashion. Likewise, the lack of standardization and

Recommendations

Based on these themes, as well as the committee's work directly with patients, the committee recommends focusing on six areas with the potential for both immediate and long-term positive impact for precision medicine to develop in a way that is responsive to health participants and patients. To do this, the committee believes it is important to make patients stewards of their own data. Additionally, there needs to be an ecosystem for patients, providers, and researchers to share data. The emphasis needs to be on patient-centered outcomes and continuing to address the SDOH and non-medical interventions that could improve quality of life for patients. Lastly, breaking down barriers to research participation and providing incentives that are meaningful to patients will be necessary to move this emerging field forward.

1. Through legislation and incentives, California should reduce barriers for patients to obtain and share their data and correct errors in their electronic health records. For EHR data to be truly leveraged for precision medicine research, the data have to be accurate. Today, healthcare institutions see themselves as the owners and stewards of patient data. Although providers are required by law to give patients access in accordance with HIPAA regulations, a combination of poor systems, misunderstood regulations, and healthcare that has historically not focused on designing patient-centered systems means patients spend days or weeks to get complete copies of their own data. Patients have limited visibility into whether their own records are accurate, and have little or no ability to correct them. As a result, providers in emergency settings or outside of the primary care system may treat patients with incomplete or inaccurate records, and patients may need to delay second opinions and treatment decisions while waiting on records. Accurate records create accurate data for analysis and insights into precision medicine.

The legislature should clarify and/or build upon the existing federal framework of HIPAA and HITECH to require that Californians be able to: 1) see medical data about themselves, including data collected as part of a clinical trial, within a specific, reasonable timeframe, balancing costs for production; 2) allow for modification corrections to their medical data, to ensure that providers have a complete picture before treating; 3) share their online data with any provider, regardless of the brand of electronic health record system in use by the provider; and 4) consent to share any subset of their data for medical research, either broadly or for specific studies (and withdraw consent if they wish to do so). Proprietary study data outside of typical care may be subject to some limitations for research.

2. As recommended in Chapter 2, "Data in the Context of Precision Medicine," which would have OSHPD incorporate interoperability and enhanced data collection in the Health Care Cost Transparency Database, the committee recommends that the database incorporate patient registry data for a cohesive and connected system. Over time this database would be able to serve multiple integrated functions and ultimately advance precision medicine research. California Health and Human Services Agency along with the California Office of Health Information Integrity could conduct further assessments to determine how consent, study recruitment, and participation by individuals and researchers could be realized through the build out. Although complex, this expanded ecosystem would make California a uniquely appealing place to conduct precision medicine research by offering better access to patient data for research as well as more efficient and targeted study recruitment.

3. OPR should name a public-private working group to study the feasibility of a California Patient Record. This can include looking at different types of incentives that enable the patient and providers to contribute to and have immediate access to medical records in order to serve patient care delivery needs first, and can be expanded upon to provide unique access to research participants and data. This recommendation further builds off the data recommendation to increase API access. To facilitate patient control of data and ensure quality of care wherever and whenever Californians need it, California should support incentives to enable the development of a statewide patient record that gives every Californian a unique identifier and immediate online access to their complete medical records, with the ability to contribute their own data and share with any provider. Participation would ideally be required for healthcare providers and study sponsors, though this could be phased in through incentives. This would improve the accuracy of clinical data and empower patients to be partners in their own care, both of which should improve patient outcomes.

4. OPR should work with public and private partners and academic research institutions across California to develop a model consent framework and education toolkit, and explore incentives for adoption. This group should coordinate with the group established to work on data sharing. A critical aspect of the study experience is informed consent. Informed consent is often cumbersome and uninformative for patients; many still do not understand the risks of sharing their data, for example. In addition, many research studies do not effectively explain consent, and may not use entirely patient-centered consent terms. For these reasons, California should:

- Develop a model consent framework that covers issues including unanticipated future studies, withdrawal of consent, and use of new data sources.
- Pilot a universal electronic consent that explains the process and implications (e.g., via diagrams, videos, etc.) in a culturally and linguistically competent way.
- Develop consumer-friendly explanations of common risks, such as learning things that affect one's identity, consequences of data exposure, and similar issues. This content should be tested with patients to refine and standardize it.
- Define any consent (or absence-of-consent) practices that are unacceptable for studies performed in California, while minimizing unnecessary deviation from federal norms.
- Make it possible for patients to see how medical data are being used and consent for the usage of their data.

5. The Governor's Office should work with its federal partners, who fund the majority of research, to promote participant-centered study design. If more Californians are going to participate in medical research, the state should support researchers in creating more participant-centered study experiences. This could be addressed via several different potential mechanisms:

- Create content and tools (such as an online resource library) to educate study sponsors and researchers about participant-centered trial design. Many of the issues that make research studies frustrating for patients are solvable with common user-centered design and marketing techniques.
- Incentivize patient involvement in protocol and patient protections design.
- Share lessons learned from the California precision medicine projects that have statutory guidance and actively promote patients as partners.
- Adopt minimum standards for patient-centered studies, including access to results and ongoing access to study medication to the extent feasible with current federal law.

6. The University of California in partnership with other health systems should create programs to promote an understanding of and access to research participation. California is fortunate to have the University of California system where many cutting-edge trials are conducted, but not all Californians live near an academic center. To encourage broader research participation, the University of California in partnership with other health systems should:

- Partner with private companies for virtual and remote access; e.g., mobile phlebotomy vendors, home sample collection, apps, wearables.
- Seek grant funding to minimize the burden of patient participation, including addressing issues related to the SDOH.
- Develop a research marketing campaign aimed at Californians, especially those groups who tend to be underrepresented in research, to "make your experience matter." Such a campaign should promote the benefits of research and address common misconceptions, such as "experiments" vs. the best care, or trust issues in certain communities.

Concluding Thoughts About Precision Medicine Designed for Californians

California's diverse population and abundance of qualified researchers make it an attractive destination for precision medicine investment. Most importantly, California's investment in, and regulation of, precision medicine must serve the people who live here. It is essential to recognize

that for patient care to be individualized and more “precise,” it must start with a complete and accurate understanding of the patient, which is nearly impossible with today’s fragmented and provider-centric approach to health records. We must move beyond today’s disease-centric interventions towards precision care.

Chapter 4: Education and Workforce

Introduction

The Education and Workforce development workgroup was charged with addressing the implications of precision medicine and health disparities on workforce development and proposing strategies to train the workforce required to foster a precision learning health system. By providing the necessary interdisciplinary training to all types of healthcare providers at all ages and stages of their career, the proposed recommendations aim at developing a healthcare system that utilizes data to optimize the delivery of healthcare in a patient-centric manner.

Education as a Powerful Strategy for Advancing Precision Medicine in California

Precision medicine promises to thoroughly transform medicine, ranging from how individuals manage their own health, how healthcare practitioners diagnose and treat their patients, to how medical scientists understand health and disease and determine what works best for whom. Such a fundamental change in the practice and science of healthcare will require a major overhaul in how we train our healthcare workforce. Education of healthcare professionals is no longer separate from the clinical care delivery systems, and the continuum of training must reflect a continuous competency-based learning environment. To maintain California's leadership in health sciences and education, we need to build a strong, forward-looking statewide precision medicine educational program.

The need for new educational strategies guided by precision medicine is evident when we consider the ways in which precision medicine has (and will) transform medicine. At the most basic level, there has been a vast explosion in the amount of data and the types of data available to healthcare providers. Fueled in large part by advances in computing power, biomedical technology, and the digitization of clinical data, healthcare professionals (and clinical and translational scientists) have an unimaginable ability to better define both disease and its specific treatment for both individual patients and for population health. These powerful new data technologies, combined with equally powerful biotechnologies, allow clinicians to dig much more deeply into the multitude of factors likely to affect their patients' health and to better predict the outcomes of treatment. The sources of data that clinicians either have now or will have in the near future include EHRs, genetic/genomic sequencing, biomarkers, activity tracking, and biochemical information from health sensors, imaging, and environmental and socioeconomic information. However, there is a need to ensure that clinicians are able to interrogate these data in ways that are meaningful and clinically actionable so as to not be overwhelming. The data will need to be provided to patients, families, and populations in packets that are understandable and form the basis for patient engaged care plans. The development of novel technologies that leverage AI to train and evaluate physicians from the emergency room to the operating room could provide quicker and more objective measures of skill, fatigue, hand sanitation, and other important factors that can ultimately impact patient care (74). The pathway from data to information to knowledge will require nontraditional multidisciplinary teams of data scientists, clinicians, and researchers and patient/community stakeholders to better understand the broader determinants of health and disease and the population effects of treatments, and evaluate what modalities of treatments work best for whom and under what circumstances.

In fact, precision medicine offers a powerful set of tools for addressing disparities, but also unprecedented risk for ethical lapses without keen attention and purposeful education. Through the linkage of socio-demographic data to health status and outcomes, we will be able to document disparities more precisely and, using the analytic tools of precision medicine, develop sustainable models to ensure that precision medicine is not just an option for a small percent of the population that can afford it. The policy implications—including the structure of health systems, the reward and reimbursement mechanisms, and the potential for discrimination in this area—are significant and addressing them effectively will benefit from educational strategies that include an emphasis on

community engagement, policy, and advocacy. The United States pays more for healthcare than any other nation and yet has greater health disparities and social inequity (75).

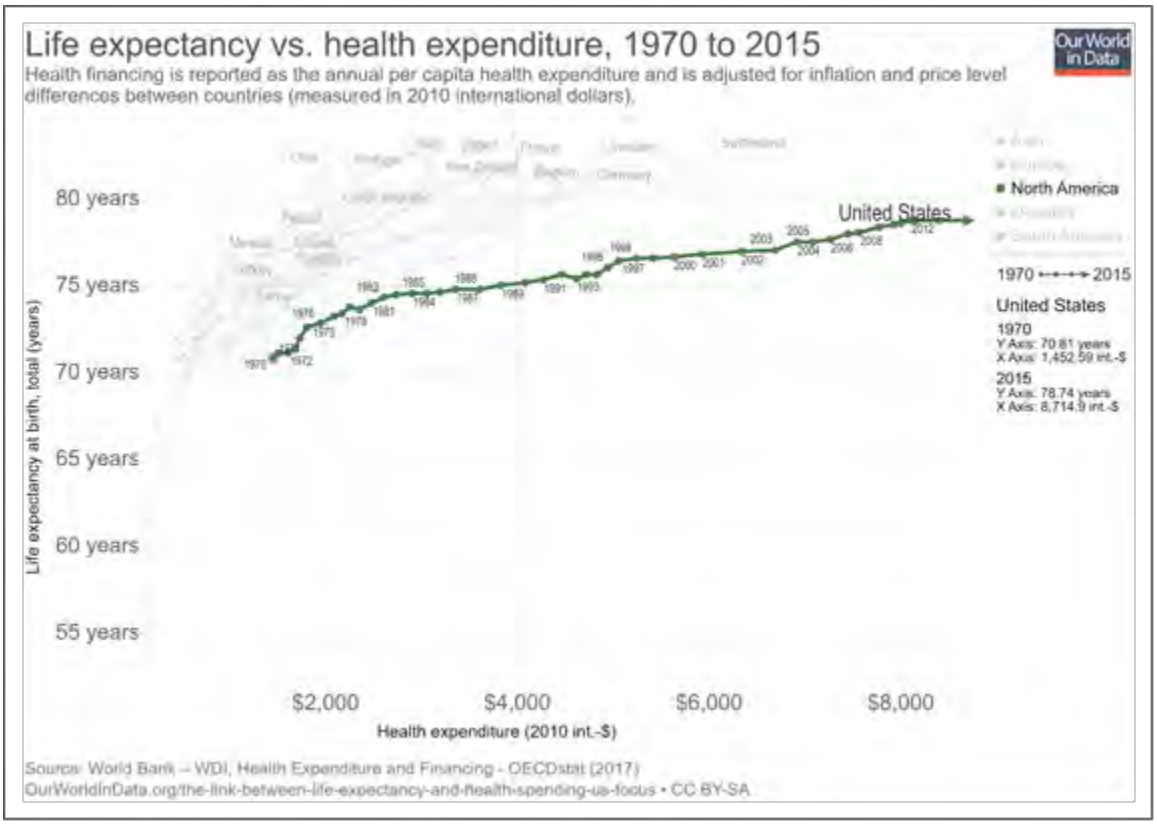


Figure 5: The United States pays more for healthcare than any other country yet has shorter life expectancy outcomes when compared with other developed nations.

Within Los Angeles County alone, there is a 15-year variance in life expectancy, including an 11-year difference between neighborhoods that are only two-miles apart from one another (76). The mental health community has long been aware that patients with significant mental health issues have a life expectancy 25 years less than the general population. The committee was aware that one must ask the right questions in order to begin to solve some of these problems of inequity. Precision medicine in and of itself will not solve these issues without a conscious effort to develop new strategies to create social awareness and trust, while optimizing utility and adoption in highly resource-constrained settings.

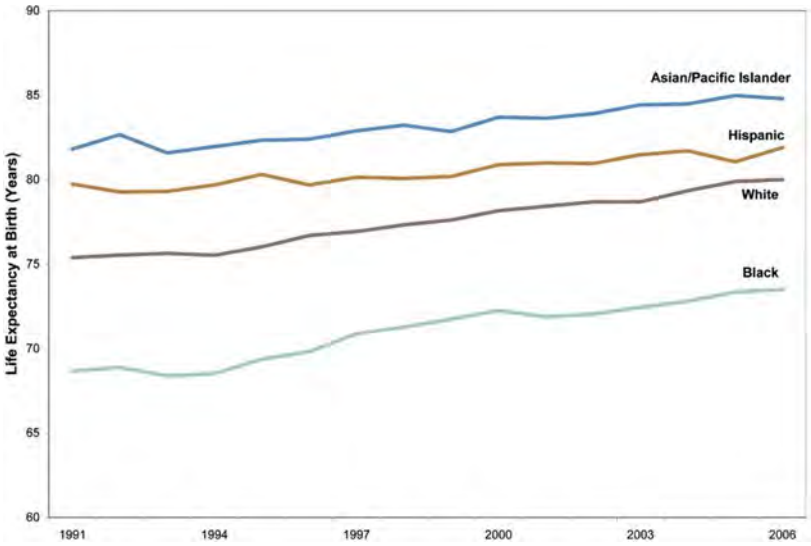


Figure 6: Life Expectancy in Los Angeles County by Race/Ethnicity. Life expectancy in Los Angeles County varies across populations. Image Source: Los Angeles County Department of Public Health, Office of Health Assessment and Epidemiology

With these considerations in mind, the committee decided to address workforce needs in precision medicine, including new models for training individuals entering the workforce as well as for retraining an existing workforce that is ill-equipped to handle the onslaught of information generated from these new paradigms (77). Training programs must have an educational emphasis on addressing inequality in healthcare and empowering patients as partners in research so that precision medicine is as much about improving individual health as it is about improving the health of all Californians. Initial focused efforts may be necessary before large-scale implementation.

California as Leader in Healthcare Education

California is a national leader in healthcare education and, as such, has a particular obligation to lead education in precision medicine. This is particularly the case in training physicians. In 2018, over 15% of all U.S. medical students were trained in California and, of these, 60% were enrolled in University of California medical schools (78), highlighting the role of the state in medical education. California is second in the nation (after New York) in the number of medical residents and fellows and leads the nation in residency retention, with 77.7% of residents remaining in California to practice medicine after Graduate Medical Education (GME) training (79). These physicians-in-training receive their training in the nation's top hospitals: California is home to four of the top ten hospitals in the United States as ranked by U.S. News and World Report in 2018 (80). Of note, it is the only state that has more than one hospital in the top ten list, and two of the top-ten ranked hospitals are part of the University of California system.

California is equally active in the training of other health allied professionals, with 142 pre-licensure nursing programs enrolling over 13,000 new students each year (81), NP training programs graduating nearly 1,800 NPs each year (82), and 15 Physician Assistant (PA) training programs graduating nearly 400 PAs each year (83). Indicative of the importance of these allied health professions, the Healthforce Center at the University of California, San Francisco (UCSF) has estimated that by 2030, NPs and PAs will comprise nearly half of California's full-time equivalent (FTE) primary care clinicians (84).

California as a Leader in Data Science, Engineering and Biotechnology Innovation

California is also a pioneer in the data science, engineering, and biotechnology disciplines that are critical to precision medicine. More advanced degrees are awarded to students in the sciences, engineering, technology, and mathematics in California than in any other state. Many of these

graduates then join California's robust technology and biotechnology industry. The birthplace and epicenter of information technology, California also leads the nation in the biotechnology industry, housing more than 3,200 life science industries, including nearly 1,800 device and medical equipment manufacturers (85). These industries are developing the technologies—from health sensors to data analytics—that advance the field of precision medicine. California also leads the nation in biomedical research, capturing $4.16 billion of funding from the NIH in 2018, representing 15.4% of all NIH funding (followed by Massachusetts, which receives 10.5% of NIH funding). The University of California system alone received $2.14 billion of grants, which at 8% of the NIH extramural budget is the leading institutional recipient of NIH awards in the country (86). A significant component of NIH funding is tied to interdisciplinary career development, including the National Center for Advancing Translational Science (NCATS) Clinical and Translational Science Awards (CTSA) and the National Cancer Institutes (NCI) Comprehensive Cancer Centers. As highlighted previously, the five UC campuses that have CTSAs and Cancer Centers have come together to form the UC Biomedical, Research, Acceleration, Integration and Development (UC BRAID) and the UC Cancer Consortium. These statewide NIH-funded programs can be leveraged to benefit precision medicine training in California.

Given its dominance in the central disciplines that underlie precision medicine, from data sciences to biosciences to clinical care, California is in an ideal position to take a proactive and leading role in educating the workforce for the future of precision medicine. Statewide educational programs in precision health also promise to have significant economic impact: according to the U.S. Bureau of Labor Statistics, of the top 20 fastest growing occupations nationally, 9 are in healthcare and another 3 are in data science and technology fields critical to precision medicine (87). As important as data science is to precision medicine, it is equally important to train healthcare providers to think in new ways, with new forms of evidence, and to think about the forces that impact their patients' health and disease.

Key Issues

Preparing the Future Precision Medicine Workforce

Many studies have indicated that developing a pipeline in healthcare before college is key to modernizing and diversifying the healthcare workforce. California is already home to many innovative training programs that expose high school students to careers in healthcare. A handful of examples include: the California Health Occupations Students of America (Cal HOSA) program, the state chapter of a national leadership and training program in healthcare careers for middle and high school students (88); the California Department of Education Health Careers Education program, which provides grants to K-12 California schools for the development of curricula that encourage students to consider careers in healthcare (89); the Stanford Summer Math and Science Honors (SMASH) Academy for underrepresented minority high school students, which includes a medical curriculum (90); and the Allied Health Careers Program at University of California, Los Angeles (UCLA), a partnership with Los Angeles Unified School District (LAUSD) high schools that teaches high school students about the array of allied health careers, and brings a cohort of students to UCLA Health for a hands-on introduction to these careers (91). These types of programs are complemented by recent programs that introduce high school students to the field of big data science, e.g. a National Science Foundation funded partnership between UCLA and LAUSD called Mobilize Introduction to Data Science, which features a year-long course in data analysis and programming, including training for LAUSD teachers (92). Together, these programs contain the elements that would be required to introduce a diverse population of high school students to careers in precision medicine.

Training the Next Generation of Data Scientists

As highlighted in the Data in the Context of Precision Medicine Chapter, data science has now emerged as one of the most important disciplines required for precision medicine to advance. The

enormity of data that will be generated will require a very skilled workforce that can manage the breadth of clinical, imaging, and other biological data sources. Californian colleges and universities are only now developing training programs to support this burgeoning field.

California is home to over two million college students, 74% of whom are in public colleges, including California Community Colleges (44%), California State Universities (18%) and the University of California (12%) (93). College campuses provide tremendous opportunities for training the next generation of healthcare providers in precision medicine. In recent years, many of these campuses have pioneered bachelor and master's degree programs in data science. It is illustrative of the emergence of data science studies on college campuses that the fastest growing class at UC Berkeley is "Introduction to Data Science" (94). In what UC Berkeley administrators have described as their biggest reorganization in decades, the campus recently announced the formation of a new Division of Data Science and Information (95). The rising interest in data sciences on college campuses has been accompanied by an increase in pre-health baccalaureate programs, which have more than quadrupled in number in the United States since 2000 (96). These programs prepare college students for a variety of careers in healthcare rather than for a single professional school. Providing data scientists with opportunities to train alongside students enrolled in other science, technology, engineering, and mathematics (STEM) programs (e.g., human genetics, genetic counseling, biostatistics) will foster a multidisciplinary team-based approach to translational research and clinical medicine. Furthermore, most public and private institutions in California have established leading Centers for Precision Health and Medicine. Those centers should include clear pathways for research career development, workforce development, and education of patients as part of the precision medicine workforce, more broadly.

Leveraging Gap Years to Incentivize Young People to Consider Careers in Computational and Biomedicine

Gap years before, during, or after college have become increasingly popular in the United States. In a recent perspective from the Journal of the American Medical Association, *Training the Workforce for 21st-Century Science*, Jeremy Berg, Freeman Hrabowski and Elias Zerhouni (former director of the NIH) argued for the creation of a "health-science corps for the 21st century" (97). In the tradition of the U.S. Peace Corps or Americorps, the goal would be to attract and train would-be scientists hoping to contribute to improvements in health.

Summer internships also provide a valuable opportunity for college students to learn about precision medicine. One strong example is the UCSF OptumLabs Summer Internship program for students from UC campuses to participate in a summer internship that trains them to apply data science to biomedicine and healthcare (98).

California could see immense value in a Precision Medicine Corps for high school and college students in which they spend time in varied settings (e.g., a rural healthcare delivery setting, a healthcare payer company, a hospital ward or clinic, an information technology company). The goal of this program would be to expose future precision medicine workers to the full landscape of fields and factors that must be integrated to create an effective statewide precision medicine program.

Patient Education and Counseling

While there are many areas in which masters-level educational programs would benefit the future of precision health, there is an urgent need to train more genetic counselors in the era of precision genomic medicine. Genetic testing laboratories and pharmaceutical and biotechnology companies are recognizing genetic counselors as an important subject matter expert they need in order to contribute to their success. Communicating effectively with patients about genetics and genomic medicine is a focus of genetic counselor training. This focus allows for a wide variety of opportunities in this rapidly expanding field.

It is not surprising that Genetic Counseling has emerged as one of the fastest growing professions according to a recent report by the U.S. Bureau of Labor Statistics, which predicts a 29% growth rate for genetic counseling jobs between 2016 and 2026 (99). This represents a significantly faster rate of growth than the average rate of 7% across all occupations. In 2017,

U.S. News and World Report ranked genetic counseling as one of the top 15 healthcare support jobs in the country based on the increased hiring demand and projected job growth (100). At present, California only has four accredited master's programs in Genetic Counseling, graduating just over 100 students each year, an insufficient number to fill open positions in the state. Genetic counseling programs are now incorporating coursework in bioinformatics to help prepare students to understand how exome/genome data are generated, analyzed, and interpreted. This cross-training will help establish them as critical partners in the precision medicine ecosystem.

As mentioned in the Californians as Partners in Care and Research Chapter, educating patients about research, and empowering them to serve as vehicles to disseminate information through their own social networks, is a critical part of the precision medicine ecosystem. In underserved or rural communities, the Promotora-model offer culturally appropriate and effective ways to reach Hispanics to reduce barriers and improve access to screenings such as for cancer (101). Patients also need to understand the benefits and risks of participating in research, especially genetic research, and the protections that are in place to protect patients while participating in research trials. Web-based educational programs are emerging as tools for educating patients across a variety of areas in medicine (102) but more rigorous comparative effectiveness studies are required to determine how effective they are in improving target outcomes. Precision medicine programs should create libraries of web-based educational materials for patients, and interventions should include strategies to reach rural and underserved communities using evidence-based models that are culturally appropriate.

Retraining the Existing Workforce

One of the things that precision medicine has brought to light is a healthcare workforce that's ill-equipped to meet the increasing needs of patients in this new era of genomic medicine.

The state of California is home to 139,000 licensed physicians (103), a third of whom are over the age of 60 (104) and a majority of whom were trained well before the advent of data sciences and precision medicine. Under California law, physicians and surgeons are required to complete a minimum of 50 hours of approved continuing medical education (CME) during each biennial license renewal cycle (105). The goal of this legislation is to ensure that physicians and surgeons are as competent and well-informed about modern medical practice as possible. The California Medical Licensing Board must approve all CME training programs. The University of California campuses have come together to create a consortium of CME programs called CMECalifornia (106). This provides a unique opportunity to develop courses to educate physicians in primary and specialty care about precision medicine, including the utilization of genetic and genomic medicine.

Retraining is also essential for other health professionals. For example, there are approximately 396,000 registered nurses licensed in California, of whom 22.3% are over the age of 60 (107). Of California's 20,000 NPs, more than 30% are 55 years of age and older (108). In addition, there are 16,700 licensed psychologists, 31,350 licensed marriage and family therapists (LMFTs), and 1,200 licensed professional clinical counselors (LPCCs) in California. Approximately 37% of active psychologists and 17% of active behavioral health counselors are over the age of 60 (109). As with physicians, California law requires registered nurses and licensed behavioral health specialists to complete approved CME for their biennial license renewal. Nurses must complete 30 hours of approved CME for their license renewal (110). Psychologists and other mental health specialists generally must complete 36 hours of training (111,112).

Recommendations

Based on the above considerations, the committee's recommendations are aimed at developing a statewide precision medicine educational program that is: 1) inclusive of new disciplines; 2) fosters interdisciplinary work; 3) prepares healthcare providers for adaptability as new technologies emerge in the future; 4) empowers community members to be equal partners in training and dissemination through their social networks; and 5) effectively promotes health equity within our state. We divide these recommendations into workforce development at different ages and stages of training. The committee's recommendations focus on the training of healthcare providers, but complementary approaches that focus on education of research scientists, data scientists, and engineers will also contribute importantly to the future of precision medicine in California.

1. The committee recommends that California colleges and universities develop interdisciplinary health informatics and precision medicine training programs that integrate the expertise available in healthcare, engineering, biomedical sciences, social and environmental sciences (focused on ethical issues, social policy, social, and environmental determinants of health), and data sciences. The focus of these programs should be on the interdisciplinary fields that underlie precision medicine with opportunities for all providers such as medical assistants, nurses, NPs, PAs, pharmacists, and physicians. While state funding can incentivize the development of these programs, they will likely also attract funding from private industry since the programs will provide a trained workforce for healthcare and precision medicine industries.

2. The committee recommends that the Legislature invest in the development of additional masters programs in Genetic Counseling to meet future workforce needs. In 2016 there were approximately 500 job openings for genetic counselors for 250 graduates signaling the beginning of a new era in genomic medicine. The development of new genetic counseling master's programs in the UC system speaks to the demand for genetic counselors to be trained in California. To put this in perspective, while the University of Arkansas-Little Rock campus receives between 30-40 applications each year for 4-7 slots (113), the UC, Irvine genetic counseling master's program received >130 applications in each of the past 3 admissions cycles (for Fall 2015, 2016, 2017) for 4-6 slots. In the most recent cycle (Fall 2017), they received >150 applications (114). Meanwhile, 103 of the students matriculating into the 378 slots (27.2%) available across the 40 genetic counseling master's programs in Fall 2017 are California residents, demonstrating not only demand among California residents for training in genetic counseling, but that these applicants are highly competitive applicants.

3. The committee recommends that academic programs in California institute new admissions requirements for medical, nursing, and PA training that include courses in data science (in place of prior requirements for mathematics/calculus) and in social sciences that are relevant to understanding the SDOH. As described above, California is a leader in training healthcare providers. The current challenge is to determine how to refine their training to prepare them for practicing in an era of precision medicine. Two major areas of importance that emerged from our discussions were the need for greater training in: 1) data science; and 2) the SDOH. Specifically, the committee would like to highlight that future healthcare providers need to be trained in working with large amounts of data—to assess the quality of the data and to understand how to apply them to their practice. In addition, healthcare providers need to have more in-depth training in the social and environmental contributors to health in order to provide accessible and affordable healthcare to everyone in California.

Given the popularity and the number of medical, nursing, and PA training programs in California, this change in prerequisites would have a national impact on future healthcare providers. The committee also recommends that medical, nursing, and PA curricula incorporate training in health analytics and

in the cultural competency/SDOH. As one mechanism to enforce this training, the California Medical Licensing Board could mandate it as part of medical training in the state of California.

4. The committee recommends that California's 72 GME-sponsoring institutions work with the Accreditation Council for Graduate Medical Education (ACGME) to design and implement novel residency and fellowship programs in clinical informatics, genomic medicine, and bioengineering. GME, the training of residents and fellows, provides a unique opportunity to have a near-term impact on the practice of precision medicine in California. Residents and fellows are at the end of their medical training and about to begin decades long careers as medical practitioners. As such, incorporating the disciplines that advance precision medicine into their training will be impactful in the near future. In the field of clinical informatics, there are currently 32 accredited fellowships in the United States (up from 21 in 2016), six of which are in California (115). These fellowships introduce clinically trained residents and fellows to the field of clinical informatics and serve as an example of the interdisciplinary training that will impact their clinical practice. Since California leads the nation in retaining residents and fellows in state, these individuals are likely to contribute to the industry and practice of precision medicine within our state. These programs would expose clinically trained individuals to the fields of data sciences, genetics and genomics, and to fields of engineering that will give rise to novel healthcare devices and sensors. Such fellowships should be designed as interdisciplinary programs that simultaneously expose data scientists, geneticists, and bioengineers to clinical medicine.

5. The committee recommends that the California Medical Licensing Board and CME California invest in a curriculum of CME courses that would expose physicians to the disciplines of precision medicine. These would include courses in EHRs, clinical informatics, genetics and genomics, and in various aspects of data analytics.

6. The committee recommends that the UC BRAID consortia develop educational programs for research participants and establish partnerships with community-based organizations to train and disseminate information using evidence-based models. UC BRAID is a consortia of NIH-funded Clinical and Translational Science Institutes across the University of California that brings together talent and resources to reduce barriers and accelerate translational research across California. Leveraging this statewide network would bring together experts in community engagement and implementation science to develop the tools and methodologies to engage patients as partners in research.

Concluding Thoughts About Precision Medicine and Education

A common theme in all of the recommendations made by the committee is the importance of interdisciplinary education in preparing the future precision medicine clinical, population health, and research workforce. This approach to education requires inter-professional education, creating explicit linkages between what previously were seen as unrelated fields, from clinical medicine to genomics, bioethics, engineering, environmental, and social sciences, to clinical informatics and community engagement. The acceleration in the development of new tools and technologies in precision medicine also means that healthcare providers must engage in life-long patient and population centered education. Healthcare systems can accelerate quality of care improvement by using longitudinal education (e.g., from undergraduate, to graduate, to continuing education) as a vehicle to disseminate precision medicine into practice and into research and career development. These approaches share a common focus on providing patient-centric healthcare that is not defined by any one discipline but that combines disciplines to develop optimal disease prevention, diagnosis, and treatment strategies for individuals and populations.

Chapter 5: Regulatory Challenges

Introduction

Understanding the relevant federal regulatory landscape, the Regulatory workgroup was tasked with reviewing regulatory issues within precision medicine, exploring opportunities in California that could further improve patient safety and outcomes, identifying issues for the state to monitor, and putting forward recommendations that would continue to support innovation.

Precision medicine is an evolving and emerging field. As such, over time, it has posed and continues to pose unique regulatory challenges. Even the term precision medicine continues to have different meaning to different stakeholders. The uncertainty in defining precision medicine adds a challenging lack of clarity to regulatory processes, especially when new innovations and advances do not fit into the existing regulatory pathways. Some people think about precision medicine within a framework of precise drug development, while others think about it in the context of genomics; still others define it more through the use of other “omics” or all the different types of data that can be integrated through advances in technology to provide better prevention, more precise diagnosis, and tailored treatment. The latter definition is inclusive of the first two, and most consistent with the California definition provided at the beginning of this report.

Figure 7: Precision medicine spans across “omic” layers. Image source: Kevin Patrick, MD, MS, University of California, San Diego.

The potential regulatory landscape is vast as it pertains not only to all the different “omic” layers, but also to many stakeholders including, but not limited to, hospitals, clinics, academic institutions, pharmaceutical companies, healthcare practitioners, entrepreneurs, medical device manufacturers, technology companies, and biotechnology companies. A survey of some of the advances across the different areas below highlight why the regulatory landscape is so complex and also is ripe for transformation. Many advances have taken place over the last decade from genomics to gene editing. New ethical and regulatory challenges are now before us. As this report was being completed, a Chinese researcher edited the genes in two human embryos with CRISPR Cas9, a powerful gene-editing tool, in an effort to make them resistant to HIV (116). He broke Chinese laws

and caused international outrage and concern in the public and the scientific and medical community. As AI and other data tools become more predictive, privacy regulations will also need to be reviewed. The story of Target predicting and then informing the father of a teenage daughter about her pregnancy before she could tell him made the national news (117). This is commonplace as retail stores track all of our data. What happens when HIV status or mental health issues can also be uncovered through algorithms and revealed to potential employers? The California Consumer Privacy Act of 2018 that will take effect by January 1, 2020 established some protections (118), but additional issues are likely to emerge. Theranos, another story that made the national news, was a fraudulent blood testing company with big ambition but lacking in scientific rigor and regulatory oversight (119).

These stories highlight the negative consequences of working outside a regulatory framework. The committee looks at precision medicine as a positive and promising advance, but with any powerful new tool, regulatory oversight must guard against exploitation. That is exactly where regulatory oversight can help provide safety. As mentioned, there are several regulatory instruments needed to support precision medicine, and the committee members focused on a few that are prime for action.

Advances in Genetic and Genomic Technology

Advances in genetics over the last few decades are astounding. The federal government funded the Human Genome Project in 1988. In 2001, over a decade later, nearly 90 percent of the three billion base-pairs had been sequenced and published in Nature (120). The initial Human Genome Project cost $2.7 billion and yet now sequencing an individual genome costs as little as $1,000, opening up not only a new market, but also many new regulatory challenges (121). Some think that with continued advances, individual sequencing will drop to as low as

$100 in the next few years (122). These advances have benefited both research and clinical care and even created an entirely new direct-to-consumer market that provides services such as genetic analysis for ancestry, common medical conditions, or drug metabolism and response (123).

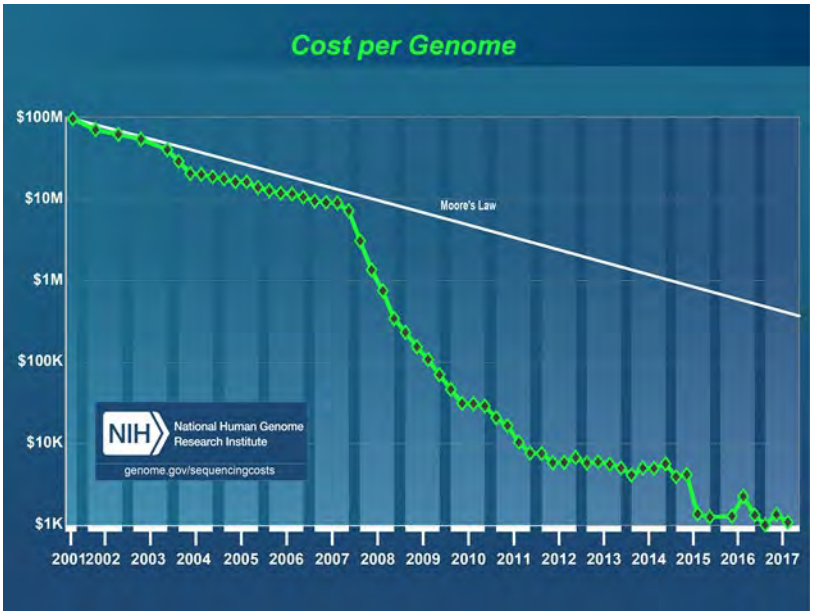


Figure 8: Genome sequencing costs are declining rapidly due to technology.

Regulatory responses have had to adapt to the fact that the accuracy of test results varies significantly. For instance, the company 23andMe started offering direct-to-consumer genetic testing that provided both genetic risks for certain diseases and links to family members, up to fifth cousins, but did so without any regulatory oversight. However, as the company grew and started offering

more tests, the Federal Drug Administration (FDA) shut down the health services offering due to concerns over communication of health risks and the potential for misinformation. A completely novel approach to regulation was required, since the service was unprecedented. The company has since been able to work closely with FDA to resume services, but with much tighter control on how test results are communicated to consumers and greater assurances that the science is accurate (124). There are many new companies entering this space without clear regulatory requirements, highlighting the need for new regulatory policies for direct-to-consumer genetic testing.

Advances in Technology

Technology, a key driver of precision medicine, has flourished in the last several decades. In the 1980s, having a large, bulky, personal computer with low-computing-power was a novelty, while today the majority of people have near ubiquitous access to powerful smartphones. It is estimated that by 2020, 70% of people around the globe will use smartphones (125), and this will transform our ability to collect highly granular data about individuals from physical activity, to food consumption, to symptoms of depression, or other self-reported information. These new technologies even allow the capture of environmental data and/or geolocation (126). Beyond consumer applications, the smartphone itself has become a diagnostic tool with applications ranging from plug-ins that allow for electrocardiography (EKG, heart monitoring) to photos that screen for diseases such as skin cancer or that enable remote clinical encounters, to new technologies that run lab tests akin to a laboratory diagnostic device (127). Furthermore, other small sensor technology such as FitBits and other Internet-connected devices are under investigation for use in clinical decision-making (128).

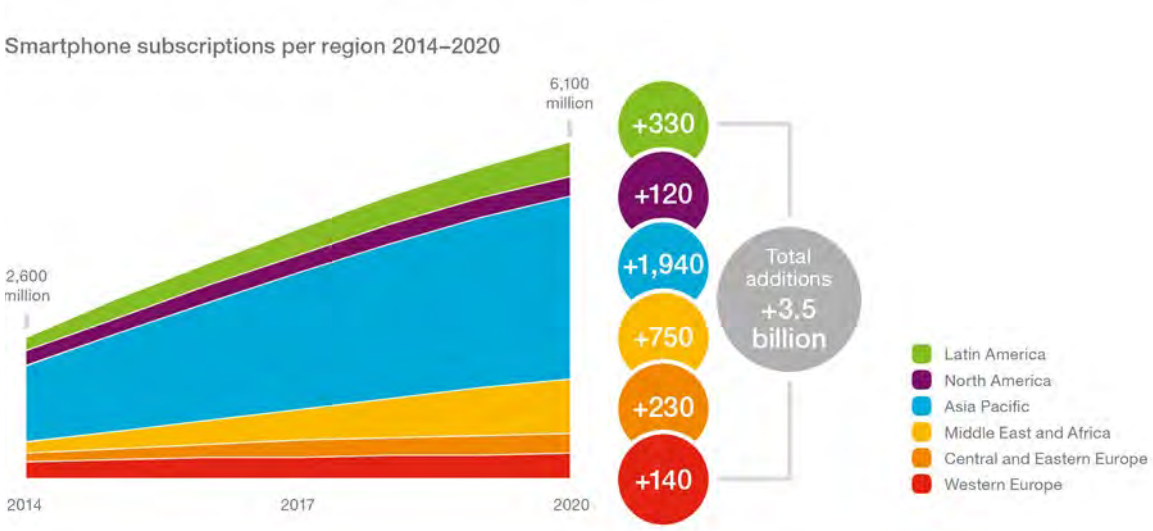


Figure 9: Granular data collected from smartphones will improve as the technologies become more accessible around the globe.

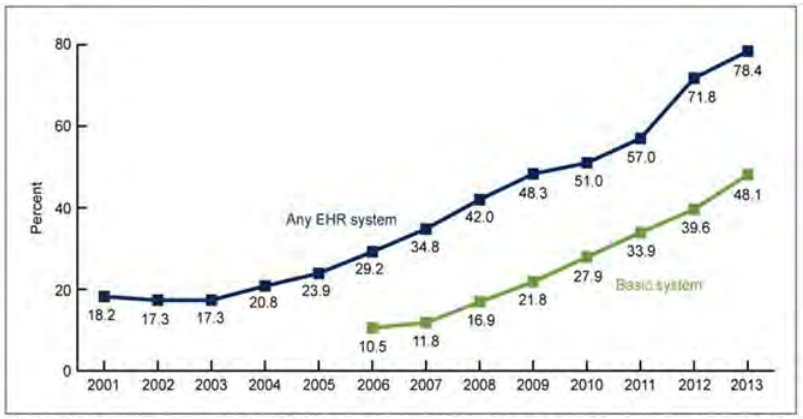
California Spotlight:
Early Prediction of Major Adverse Cardiovascular Events (MACE) Using Remote Monitoring
Funded by California

Cardiovascular disease is the leading cause of death for both men and women in California. Prevention and treatment of heart disease are most effective when disease is detected early, but early signs can be easily missed since people spend most of their life away from a doctor or hospital where it is challenging to monitor disease progression. If predictive markers are identified earlier, then impending MACE may be prevented through treatment intensification and efforts to enhance compliance with life-saving therapy. The Early Prediction of Major Adverse Cardiovascular Events Using Remote Monitoring project aims to use novel remote monitoring to see if early signs of a major cardiac event might be able to be predicted. Remote monitoring consists of a FitBit to monitor step counts, heart rate, and sleep, a portable electrocardiogram monitor, and other at-home biomarker blood tests. Patients also report quality of life issues on their mobile device. Already a likely MACE event was detected and prevented when an arrhythmia was picked up with the at-home EKG. The study is still ongoing, but this event demonstrates the potential for this type of remote monitoring (11).

Advances in Electronic Health Records

As digital advances in personal computing progressed, and as paper health records were digitized, national policy created a significant incentive for EHRs to be implemented. As noted previously in the report, the HITECH Act of 2009 allowed for payments and incentives to encourage systems to be converted from paper to digital health records. While only 18% of office-based physicians had an EHR in 2001, that number increased to 78% by 2013 (129).

Prior to this transition, data in medical charts were largely inaccessible to other clinicians and researchers. However, with the transition to electronic systems, health data became accessible in unprecedented ways. This increased availability introduced new regulatory challenges. For instance, how can a health system continue to ensure patient privacy and protection when data is shared across institutions? If a smartphone or mobile device collects personal health information, should it be subject to the same regulations and protections as the EHR? This new treasure trove of technologies has created multiple opportunities but has also introduced important regulatory questions. These questions include approaches to the new cybersecurity threat that exists due to data being stored in a digital form.



NOTES: EHR is electronic health record. "Any EHR system" is a medical or health record system that is either all or partially electronic (excluding systems solely for billing). Data for 2001–2007 are from in-person National Ambulatory Medical Care Survey (NAMCS) interviews. Data for 2008–2010 are from combined files (in-person NAMCS and mail survey). Estimates for 2011–2013 data are based on the mail survey only. Estimates for a basic system prior to 2006 could not be computed because some items were not collected in the survey. Data include nonfederal, office-based physicians and exclude radiologists, anesthesiologists, and pathologists.
SOURCE: CDC/NCHS, National Ambulatory Medical Care Survey and National Ambulatory Medical Care Survey, Electronic Health Records Survey.

Figure 10: Percentage of office-based physicians with EHR systems: United States. The majority of office-based physicians in the United States have an EHR system.

An overview of the precision medicine landscape quickly highlights a complex regulatory structure for medicine, data, and devices that primarily exists at the federal level through the FDA, U.S. Centers for Medicare and Medicaid Services (CMS), the Federal Trade Commission (FTC), and/or the Office of the National Coordinator for Health Information Technology (ONC). Given the sheer number of different regulatory issues across precision medicine, it is not possible to highlight all areas. Instead, the committee decided to focus on a few areas deemed to be of greatest impact with potential for transformation. Some recommendations highlight working with our federal partners more closely, and others recommend actions that California, and institutions within California, can take to improve the regulatory environment.

Key Issues

Several barriers threaten the potential of precision medicine to have a substantial impact. Several have been highlighted in other chapters, such as lack of data sharing, transparency, and education. As noted above, the regulatory landscape is vast, but the committee believes the following are key regulatory issues to consider for precision medicine to advance in California and merit particular attention.

Misuse of Genetic Information—The Need for Increased Patient Protections

As discussed earlier in this report, genetic technologies and big data hold significant promise to change dramatically the landscape of medicine and healthcare. However, genetic information can also be used to discriminate or create stigma against people with genetic predispositions to certain diseases, individuals with family histories of genetic disorders, or members of a racial or ethnic group with increased risk for specific genetic disorders. The U.S. Bureau of Labor in a 1998 report highlighted several cases where people faced discrimination by insurance companies, employers, and other organizations that used genetic information across these key segments (130).

To prevent employers or payers from misusing genetic information to influence employment decisions or deny individuals access to health insurance, the Genetic Information Nondiscrimination Act (GINA) was signed into law in 2008 (131). The goal of this federal law was to ensure that patients felt comfortable freely sharing family history information with healthcare providers or better understanding health risks by undergoing genetic testing or receiving genetic counseling, without consequences that could affect their jobs or healthcare coverage. Despite the significant advances provided by this legislation, GINA protections still leave individuals open to discrimination since they do not currently apply to life, long-term-care, or disability insurance. As a result, many states, including California, have passed their own laws that further prevent genetic discrimination by employers, insurance companies, or state funded agencies.

A review of state genetic privacy laws highlights the 48 states and the District of Columbia that have passed laws preventing genetic discrimination by health insurers. Seventeen states have additional laws restricting the use of genetic information in determining coverage for life insurance, 17 states for disability insurance, and eight states for long-term care insurance (132). Lastly, 35 states and the District of Columbia have passed laws to prevent genetic discrimination in employment. The ACLU cites at least sixty bills pending in eighteen state legislatures that would further expand these protections (133).

In 2011, California passed the "California Genetic Information Nondiscrimination Act" (CalGINA), which extended protections even further to prohibit genetic discrimination in emergency medical services, housing, mortgage lending, education, and other state-funded programs. CalGINA added “genetic information” to the list of protected classes found in California laws, including public accommodations statutes, the California Fair Employment and Housing Act (FEHA), and the Health and Safety Code (134).

One bill that has been moving through Congress, HR 1313, The Preserving Employees Wellness Program Act, could compromise and perhaps nullify many of the safety provisions provided under GINA (135). If passed, this bill would allow employers to impose penalties on employees who choose not to participate in wellness programs, which would require or at least allow for a review of any genetic testing results of the individual and their family members. This information is currently not allowed under GINA. According to the American College of Human Genetics, withholding such information could increase one's health insurance costs by approximately 30% (136). This would significantly compromise someone's ability to remain gainfully employed across different sectors.

Lab Development Tests Need More Oversight and Standards

Genetic Test Regulation and Oversight

In the United States, three federal agencies are involved in regulating use and availability of genetic tests: CMS, FDA, and FTC. Through the Clinical Laboratory Improvement Amendments of 1988 (CLIA), CMS is responsible for regulating clinical laboratories performing LDTs. Most genetic tests are marketed as LDTs, which by definition are manufactured and intended for use within a single laboratory. LDTs can be marketed without undergoing an FDA regulatory clearance or approval process. While FDA states that they have the authority to oversee LDTs, to date they have exercised regulatory discretion with respect to such oversight. However, FDA regulates commercially available genetic test kits through its Center for Devices and Radiological Health (CDRH) and three medical device pathways that CDRH oversees: premarket approval (PMA) applications; de novo clearance; and 510(k) premarket notification for tests substantially equivalent to an already marketed test. FTC regulates how tests are advertised to ensure that the company marketing the test does not make false or misleading claims. Some states also regulate laboratories and their LDTs, and the degree of regulation varies from state to state.

Aside from federal and state agencies regulating tests and laboratories, certain professional organizations accredit laboratories according to standards set by the accrediting organization. The College of American Pathologists (CAP) is considered to be an important accrediting body for labs.

CMS, CLIA, and Laboratory-Developed Tests

Most genetic tests come to the market as LDTs. According to the National Human Genome Research Institute, "over 500 clinical laboratories in the United States perform chromosomal, biochemical, and/or DNA-based tests for genetic diseases" (137). LDTs are developed and performed by a proprietary laboratory that may be either a reference laboratory within a health system institution or a commercial laboratory that develops and performs a particular genetic test. For LDTs, the sample must be collected by the ordering clinician and sent to the lab for testing. The lab returns the results with a report to the ordering clinician. For LDTs, CMS does not assess individual tests. Rather, CMS enforces compliance with CLIA regulations for education requirements for lab technicians, quality control of laboratory processes, and proficiency testing. Specific CLIA requirements depend on the nature and complexity of the tests.

FDA is responsible for complexity determinations of the various LDTs. Most genetic tests are classified as moderate or high complexity. According to the National Independent Laboratory Association, "most laboratories that offer LDTs follow only the regulatory requirements of CLIA, which are intended to regulate the operations of laboratories, but are not specifically intended to regulate in vitro diagnostic devices" (138). Thus, many LDTs are marketed without published evidence of analytic validity, clinical validity, or clinical utility.

FDA Regulation and Guidance

When a laboratory wishes to market a test kit to other laboratories or seeks FDA approval or clearance for a genetic test, it must submit the appropriate application and notification to FDA. FDA regulates genetic tests sold as kits, defined as, "a group of reagents used in the processing of genetic samples that are packaged together and sold to multiple laboratories" (139). FDA considers these kits as in vitro diagnostic devices and regulates them as medical devices. Oversight is based

on the test's intended use and risk of producing inaccurate results. FDA categorizes genetic tests into three classes: class I (relatively low risk); class II (moderate risk); class III (greatest risk). Generally, Class I and II tests require 510(k) marketing clearance or a de novo clearance (if no substantially equivalent test is already on the market and the test is Class II). Class III tests require a PMA application and evidence substantiating its clinical validity. FDA provides a complete listing of test kits that have received marketing clearance or approval.

FDA Plans for Changes to Genetic Test Regulation

Historically, FDA has not regulated LDTs and practiced regulatory discretion instead. However, in 2010, FDA announced plans to regulate some LDTs due to the increased complexity of some genetic tests and their use in treatment decisions for life-threatening diseases. At that time, FDA had "identified problems with several high-risk LDTs including: claims that they were not adequately supported with evidence; lack of appropriate controls yielding erroneous results; and falsification of data." Specifically, FDA became aware of "faulty LDTs that could have led to patients being over- or undertreated for heart disease; cancer patients being exposed to inappropriate therapies or not getting effective therapies; incorrect diagnosis of autism; unnecessary antibiotic treatments; and exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease" (140). In response to these concerns, FDA held a workshop to obtain stakeholder input on FDA's intent to reconsider its policy of enforcement discretion for LDTs. Based on feedback from this workshop, FDA issued draft guidance titled, "Framework for Regulatory Oversight of LDTs" in October 2014. In this document, FDA "proposed to phase out the enforcement-discretion policy that shields many LDTs from being regulated as medical devices" (141). FDA has not yet published final guidance, but in January 2017, FDA issued a discussion paper based on a synthesis of the feedback received on the agency's draft guidance on regulation of LDTs. The conclusion of this paper reads as follows:

> Many stakeholders, in addition to FDA, have indicated that there is a public health need for greater oversight of LDTs. For example, payers such as CMS expect FDA review of analytical and clinical validity to precede determinations of clinical utility for coverage. Extensive stakeholder feedback further confirmed the importance of balancing the unique qualities of LDTs, while still providing a reasonable assurance that such tests are analytically and clinically valid. An oversight approach should be undertaken in an efficient manner that effectively leverages, without duplicating, CLIA requirements, keeping in mind that CLIA certification only includes the laboratory where such tests are performed. It should include many of the same features that have been proposed by various groups recommending greater oversight of LDTs. Such an approach could appropriately balance patient protection with continued access and innovation. FDA looks forward to continuing to work with all stakeholders in future conversations around the right path forward on LDT oversight (142).

In November 2017, FDA issued a statement on the implementation of the agency's streamlined development and review pathway for consumer tests that evaluate genetic health risks. This statement, which details FDA plans to implement a flexible regulatory approach for genetic health risk (GHR) testing, reads as follows:

> FDA issued a notice of its intent to allow GHR tests to be exempted from premarket review under certain conditions. If and when finalized, manufacturers of these types of tests would have to come to FDA for a one-time review to ensure that they meet the FDA's requirements, after which they may enter the market with new GHR tests without further review. The agency also established special controls for these tests in a separate de novo classification order, which outline requirements for assuring the tests' accuracy, reliability and clinical relevance and describe the type of studies and data required to demonstrate performance of certain types of genetic tests…The agency also issued a final order exempting genetic carrier screening tests from premarket review (143).

Direct to Consumer Tests Should be Validated Through 3rd Party Reviewer

Federal Trade Commission

The FTC states its mission as working “for the consumer to prevent fraudulent, deceptive, and unfair business practices in the marketplace and to provide information to help consumers spot, stop, and avoid them” (144). Companies providing genetic tests that consumers can order directly have recently pushed the envelope from providing ancestry-related testing information to providing tests purporting to offer health information as well. To that end, FTC provides information on its website advising consumers to beware of Direct-to-Consumer (DTC) genetic tests purporting to offer health information for decision-making (145). The advice FTC provides about DTC genetic testing has implications for healthcare providers, health systems, and genetic counselors within those systems that few health systems have yet considered.

Such testing may cause an increase in genetic-test-related follow-up with practitioners and genetic counselors to help individuals understand what the results mean, what actions they may need to take, and to schedule any necessary follow-up testing.

State Regulation

Some states have certification programs for genetic testing. New York State is considered to have the most rigorous requirements. According to the National Human Genome Research Institute, New York state law requires that laboratories performing tests on New York residents participate in its quality assurance programs for both DNA-based and biochemical genetic tests (146). In November 2017, FDA announced accreditation of the New York State Department of Health (NYSDOH) as an FDA third-party reviewer of in vitro diagnostics, including next-generation sequencing (NGS) genetic tests. FDA released a statement that, “Moving forward, laboratories whose NGS-based tumor profiling tests have been approved by NYSDOH do not need to submit a separate 510(k) application to FDA. Instead, developers may choose to request that their NYSDOH application, as well as the state’s review memorandum and recommendation be forwarded to FDA for possible 510(k) clearance. Other accredited, third-party FDA reviewers also may become eligible to conduct such reviews and make clearance recommendations to the agency” (147).

College of American Pathologists Accreditation

Many genetic testing laboratories also seek CAP accreditation. CAP offers a Laboratory Accreditation Program that includes inspecting laboratories including medical centers and physician offices across a variety of testing procedures” (148). CAP accreditation involves a peer-based inspection model that uses teams of qualified professionals and on-site inspections every two years using CAP accreditation checklists.

Recommendations

Although there are many regulatory issues pertaining to precision medicine, there are a few specific actions the state can take in the short and near-term to provide more oversight and protect patients and consumers. To move towards the committee’s vision of precision medicine where innovation thrives and community members and patients are protected, we recommend that the state take the following actions below.

1. Enact legislation to further strengthen CalGINA provisions to ensure that it prevents the unauthorized use of genetic information to influence employment decisions, or affect access to health, life, long-term-care, and disability insurance. The State of California has emerged a national leader in anti-discrimination laws and privacy protections for Californians. The rapidly expanding field of precision medicine, however, calls for further evaluation of existing genetic privacy protections to ensure that individuals are not stigmatized and marginalized by the rapidly changing landscape. To this end, California should ensure that both the state and federal genetic privacy laws provide maximal protection for all citizens and balance various policy decisions. Within this consideration, the state should also consider broadening beyond genetic protection to include

protections from other “omic data” such as proteomics or biosensor data, or other data that can be predictive of a major health event.

2. Direct precision medicine staff at the state level to participate in a federal standards working group to improve LDTs. There is currently a lack of regulation and standards across LDTs leading to great variability and a lack of reproducibility of results. This puts patients and users at risk for both false positives and false negatives, and does not allow findings to be consistently compared across tests. Additionally, reimbursement is not currently reflective of the test improving patient outcomes. Reimbursement should be based on better data. A further discussion of precision medicine reimbursement follows later in this report and is an important aspect of LDTs that are not approved consistently or validated. Ensuring that California is a partner at the table as standards are set will be important not only for users and patients, but also industry, entrepreneurs, and academic partners.

3. The Governor’s Office should appoint a committee to conduct a study of the feasibility to implement a model for conducting 3rd party review for LDTs and DTC tests. This committee should conduct an evaluation of current processes and other models, similar to NYSDOH, that exist and propose various solutions to ensure consumer safety without stifling innovation.

Concluding Thoughts About Precision Medicine and Regulation

These recommendations serve as a starting point in the expansive regulatory issues emerging around precision medicine. Future considerations should include the broader data context, privacy, reimbursement, and mobile health applications.

Chapter 6: Finance and Cost Models

Introduction

The Finance and Cost Models workgroup was tasked with reviewing finance issues within precision medicine and exploring possible financing or cost models that could further develop or sustain precision medicine approaches in health and healthcare delivery. Additionally, the Finance and Cost Models workgroup considered how a framework to enable the recommendations of the other workgroups might be developed. Finally, this workgroup sought to understand and put into context both the impact of precision medicine within the healthcare economy, as well as the broader California economy.

It is well known that healthcare spending in the U.S. is vast and growing. Healthcare expenditures reached $3.5 trillion in the US in 2017, or 17.9% of the U.S. gross domestic product (GDP), and is projected to reach $5.7 trillion or 19.7% of GDP by 2026 (149). In California alone, total healthcare spending reached $400 billion in 2017-18 (150), and researchers project that this level will grow to $548 billion by 2022 (151). California's Department of Public Health estimates that chronic conditions account for 80 percent of California's healthcare expenditures (minus administrative costs and investment) (152).

Because of their enormous budget impact, the debate over cost vs. value in healthcare has been ongoing for decades. Precision medicine offers both a significant opportunity and a cautionary tale with respect to impacting healthcare spending growth.

Unlike other sectors where new technologies or business models are seen to drive gains in productivity and efficiency, new technologies and therapies in healthcare are generally viewed as having additive costs, even if savings are produced in the longer term. Traditionally, it has been difficult to quantify benefits and create a timeline for their achievement. Few would disagree, for example, that the development of improved public sanitation, antibiotics, polio vaccines, antipsychotics, statins, and other advances of the last century—most of which came from American laboratories—have saved innumerable lives, increased productivity, and reduced treatment costs. Yet the precise return on investment, by year, remains elusive because of "the other pocket problem."

One dollar spent on research grants for California medical centers might save three dollars over ten years, but the benefits are distributed widely. It has been difficult to parse the direct lines of research's cause and effect on jobs, wages, taxes, health costs, and productivity in real time. All that can be said with certainty is that we have reaped the financial and quality of life benefits by past breakthroughs.

The cost of healthcare includes labor-intensive research and development, complicated production, the need for high levels of expertise and specialization, intellectual property ownership, litigation, and regulatory risk (153). These are all rational costs that are factored into pricing, which market forces may drive further upward. Because healthcare spending is already high and budgets are finite (whether at the government, employer, or individual levels), it is difficult to finance new therapies and treatments without adding significant costs to the system. The promise of precision medicine is that it will lead to more targeted and fewer unnecessary treatments as interventions are personalized. On the other hand, because new therapeutics often come with sky-high costs, concerns abound as to whether precision medicine will actually cause healthcare spending to overwhelm payer budgets. There is also a risk that in efforts to manage costs, payers will limit access to new approaches in order to keep premiums affordable but thereby exacerbate existing health disparities among income, ethnic, and/or geographic populations.

Harnessing the power of precision medicine is in its early stages, and an approaching crossroads—using precision medicine to contain costs and improve outcomes for all populations, or fanning the flames of rising healthcare costs and potentially driving greater disparities—represents an opportunity to make conscious, strategic adjustments in the course of healthcare spending and outcomes. Arguably, the stakes are higher now than ever before: hundreds of billions of dollars more on healthcare will be spent over the next several years for scientific advances and there is widespread recognition of an aging population on the horizon.

California, with its robust academic medical centers, integrated healthcare delivery networks, mixed payer system, robust science and technology base, and diverse population, should lead the way and develop a value-based precision medicine model that balances higher quality with lower cost. Our framework for value-based precision medicine includes:

- Aligning financial incentives to ensure shared goals around precision medicine funding and adoption.
- Making prevention and wellness specific to individuals and manageable at minimal personal cost. This also means finding ways of linking the long-term return on investment of wellness and prevention to those who pay for it in early years.
- Integrating social and environmental factors with medical and genomic factors, given the strong correlation between social and environmental factors and health outcomes. For example, First Five and other early childhood development entities are working to reduce adverse childhood experiences (ACEs) that drive poor health later in life.
- Ensuring that good health and health outcomes and care are equitable.
- Ensuring that interventions have proven value and that those who pay for the interventions can capture the value.
- Accessing a robust knowledge and data network that can be readily applied.
- Interacting with people where they are or would like to be—at home, rather than a facility or office.
- Reframing the conversation and the financial incentives to move from disease management to health.
- Creating economic incentives for entrepreneurs to build their precision medicine advances in California to drive the economic development that ultimately helps pay for precision medicine utilization.

None of these ideas are new, but in order to have the desired effect of higher quality and lower cost, they must be executed in concert. Together, not only can they create a healthier population, they can also generate a more rational, thriving healthcare economy.

Key Issues

Many barriers stand in the way of executing on this vision. Several have been highlighted in other chapters, such as lack of data sharing, transparency, and education. We believe the following are key issues in considering the financing and cost modeling of precision medicine and merit particular attention.

Integrating Social and Environmental Factors into Precision Medicine

Precision medicine is not just about genetics and genomes. Construed broadly, precision medicine acknowledges the multiple layers of “inputs,” such as social, environmental, behavioral, genomic factors, and the interrelationships through which diagnosis, disease, and treatment must be

understood. In fact, current estimates indicate that genetics explain an important but modest ~30% of an individual's variability in health. Health behaviors (e.g., physical inactivity, diet, tobacco use) explain an additional 40 percent of variance, with the remaining variance attributed to environmental factors, social circumstances, and healthcare utilization and delivery (154).

Integrating the non-genetic factors, as mentioned as one of the recommendations in the Data in the Context of Precision Medicine Chapter, with the genetic factors offers the greatest promise for lowering costs and improving outcomes. Achieving that full integration, however, represents a costly undertaking. Smaller opportunities for integration, nevertheless, do exist. Rather than starting with the most scientific questions (e.g., what's the best type of sequencing for identifying genetic variation?), we can execute more fully on easier-to-obtain information: Does the doctor or patient have a complete family history? Does the patient have access to a refrigerator to store medication that needs to be refrigerated? "That's precision medicine and that's doable today" (155).

Integrating and applying social, environmental, and behavioral data is challenging, but these data can help us understand which interventions have the highest likelihood of success and ultimately factor into decisions about how to enable value. Efforts such as the National Academy of Medicine's effort to recommend a minimum data set that should be captured as part of the medical record represent progress in this integration (156,157).

Seeking Value and Applying Cost Containment Strategies.

The expense and growth trajectory of the existing healthcare system has been well-documented and includes U.S. overspending on prescription drugs, expensive procedures, and overtreatment of patients compared with other countries. Discussions on value-based payment systems have occurred for the last decade and a half, but implementing them on any broad scale has proven elusive. While accountable care organizations (ACOs) and value-based payment models continue to grow (with the current federal administration supporting value-based payment) (158), efforts to address the cost challenges through healthcare payment reform have produced relatively limited results. The Medicare Shared Savings Program, which provides financial incentives to ACOs that meet quality targets while holding down costs, produced savings of $314 million for the CMS in 2017 (159). The Hospital Readmissions Reduction Program, which penalizes hospitals with high rates of readmission, led to reductions in readmission of between 2.3 and 3.6 percentage points for conditions covered by the policy between 2010 and 2016 and reduced mortality across those conditions (160). Yet, while these examples indicate overall progress, CMS reimbursement and payment reform programs have not bent the cost curve in a meaningful way or produced significant improvements in quality of care (161).

In the face of rapid innovation, this historical lack of discipline or success in curtailing inefficient spending and exerting downward pressure on prices portends large-scale negative effects on budgets. Consider the proposal that all babies be sequenced at birth (155). Even though the cost of DNA sequencing is magnitudes lower from a decade ago, who will pay and what is the evidence of benefit? It is expected that precision medicine will be imprecise until the tools are refined and economic models are better employed. The imperative to find value in both traditional and precision medicine will be greater than ever, as new, more sophisticated and expensive tests and therapies become available.

"Evidence" is Becoming More Complex.

Just as the committee has highlighted the need to embrace value more fully through better integration of data and stronger reliance on evidence, precision medicine is making the job of understanding evidence much harder.

The Australian Council of Learned Academies notes in its Future of Precision Medicine Report (162):

> Current health technology assessment approaches rely on clinical evidence produced by clinical trials…. Robust trials require large groups of homogeneous patients to achieve

> statistical significance. In contrast precision medicine is exploding the differences between individuals to better target therapy. This produces a challenge in generating scientifically valid evidence. Adding to this complexity, scientific knowledge is expanding at a rapid rate and is likely to change the relationship between genetics, disease progression and therapy. This complex relationship suggests that it is difficult to assess or predict the overall impact of genomics on the healthcare system and terms of health outcomes costs and delivery.

Moving from randomized control trials to “N of 1” trials (where an individual patient is the whole unit of study), or somewhere in between, will make evidence (and hence value) more difficult to determine.

Tools to aid in clinical decision-making can help. For example, the bases for clinical decision making has already expanded at Stanford hospitals to include machine-computed patient similarity analytics (163). It is highly likely that clinicians will increasingly encounter computed probabilities of multiple desirable and undesirable predicted responses to potential treatment options. However, the increasingly probabilistic data on which they are based, and the complex cognitive burden that they portend, may not be wholly embraced by clinicians and patients.

Efforts to collect “real world evidence,” both during and after clinical trials, which demonstrate what is really happening to the patient outside the trial construct, will also be an important component of the “evidence” landscape to understand value. Finally, we need to address also the challenge of pairing precision diagnostics with precision therapeutics, so patients are not unnecessarily distressed and providers have a reasonable basis to believe that a patient is likely to benefit from a particular treatment.

Disparities, Again.

The issue of health equity and disparities has been raised throughout this report. We have warned specifically about the potential for exacerbating disparities if precision medicine is not thoughtfully applied. It is worth highlighting, however, why addressing disparities is critical to the future financing of precision medicine, and is necessary in order for precision medicine to succeed.

The UCLA Center for Health Policy Research estimates that healthcare spending for Medi-Cal and other public insurance programs amounted to more than $100 billion 2016 (164,165). Almost a third of California’s population (13.5 million) is enrolled in the Medi-Cal program (166), a significant increase from just a few years ago. For California and many other states, increases in healthcare spending ironically and unfortunately dampen or restrict states’ abilities to support the very same population in other ways, such as through housing, childcare, income support, and workforce development—the lack of which has the circular effect of causing poorer health outcomes. In order to break this cycle, considerable attention must be paid to improving outcomes for the highest cost patients, many of whom experience the greatest health disparities. Keeping healthy people healthy and treating acute episodes effectively are surely good goals of our health system, but without a focus on tackling the most common chronic diseases—cardiovascular disease, arthritis, diabetes, cancer and asthma—experienced most frequently or with greatest mortality by specific populations and providing them with additional nonmedical supports, we are scratching the surface of the cost conundrum.

Moreover, if health disparities remain or worsen with the availability of new technologies and treatment, policymakers, healthcare and equity advocates, as well as the broader public, may lose faith in precision medicine approaches, and funding for further investments and innovation in this area may disappear.

Recommendations

In order to begin to finance the value-based precision medicine the committee envisions rather than the cost-burdensome “imprecise” precision medicine we do not want (more expensive new tests and

treatments, with uncertain value, limited to those with the means to pay for them), the committee recommends that the state and healthcare leaders take the following actions, with the understanding that these actions taken in concert will have a greater net effect than any taken alone, and that collaboration between public and private sectors and across disciplines and industries is necessary to have broad impact.

1. OPR in collaboration with the California Governor's Office of Business and Economic Development should establish a research consortium of business leaders (both entrepreneurs and technology leaders), patients, academics, healthcare practitioners, and payers to develop a pilot that integrates social, environmental, behavioral, and medical data and healthcare delivery, leverages available technology tools, and evaluates outcomes and cost-effectiveness of a precision medicine approach to care. This could involve government programs working with private initiatives to create incentive structures and a cohesive system design, which could then be piloted in a defined, potentially large-scale, high-needs population, and measured across an appropriate but reasonable timeframe to "ensure that all downstream costs and benefits are captured" (162). Such a demonstration project could model how to ameliorate health disparities as well as more cost-effectively serve a high-needs population. The state's leading public and private academic medical centers can also take the initiative to establish such a consortium and request state funding for the pilot.

2. State agencies should institute programs and policies that position the state as the leader in value-based transformation for both traditional and precision medicine. In order to buffer the initial adverse impact on healthcare spending from additional testing and data collection and analysis required for precision medicine (and thereby assure that precision medicine reaches its full potential to improve health and slow rather than accelerate California's per capita healthcare spending growth), the state can apply various policy tools. For example, California can require state-sponsored health plans such as those funded by Medi-Cal and California Public Employees' Retirement System (CalPERS) to preferentially select and/or pay healthcare providers based on measures of value in order to encourage providers to use precision medicine tools cost-effectively. To boost the impact of such a policy, measures should align with those such as the Merit-based Incentive Payment System (MIPS) used by Medicare to assess providers' value of care. Additionally, this recommendation is aligned with the Data in the Context of Precision Medicine Chapter recommendation. California could require regulated health plans and insurers to contribute claims data to the newly authorized Health Care Cost Transparency Database (27), with accountability for calculating and reporting to California physicians the incremental cost-effectiveness ratio (ICER) of precision diagnostic tests on a disease-specific basis. To enable the optimal calculation ICER, healthcare providers licensed by the state could be required to collect data on the SDOH (also highlighted by the Data in the Context of Precision Medicine Chapter) endorsed by the National Academy of Medicine and to contribute all EHR data to a state-designated health information exchange that includes the database.

While some current aspects of healthcare can be eliminated as they are replaced by more advanced precision medicine models, there are likely to be certain cases where precision medicine is not needed. If medicine is more targeted, it should supersede, not just add to, the array of available interventions, and investments are needed in physician and clinician education to ensure that this occurs. By moving aggressively to contain cost and increase value within the present system now, we can free up resources can be made available for new personalized alternatives for all Californians.

3. Healthcare system leaders should actively build on existing efforts and partner with existing organizations. Several organizations have made notable and tangible progress in examining evidence and determining relative value. The California Technology Assessment Forum, part of the Institute for Clinical and Economic Review, is considered highly effective within the state payer community. The state and other healthcare leaders could actively partner with such an organization, or other national organizations that have invested in examining methods for precision

medicine adoption, to create an overarching value framework for precision medicine that takes into account the changing nature of what will constitute evidence, or actionable evidence, in the context of changing data and analysis. Priority should be given to “best thinking” rather than reinvention of models that do not have to be reinvented.

4. The Governor should appoint a commission or workgroup of public and private academics and practitioners to develop a consensus economic model for healthcare. The economic structure of existing insurance and delivery systems are built on a more generalized approach to healthcare with a primary emphasis on disease management. To be successful, precision medicine must disrupt the existing healthcare delivery and payment structure by: 1) understanding where current intervention is adequate; 2) replacing the general with specific individual intervention when current intervention is not as effective; 3) replacing facilities and services with home-based information driven approaches; and 4) broadening the focus from purely that of disease management to one that also incorporates health maintenance. New incentives and economics for patients, providers, and payers will be essential to maximizing the speed, innovation, and transformation of the current healthcare system to this new model in the future. California is ideally positioned to devise that model. The state leads the nation in cost-effective delivery of care (though we cannot be satisfied with the status quo) and stands out as a disruptor in many elements of the economy. As such, California can ease the transition, guard against disparities, and provide a private and public environment that would be hospitable to effective change. Public and private academics and practitioners should be brought together, with clarity of focus and adequate resources, to develop the new economic model of healthcare.

Concluding Thoughts About Precision Medicine and the California Economy

Precision medicine is on a trajectory. With purposeful intervention, precision medicine— particularly advances in genomics—will improve our collective knowledge about the risks of developing disease; create the opportunity to mitigate risks through behavior modification, screening or preventive treatment; increase the capacity to predict response to treatment and target treatments more effectively; and provide the opportunity for patients and healthcare practitioners to make more informed choices (162).

Relevant questions are: 1) can we apply these advances equitably across populations; and 2) how do we mitigate the significant increases in per-capita healthcare spending that come with new technologies and therapies?

At the same time, the use of precision medicine tools needs to be kept in check while there is interest in fostering and growing the precision medicine economy, which is a vibrant part of the California economy. The Bay Area Council estimates that, in 2017, precision medicine accounted for almost 29,000 jobs across industry subsectors, and stimulated an additional 70,000 jobs. Additionally, precision medicine spurred almost $31 billion in economic activity last year. All of this occurred with minimal support from the state (167).

Other states and countries, as well as other hospital systems and academic medical centers, are making targeted and significant investments in precision medicine. Last year, the World Economic Forum (WEF) reported: “China is poised as a global leader in precision medicine and the Fourth Industrial Revolution technologies that power it…In 2016, China announced precision medicine as part of its five-year plan, with an expected investment of…more than $9 billion for research (168). Nearly 40 countries have their own version of a precision medicine initiative, but China’s is the largest.” WEF further noted that for every $1 the United States plans to spend on its Initiative (169) China is spending $43 (17). It may be worth tracking such investments and activities in other states and countries to highlight areas for collaboration and competition.

There is no question that precision medicine breakthroughs are coming; the only question is whether disruptive innovation will be driven from California or from Beijing, London, Singapore, Boston, New York, Austin, or some other technology hub. The risks and opportunities of precision medicine have been highlighted. Through strategic policymaking and seed funding, California can become a global exemplar in the development and use of precision medicine tools that improve health and reduce health disparities without breaking the bank.

Chapter 7: Overarching Considerations and Conclusion

During the course of creating this report, committee working group discussions were collaborative. Throughout, our aim was to identify key themes and opportunities for precision medicine such as new systematic approaches to combine, analyze, and act on the universe of data for more precise insights and outcomes.

Introduction

The committee offers overarching considerations, and **acknowledges that without more purposeful attention, California may be chasing how others develop and implement precision medicine, rather than leading and demonstrating how precision medicine should be responsibly and sustainably delivered.**

Key Issues

Investments

As noted in the international section at the beginning of this report, countries outside the United States are investing heavily in precision medicine. Although the NIH and other sources provide funding available for national competitively awarded research (and California can compete for this), it is important for California to have dedicated funding for both research and implementation of precision health and medicine within the state. In fact, other countries have created programs to recruit researchers away, and there is a real risk of losing incredible talent from our state (170).

Strategic Thinking

As noted throughout the report, medicine is at an inflection point. There is significant opportunity, and also risk if California is not prepared to drive this forward strategically and thoughtfully. In that vein, advances depend on fostering cross-sector, interdisciplinary, public-private conversations. Increasing shared knowledge, resources, thought leadership, and implementation science will be key, but it needs to be done in a holistic way. Since precision medicine is fast moving and spans broad expertise, it will be vital to continue to support on-going dialogue in the form of a precision medicine council beyond the work of this committee.

Broad Disease Areas

Lastly, this committee has stressed that precision health and medicine is not about one disease, or one specific type of data (e.g., genomics or proteomics), but more about the transition of medicine to unlocking new exciting insights and expanding our knowledge beyond what we currently know. In the near future, precision medicine will just become part of the standard practice of medicine, but there are some unique near-term opportunities to apply these precision medicine approaches to some of the more common yet complex diseases. Some of those areas include:

- Diabetes
- Mental Health
- Environment impact on health and disease- including climate change
- Heart Disease
- Cancer

Recommendations

Given all of these overarching considerations, the committee recommends bold action to ensure California has an active global leadership role in precision medicine.

1. Continue to invest in precision health and medicine. To date, the state has directly invested $53 million in precision medicine. Some of these funds have been augmented by the private sector (11). As this work progresses, on-going administrative and legislative support are vital for California to maintain its leadership role.

2. Establish an Economic and Cost Model Council to continue the work identified in this report and inform future funding and policy decisions for precision medicine. This report highlights opportunities and risks for precision medicine, yet we are in the early phases of both understanding and implementing precision medicine, with the only clear constant being an accelerating pace of change and greater complexity in our knowledge networks. It is difficult to predict how developments in AI or human longevity may change the trajectory of healthcare cost and delivery and health outcomes. A council that can oversee and guide more granular economic assessments and tactical roadmaps could prove valuable, given the right charge. A key purpose of this group should be to identify and measure the return on investment from various precision medicine advances, as well as designing models to align financial incentives that capture the time span between prevention and intervention in later life.

3. Invest in broad disease areas. The California health ecosystem has the ability to push discovery and implementation in many broad areas from diabetes to mental health. Ongoing funds should foster this innovation in understanding with an aim to have more positive health outcomes in the near-term for all Californians.

Conclusion

The Oxford dictionary defines medicine as, “The science or practice of the diagnosis, treatment, and prevention of disease” (171). However, just as with the advent of the microscope, we now have new, more precise technologies, data, and computing to accelerate our understanding of medicine and increase precision. An unprecedented ability exists to harness all available data and technology tools to prevent disease, treat patients and improve human health. Other countries are acting; our time to act is now.

Image Credits

Figure i. [Cover Image] Computed by Olivier H. Beauchesne and SCImago Lab, data by Elsevier Scopus. Available from: http://olihb.com/wp-content/uploads/2014/08/map_clusters_hi.jpg

Figure 1. Source of data: Spear B, Heath-Chiozzi M, Huff J. Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, pages 201-204.

Figure 2. California Biotech Foundation

Figure 3. Precision Medicine: An Action Plan for California. 2018 Dec 26.

Figure 4. Blasimme A, Fadda M, Schneider M, Vayena E. Data Sharing For Precision Medicine: Policy Lessons And Future Directions. Health Affairs. 2018 May 1. Exhibit 2: Frequency of references to the policy themes, by organization type; p. 705.

Figure 5. World Bank - WDI, Health Expenditure and Financing - OECDstat (2017). Available from: OurWorldInData.org/the-link-between-life-expectancy-and-health-spending-us-focus. CC BY-SA.

Figure 6. Los Angeles County Department of Public Health, Office of Health Assessment and Epidemiology. Life Expectancy in Los Angeles County: How Long Do We Live and Why? A Cities and Communities Report. July 2010. Figure 2: Trends in Life Expectancy by Race/Ethnicity, 1991-2006; p. 4.

Figure 7. Image courtesy of Kevin Patrick, MD, MS, University of California, San Diego

Figure 8. National Human Genome Research Institute. DNA Sequencing Costs per Genome. 2017. Available From: https://www.genome.gov/27541954/dna-sequencing-costs-data/

Figure 9. Smartphone Subscriptions per Region 2014-2020. Available from: https://www.ericsson.com/en/press-releases/2015/6/ericsson-mobility-report-70-percent-of-world s-population-using-smartphones-by-2020

Figure 10. Percentage of office-based physicians with EHR systems: United States, 2001–2013; pg 1. Available from: https://www.cdc.gov/nchs/data/databriefs/db143.htm

Appendix 1: Committee Biographies

Arnold Milstein: Milstein has been a professor of medicine and director of the Clinical Excellence Research Center at Stanford University since 2010. The Center designs and demonstrates scalable healthcare delivery innovations that provide better care with less healthcare spending. His research spans positive value outlier analysis, human experience of healthcare and, in partnership with Stanford's Artificial Intelligence Lab, the development of artificial intelligence systems to assess and support care for medically fragile populations in home and institutional settings. In 1984, Milstein founded a national healthcare performance improvement firm, National Medical Audit, which he expanded globally after its acquisition by Mercer. He also co-founded three nationally influential public benefit initiatives, the Leapfrog Group in 1998, the Pacific Business Group on Health in 1985 and the Consumer-Purchaser Alliance in 2001. As a member of the congressional Medicare Payment Advisory Commission from 2004 to 2010, he originated two legislative changes to align healthcare provider revenue with value to patients. He served as chair of the National Academy of Medicine Planning Committee series on improving the efficiency of U.S. care delivery. Milstein earned a Doctor of Medicine degree from the Tufts University School of Medicine and a Master of Public Health degree from the University of California, Berkeley.

Atul Butte: Butte has been principal investigator of the California Initiative to Advance Precision Medicine, director of the Bakar Computational Health Sciences Institute, and the Priscilla Chan and Mark Zuckerberg Distinguished Professor at the University of California, San Francisco since 2015. He has been the Chief Data Scientist for the entire Univeristy of California Health system since 2018. Butte has been a founder and scientific advisor at NuMedii Inc. since 2009 and at Personalis Inc. since 2011. He previously held several positions at the Stanford University School of Medicine from 2005 to 2015, including assistant professor, professor of pediatrics and division chief. Butte was elected into the National Academy of Medicine in 2015, and in 2013, he was recognized by the Obama Administration as a White House Champion of Change in Open Science for promoting science through publicly available data. Butte earned a Doctor of Medicine degree from the Brown University School of Medicine and a Doctor of Philosophy degree in health sciences and technology from the Massachusetts Institute of Technology and Harvard Medical School.

Frederick J. Meyers: Meyers has been associate dean for precision medicine at University of California, Davis Health since 2016, where he has served in several leadership positions since 1992, including chairperson of the Department of Internal Medicine and vice dean of the School of Medicine. He was one of the first in the country to develop the concept of simultaneous care, a system of patient-family centered caring that provides both treatment for advanced cancer using investigational clinical trials as well as intensive palliative care. Meyers has been an active medical oncologist at the University of California, Davis Comprehensive Cancer Center since joining the University of California, Davis faculty in 1982. Meyers earned a Doctor of Medicine degree from the University of California, San Francisco School of Medicine. He is a Master of the American College of Physicians.

Hakan Sakul: Sakul has been vice president of diagnostics at Pfizer since 2016, with responsibility for development of companion diagnostics across Pfizer's pharmaceutical portfolio. He has held several positions at Pfizer since 2002, including executive director and head of diagnostics for Worldwide R&D; senior director of translational oncology in the Oncology Business Unit; senior director, global head of diagnostics and oncology leads for the Molecular Medicine Group and Clinical R&D; senior director of the Molecular Profiling Group and diagnostics lead for Clinical R&D; and director and site head of the Clinical Pharmacogenomics Group. He led Pfizer's flagship program in companion diagnostics for Xalkori(R), a non-small cell lung cancer drug that received FDA approval in 2011 along with its diagnostics test. He was director of the Human Genetics, Statistical and Pharmacogenetics Department at Parke-Davis Pharmaceuticals from 1998 to 2001. Sakul is a member of the Board of Personalized Medicine Coalition, and author of over 30 referred

scientific articles. Sakul earned a Doctor of Philosophy degree in quantitative genetics from the University of Minnesota and a Master of Science degree from Ankara University.

Jay Gellert: Gellert was president and chief executive officer at Health Net Inc. from 1998 to 2016. Gellert was president and chief operating officer of Health Systems International Inc. (HSI) from 1996 to 1998 and was a member of the Health Systems International Inc. Board of Directors and chairman of the board for HSI's principal operating subsidiaries, Health Net and QualMed, from 1996 to 1998. Gellert directed Shattuck Hammond Partners Inc.'s strategic advisory engagements from 1990 to 1996, was president and chief executive officer of the Bay Pacific Health Corporation from 1988 to 1991 and was senior vice president and chief operating officer for California Healthcare System from 1985 to 1988. Gellert is a member of the Ventas, Inc. Board of Directors. He was as chairman of the America's Health Insurance Plans Board of Directors and served in several positions at the Council for Affordable Quality Healthcare, including co-chair of the Provider Council, chairman of the Administrative Simplification Committee and member of the Board of Directors and the Executive Committee.

Jessica Mega: Mega has been chief medical officer at Verily Life Sciences since 2015. She led large, international, randomized trials evaluating novel cardiovascular therapies as a senior investigator with the TIMI Study Group and a cardiologist at Brigham and Women's Hospital from 2008 to 2015, and as a faculty member at Harvard Medical School, where she is currently on leave. Mega directed the TIMI Study Group's Genetics Program from 2011 to 2015, focusing on applications for precision medicine. Her research findings have been published in the New England Journal of Medicine, Lancet, JAMA and elsewhere. Mega earned a Doctor of Medicine degree from the Yale School of Medicine and a Master of Public Health degree from the Harvard School of Public Health. She completed an internal medicine residency at Brigham and Women's Hospital and a cardiovascular fellowship at Massachusetts General Hospital. She has won the Laennec Society, Samuel A. Levine and Douglas P. Zipes awards and is a fellow of the American Heart Association and the American College of Cardiology.

Jill P. Mesirov: Since 2015, Mesirov has been associate vice chancellor for computational health sciences, professor of medicine at the University of California, San Diego School of Medicine and a member of its Moores Cancer Center where she co-leads the genomics research program. Mesirov served as associate director and chief informatics officer at the Broad Institute of MIT and Harvard – formerly the Whitehead Institute/MIT Center for Genome Research – from 1997 to 2015, where she also directed the Computational Biology and Bioinformatics Program. She was manager of computational biology and bioinformatics at IBM's Healthcare-Pharmaceutical Solutions Organization from 1995 to 1997 and director of research at Thinking Machines Corporation from 1985 to 1995. Mesirov was an instructor in the University of California, Berkeley Department of Mathematics from 1974 to 1976, a member of the research staff in the Communications Research Division of the Institute for Defense Analyses from 1976 to 1982 and associate executive director of the American Mathematical Society from 1982 to 1985. She earned Master of Arts and Doctor of Philosophy degrees in mathematics from Brandeis University. She is a fellow of the American Association for the Advancement of Science, the American Mathematical Society, and the International Society for Computational Biology.

John Carpten: Carpten has been chair of the Department of Translational Genomics at the University of Southern California, Keck School of Medicine and co-director at the University of Southern California Institute for Translational Genomics since 2016. He was director of the Integrated Cancer Genomics Division at the Translational Genomics Research Institute from 2003 to 2015, where he was deputy director of basic sciences from 2012 to 2015. He was a tenure-track investigator at the National Institutes of Health's National Human Genome Research Institute from 1988 to1994. Carpten earned a Doctor of Philosophy degree in molecular, cellular and developmental biology from Ohio State University.

Kelsey Martin: Martin has served as dean of the David Geffen School of Medicine at the University of California, Los Angeles since 2016, where she has served as a faculty member in the departments of Biological Chemistry and Psychiatry and Biobehavioral Sciences since 1999. She served as co-director of the University of California, Los Angeles-California Institute of Technology Medical Scientist Training Program from 2005 to 2013 and was chair of the University of California, Los Angeles Department of Biological Chemistry from 2010 to 2015. Martin is a member of the Cell Editorial Board, Burroughs Wellcome Fund Board of Directors and the McKnight Endowment Fund for Neuroscience Board of Directors. She is a member of the American Academy of Arts and Sciences and the National Academy of Medicine. After serving as a Peace Corps volunteer in the Democratic Republic of the Congo from 1980 to 1982, she earned a Doctor of Medicine degree and Doctor of Philosophy degree in molecular biophysics and biochemistry from Yale University. Martin completed postdoctoral training in neurobiology with Eric Kandel at Columbia University.

Kim Goodwin: Goodwin has worked with PatientsLikeMe – a social network, decision-support tool and medical research platform dedicated to connecting patients and analyzing patient-shared data – in various capacities since 2011, including as vice president of product and user experience and as a consultant to guide the development of software tools as well as the patient experiences of longitudinal research. Goodwin is the bestselling author of “Designing for the Digital Age” and speaks around the world about designing human-centered experiences. Goodwin was vice president and general manager at Cooper from 1998 to 2009, where she led consulting projects with Cardinal Health, Varian Medical Systems, Merck Medco, Mayo Clinic and Abbott Labs, as well as consumer brands such as Lexus and NBC. Her 24 years of product design and strategy have included work on electronic health records, personal health records, pharmacy websites, consumer glucose meters and insulin pumps and clinical medical devices.

Lisa Suennen: Suennen has spent 30 years in healthcare as entrepreneur, advisor and venture capitalist. Today she leads Manatt Phelps & Phillips digital and technology businesses and the firm’s venture capital fund. Her role spans technology across all sectors, although she also works closely with Manatt Health, engaging with payers, health systems and companies to provide strategic advice on innovation, digital strategy and growth. Additionally, Lisa is co-founder of CSweetener, which matches women in and nearing the healthcare C-Suite with mentors. Lisa is also on faculty at the UC Berkeley Haas School of Business where she teaches the annual class on healthcare venture capital.Lisa spent the last 20 years in venture capital, most recently leading the healthcare fund at GE Ventures and previously as a partner with Psilos Group. Prior to that, she was part of the leadership team that built Merit Behavioral Care, an $800m behavioral healthcare company, through its successful IPO and exit. She previously worked in product management and marketing roles in the technology field. Lisa serves on several private company boards and chairs the advisory board of the NASA -funded Translational Research Institute for Space Health. She is a Fellow of the inaugural class of the Aspen Institute’s Health Innovators Fellowship. She also writes the Venture Valkyrie blog and co-hosts the Tech Tonics podcast.

Mary E. Maxon: Maxon has been associate laboratory director for biosciences at Lawrence Berkeley National Laboratory since 2017, where she was biosciences area principal deputy from 2012 to 2017. Maxon is responsible for developing strategies for the use of biosciences to address national-scale challenges in energy, environment, health and biomanufacturing. She has extensive experience in both the public and private sectors. Maxon served as assistant director for biological research at the White House Office of Science and Technology Policy from 2009 to 2012, where she developed the National Bioeconomy Blueprint. Maxon was director of the Marine Microbiology Program at the Gordon and Betty Moore Foundation from 2007 to 2009 and held executive and management roles at Cytokinetics as associate director and as leader of the Anti-infective Program from 2001 to 2004. She was scientist II and project lead at Microbia Inc. from 1999 to 2001. Maxon served as deputy vice chair at the California Institute for Regenerative Medicine from 2004 to 2006. She earned a Doctor of Philosophy degree in molecular cell biology from the University of California,

Berkeley and completed postdoctoral research in biochemistry and genetics at the University of California, San Francisco.

Mike Milken: Milken is chairman of the Milken Institute, and has long been a leader in medical research, education, public health and access to capital. Beginning in 1969, he financed thousands of companies that collectively created millions of jobs. His philanthropy, which began in the 1970s and paralleled his business career, expanded in 1982 with the establishment of the Milken Family Foundation. The Milken Institute School of Public Health at George Washington University recognizes an Institute gift. As chairman of the Institute's FasterCures center, he has worked to advance precision medicine for many years. Fortune magazine called him "The Man Who Changed Medicine" and Forbes listed him among "Visionaries Reimagining Our Children's Future." Mike graduated from UC Berkeley with highest honors and earned his MBA at the Wharton School. He and his wife of 50 years, Lori, are members of the Giving Pledge; they have three children and 10 grandchildren. Details are at www.mikemilken.com.

Sol Lizerbram: Lizerbram was co-founder and chairman at HealthFusion Inc., a web-based award winning national electronic health records software firm, from 1998 to 2016. The software collects and analyzes data, assisting physicians in meeting quality objectives. Lizerbram was medical director at The Prudential Insurance Company, San Diego from 1986 to 1992. He was appointed to the State of California Workers' Compensation Insurance Rating Bureau Board of Governors in 1993 and served on the California State Insurance Commissioner's Advisory Council from 1991 to 1993. Lizerbram served as chairman of the U.S. Senator John Rockefeller, Health Care Advisory Committee from 1989 to 1991. Lizerbram has served as chairman of the California Expanded Choice Program's Provider Advisory Board and as a member of the California Medical Assistance Commission and California Health Policy and and Data Advisory Commission. He is a fellow of the American Osteopathic College of Allergy and Immunology and received the Nathaniel J. Loeb award for outstanding achievement in medicine. He is president of the Jewish National Fund for the U.S. and a member of the University of California, San Diego Foundation Board of Trustees. Lizerbram earned a Bachelor of Science in Pharmacy from the Long Island University School of Pharmacy and a Doctor of Osteopathic Medicine and Surgery degree from the Philadelphia College of Osteopathic Medicine.

Stephen H. Lockhart: Lockhart has been chief medical officer for Sutter Health since 2015, where he has held several positions, including East Bay regional chief medical officer from 2010 to 2015. Lockhart was chief administrative officer at the St Luke's campus of the California Pacific Medical Center from 2008 to 2010, where he was the medical administrative director of surgical services from 2003 to 2008 and had a long-standing practice of 20 years. A Rhodes Scholar, Lockhart earned a Master of Philosophy degree in economics from Oxford University and Doctor of Medicine and Doctor of Philosophy in biostatistics degrees from Cornell University.

Tomás J. Aragón: Aragón has been the health officer of the City and County of San Francisco and director of the Population Health Division at the San Francisco Department of Public Health since 2011. He has been an assistant adjunct professor of epidemiology (teaching R programming) at the University of California, Berkeley School of Public Health since 2004, where he directed a Centers for Disease Control and Prevention training and research center from 2003 to 2010. Aragón earned a Doctor of Medicine degree from Harvard Medical School, a Master of Public Health degree from the Harvard School of Public Health and a Doctor of Public Health degree from the University of California, Berkeley School of Public Health. He completed a primary care internal medicine residency and a clinical and research fellowship in infectious diseases at the University of California, San Francisco. Aragón has completed leadership training with the California Health Care Foundation and earned certification in Healthcare Strategic Decision and Risk Management from Stanford University.

Appendix 2: Acronyms and Abbreviations

ACES	Adverse Childhood Experiences
ACGME	Accreditation Council for Graduate Medical Education
ACO	Accountable Care Organizations
AI	Artificial Intelligence
API	Application Programming Interfaces
BD2K	Big Data to Knowledge
CalGINA	California Genetic Information Nondiscrimination Act
CalHIPSO	The California Health Information Partnerships and Services Organization
Cal HOSA	California Health Occupations Students of America
CalPERS	California Public Employees' Retirement System
CAP	College of American Pathologists
CASCADE	California Advanced Supply Chain Analysis & Diversification Effort
CDRH	Center for Devices and Radiological Health
CIAPM	California Initiative to Advance Precision Medicine
CKCC	California Kids Cancer Comparison
CLIA	Clinical Laboratory Improvement Amendments
CME	Continuing Medical Education
CMS	U.S. Centers for Medicare and Medicaid Services
CRISPR-Cas 9	A powerful gene-editing tool, stands for Clustered Regulatory Interspaced Short Palindromic Repeats, and associated 9 enzyme
CT	Computed Tomography
CTSA	Clinical and Translational Science Award
DTC	Direct-to-Consumer
EHR	Electronic Health Record
EKG	Electrocardiography
GHR	Genetic Health Risk
GINA	Genetic Information Nondiscrimination Act of 2008
FDA	Federal Drug Administration
FEHA	California Fair Employment and Housing Act
FTC	Federal Trade Commission
FTE	Full-time Equivalent
GDP	Gross Domestic Product
GME	Graduate Medical Education
GOBiz	Governor's Office of Business and Economic Development
HIPAA	Health Insurance Portability and Accountability Act

HITECH	Health Information Technology for Economic and Clinical Health Act
ICER	Incremental Cost-Effectiveness Ratio
IRB	Institutional Review Board
LAUSD	Los Angeles Unified School District
LDT	Laboratory-Developed Test
LLNL	Lawrence Livermore National Laboratory
LMFT	Licensed Marriage and Family Therapist
LPCC	Licensed Professional Clinical Counselor
MACE	Major Adverse Cardiac Events
MIPS	Merit-based Incentive Payment System
MS	Multiple Sclerosis
NCATS	National Center for Advancing Translational Science
NCI	National Cancer Institutes
NGS	Next-Generation Sequencing
NIH	National Institutes of Health
NIMHD	National Institute on Minority Health and Health Disparities
NIST	National Institute of Standards and Technology
NP	Nurse Practitioner
NYSDOH	New York State Department of Health
ONC	Office of the National Coordinator for Health Information Technology
OPR	Governor's Office of Planning and Research
OSPHD	California's Office of Statewide Health Planning and Development
PA	Physician Assistant
PMA	Premarket Approval
PMI	Precision Medicine Initiative
SDOH	Social Determinants of Health
SMASH	Stanford Summer Math and Science Honors Academy
STEM	Science, Technology, Engineering and Mathematics
TBI	Traumatic Brain Injury
UC BRAID	UC Biomedical, Research, Acceleration, Integration and Development
UCLA	University of California, Los Angeles
UC ReX	University of California Research eXchange
UCSC	University of California, Santa Cruz
UCSF	University of California, San Francisco
USC	University of Southern California
WEF	World Economic Forum

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