Report on the California Initiative to Advance Precision Medicine
To the California Legislature
January 2019

California Initiative to Advance Precision Medicine Report
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Report prepared by the Governor's Office of Planning and Research

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Executive Summary

The California Initiative to Advance Precision Medicine (CIAPM), administered by the Governor's Office of Planning and Research (OPR), has continued to support innovative projects in precision health and medicine. Launched by the State in 2015 with $3 million in state funding, CIAPM has grown into a $53 million state initiative — the only state-run program of its kind nationwide. The program has continued to mature. In addition to proof of concept demonstration projects, OPR has started to bring together additional expertise to create a policy framework to support precision health and medicine. The last year had several notable achievements.

2018 Major Milestones:

- The original eight state funded demonstration projects have completed their work and will now undergo a formal evaluation

- Multiple projects have already published in peer-reviewed journals, changing the practice and thought around precision health and medicine interventions

- At least one project has secured a licensing agreement to use their technology, taking the project beyond an academic center and into the broader patient care arena

- A new request for proposals was issued to fund precision medicine approaches for cancer care, specifically addressing health disparities and ways to decrease them through precision approaches

- The Governor appointed the Precision Medicine Advisory Committee which issued "Precision Medicine: An Action Plan for California," a full report on policy actions the state, legislature, and partners can take to further support precision health and medicine

This report provides an update and builds on previous legislative reports for activities in California.

Background

What is "Precision Medicine?"

Precision medicine, also referred to as precision health, is an emerging field that leverages the vast amounts of growing health and other data to better prevent, predict, diagnosis, and treat individuals. There are several definitions across academic institutions as well as different definitions by national and international programs. The California definition is:

> *Precision medicine 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.*

Brief History of CIAPM: 2015-2018

Many countries, including the United States have recognized and launched precision medicine initiatives. California continues to be the only statewide program in the country. OPR administers and oversees CIAPM. The program was initially launched in 2015 with $3million of funding and since that time has grown tremendously to $53 million. The program is established in statute within OPR to do a number of functions not limited to but including:

- Develop, implement, and evaluate demonstration projects
- Collaborate with public, nonprofit, and private entities
- Select projects that have a number of intended benefits for Californians including reducing disparities, have near-term positive health benefits, elicit data understanding, help with system interoperability, and many more
- Develop metrics and monitor the demonstration projects
- Solicit public, nonprofit, and private sector input for additional guidelines
- Provide updates to the legislature

Previous CIAPM legislative reports provide additional background and context.[1] This report provides updates on active issues for precision medicine.

CIAPM Allocation of Funds

Allocation of Funds from FY 2016-17

All of FY 2016-17 funds have been awarded and contracted. The projects have continued to conduct work, and as of December 2018, have all come to completion. See Program highlights below for additional details.

[1] Available at: http://opr.ca.gov/health/

Allocation of Funds from FY 2017-18

The initial projects awarded through a competitive-peer reviewed process were across a variety of disease areas from cancer to heart disease to multiple sclerosis. For the FY 2017-18 funds, the request for proposal was focused on a single disease area – cancer – and informed by broad expert stakeholder engagement focused on the potential for precision medicine approaches to reduce health disparities. The request for proposals (RFP) was initiated in July 2018. The RFP process is currently underway.

Program Highlights

Demonstration Projects

CIAPM's portfolio of demonstration projects covers a breadth of disease areas and institutions across California. Together, the projects have established meaningful partnerships, with universities and research hospitals, companies, patient advocacy groups and institutions. Overall, more than 50 unique public and private entities are involved in the demonstration projects. Teams have continued to seek funding and support beyond the state precision medicine funding.

The projects are not only contributing to medical science, health, and prevention efforts, but they are also serving as platforms to better understand the program and policy needs from a regulatory, patient engagement, economic, educational, and systems change perspective. The program leads are both presenting at national and international conferences as well as submitting publications to help advance the field (see Appendix 1 and Appendix 2).

A brief description and high-level accomplishments of the eight projects are below. Some of the information is repeated from the January 2018 legislative report verbatim to provide background and context with additional text for update. As mentioned, the projects completed their term in December 2018, and will undergo a formal external evaluation with forthcoming reports to the legislature. Demonstration projects are listed in alphabetic order by title. Partner institutions are listed in alphabetical order. New partners added after initial launch are noted with *.

Projects started in 2015

1. California Kids Cancer Comparison (CKCC)
Principal Investigator: David Haussler, UC Santa Cruz

Partner institutions
Research hospitals for which UC Santa Cruz provided analysis in real time for kids in treatment:
British Columbia Cancer Agency*
Children's Hospital Orange County
Pacific Pediatric Neuro-Oncology Consortium (UCSF)

Stanford University

Research hospitals with which CKCC shared analysis and pipeline information:
Children's Mercy Hospital in Kansas City*
Sanford University of South Dakota Medical Center*
University of Michigan, University of Pittsburg*

Advocacy organizations with which CKCC works to monitor family and patient needs, and assist advocacy aims:
Alex's Lemonade Stand Foundation
Amazon Services
Azure
Jacob's Heart
Key for a Cure*
Kids v Cancer
Live For Others Foundation*
St. Baldrick's Foundation*
Team Finn
Team G Foundation
Unravel Pediatric Cancer

Commercial and industry companies with which CKCC has partnered on sequencing platforms, gene analysis, and cloud services:
DNAnexus
Microsoft*
NuMedii
Seven Bridges

Funding
Launched in October 2015, with $1.2 million in CIAPM state funds. CKCC completed their original grant work in April 2017 but shortly there after was awarded supplemental funding of $490,533 under "CIAPM Limited Competition for Supplemental Funds: Request for Proposals" to continue their work until December 2018.

The UCSC team has leveraged CKCC support to gain additional funding from other funding agencies, including St. Baldrick's Foundation for a 5-year grant of $2.5 million, Team G Foundation at $30,000, and Unravel Foundation at $90,000. They have obtained matching funding commitments from Live for Others Foundation at $50,000, Key for a Cure Foundation at $150,000, and local philanthropists, including George and Rafe Kraw at $50,000, creators of the Kraw Lecture Series on Science and Technology. The CKCC team is currently in discussion for other funds to establish a fellowship in big data computing at the Genomics Institute that will be dedicated to pediatric cancer analysis.

Project

The CKCC Treehouse-Stanford Clinical Registry is a collaboration between UC Santa Cruz Genomics Institute and Stanford University. The goal is to study the clinical utility of comparative gene expression analysis for children suffering from pediatric cancer and for whom no standard treatment is available (either because no standard therapy is available for the particular disease or because the child has relapsed and standard therapy is not helping the child). Comparative gene expression analysis offers a readout of genetic and epigenetic changes, which may be treatable with targeted therapies. It is complementary/additive to DNA mutation analyses, which are far more commonly used for cancer cases.

The goal is to provide molecular classification in difficult cases where the molecular or histological subtype of the tumor may not be clear, and, using large data sets (as of November 2018, the dataset of genomic data exceeds 11,000+ tumors expression levels) to identify tumors with similar molecular features. CKCC is then able to identify tumor driver pathways through outlier analyses. The belief is that expression analysis, paired (where available) with more traditional mutation findings, can be used to prioritize potential cancer driver pathways that have a history of responsiveness to certain drugs.

The CKCC pilot project revealed overexpression of genes that could serve as direct and indirect druggable targets, after analysis of 144 cases. Based on this initial finding, the team is evaluating the clinical utility of their analysis framework, by assigning patients into one of four categories based on overexpression of specific druggable pathways. These pathways are RTK: VEGFR/PDGFR/FGFR, JAK/STAT, PI3K/AKT/mTOR, Cell Cycle and a category for others where another pathway is overexpressed. The goal is to demonstrate that comparative gene expression analysis will offer information that is not available through traditional DNA analysis alone. This will benefit California kids suffering from cancers; current estimates are that at least 500 kids per year who suffer from cancer are out of treatment options for their disease. With this pilot project CKCC seeks to gather data on clinical utility of comparative gene expression analysis, which then can be used to offer the analysis to all children suffering from cancer. This extension is of critical importance because it means that children who suffer from cancer will be treated with a precision medicine approach at the outset, often removing years of unsuccessful and painful treatments, accompanied by short- and long-term side effects. The more data that can gather now as to the clinical utility of big data comparative genomic analysis, the more the CKCC team can bring this approach into a standard clinical setting, to benefit all children targeting treatment to their specific diseases early and effectively.

Lessons learned include the need for early testing and early intervention; waiting until kids reach the critical, out-of-treatments stage results in devastating consequences for the kids, family and the California health system. Many of the children reached in this pilot have gone through years of treatment and suffered serious effects from the treatment and the disease progression. The earlier precision medicine analysis can enter standard treatment protocols, the greater the changes of recovery and cure for children suffering from cancer. Time delays have devastating impacts on children's disease progression; slow moving systems (protocols, sequencing turn-around, drug approvals) are serious roadblocks to transforming how care is

provided to children. Only by accepting the need for real change by advancing beyond traditional/standard treatments and engaging with genomic analysis will practice be able to improve the health outcomes and experiences for children who suffer from cancer.

2. Precision Diagnosis of Acute Infectious Diseases (PDAID)
Principal Investigator: Charles Chiu, University of California, San Francisco

Partner Institutions
Abbott Laboratories, Inc.*
American Tissue Culture Collection (ATCC)*
Children's Hospital Colorado / University of Colorado in Denver, CO*
Children's Hospital Los Angeles*
Children's National Medical Center at Washington D.C.
DNAnexus, Inc.
Oxford Nanopore Technologies, Inc.*
Quest Diagnostics, Inc.
St. Jude Children's Research Hospital in Vanderbilt, TN*
Syapse, Inc.
University of California, Berkeley
University of California, Davis
University of California, Los Angeles
University of Maryland*
US Food and Drug Administration (FDA)*
Zuckerberg San Francisco General Hospital and Trauma Center*

Funding
CIAPM
10/1/2015 – 8/31/2018
$1.2 million in state funds
$500,000 supplemental funding under "CIAPM Limited Competition for Supplemental Funds: Request for Proposals

Cohen Foundation Award (Chiu, PI)
2/1/2017 – 2/1/2020
$1.3 million total
"Validation of sequencing-based clinical diagnostics for Lyme disease and other tick-borne infections from blood"

DoD Tick-borne Disease Research Program (Chiu, PI)
10/17/2017 -10/17/2020
$265,097 total
"Development of a combined pathogen-host genomic assay for diagnosis of Lyme disease and other tick-borne infections"

Sandler and Bowes Foundations (DeRisi and Chiu, PI)
9/1/2015 – 9/1/2018
$2.4 million total
In-kind funding for establishment of a Center for Next-Gen Precision Diagnostics (https://nextgendiagnostics.ucsf.edu) and clinical assay development

Charles and Helen Schwab Foundation Award (Chiu, PI)
6/1/2016 - 6/1/2019
$1.2 million total
"Clinical validation of host transcriptome assays for infectious disease diagnosis"

NIH/NIAID 4R33AI120977-03 (Chiu, PI)
1/1/2018 – 1/1/2021
$900,000 total
"Real-time unbiased pathogen detection in febrile illnesses by nanopore sequencing"

George and Judy Marcus Foundation Award (Chiu and Miller, PI)
9/1/2017 – 9/1/2018
$400,000 total
"Implementing precision diagnostics of infectious diseases in the clinical setting"

UCSF Medical Center (Miller and Chiu, PI)
5/1/2015 - present
$500,000 total
In-kind funding for clinical validation of metagenomic next-generation sequencing testing in the CLIA-licensed UCSF Clinical Microbiology Laboratory

Project
Failure to obtain a laboratory-confirmed diagnosis for many acute infectious diseases in critically ill hospitalized patients directly contributes to poor patient outcomes and a high cost burden to the health care system. At UCSF, the Chiu group has pioneered the use of unbiased metagenomic next-generation sequencing (mNGS) for detection of all potential pathogens – viruses, bacteria, fungi, and parasites – in a single test. The goal of this project is to develop, validate, and deploy a clinical mNGS assay for diagnosis of clinical unmet needs in infectious diseases: meningitis and encephalitis, sepsis, and pneumonia. Their accomplishments to date include clinical implementation of a mNGS assay for meningitis and encephalitis diagnosis from cerebrospinal fluid and a 1-year, prospective clinical study of 204 patients across 8 hospitals in California and United States demonstrating that this assay saves lives by yielding additional diagnoses that are not possible with conventional testing. They are further leveraging the data by using machine learning approaches to diagnose human immune responses to infection and antibiotic resistance, and are expanding our validation efforts to sepsis and pneumonia. Economic cost analyses have been performed to understand the clinical indications for the test and in what clinical scenarios is it most cost-effective.

This project will strongly impact health care in California as it provides a comprehensive clinical test to identify infections that cannot otherwise be diagnosed, guiding timely treatment and leading to better health care outcomes at lower cost. An application to the FDA as a "breakthrough device" is pending; regulatory approval would make this test available to patients everywhere and provide a pathway for self-sustainable clinical reimbursement. This project will expand in the next 5-10 years to new indications (sepsis, pneumonia, joint/bone infections, etc.) and new technologies (nanopore sequencing, host response-based diagnosis). The CIAPM seed grant directly led to additional grants from philanthropic foundations (Charles and Helen Schwab Foundation, Steven and Alexandra Cohen Foundation, Marcus Foundation) and commercial interest from top biotech companies and venture capital firms, with negotiations ongoing. A key lesson learned is that downstream implementation of translational research into clinical practice requires dedicated support, a team effort, and an urgency to advance these technologies so that they can directly benefit patients in an accelerated time frame.

Projects started in 2017

3. Artificial Intelligence for Imaging of Brain Emergencies
Principal Investigator: Pratik Mukherjee, UC San Francisco

Partner institutions
Brain Trauma Foundation (BTF)
Community Regional Medical Center in Fresno
Stanford University
TBI Endpoints Development (TED) Project*
Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Consortium*
UC Berkeley
Zuckerberg San Francisco General Hospital and Trauma Center

Funding
Launched in January 2017, with $1.2 million in state funds. In kind support from BTF, TRACK-TBI, and TED.

Project
Every 28 seconds, an American suffers a catastrophic neurologic emergency, most commonly stroke or traumatic brain injury (TBI). Neurologic emergencies affect 15 million U.S. adults and children annually at a cost of $115 billion, which is 7% of total U.S. healthcare spending per year. Since the brain is susceptible to irreversible injury within minutes, immediate diagnosis and treatment are essential. Computed tomography (CT) scanning is currently the only type of imaging used worldwide to diagnose neurologic emergencies. Unfortunately, expertise at the level of board-certified radiologists to accurately interpret these scans is not always available in

a timely fashion, especially at night, on weekends, or at rural health centers. Delayed or erroneous diagnosis can be very costly in terms of lives lost and long-term disability incurred.

In this project, the team has applied state-of-the-art artificial intelligence (AI) technology to automatically recognize life-threatening findings on emergency head CT scans in patients suspected of having TBI, stroke or bleeding due to ruptured brain aneurysms. This AI technology, known as "deep learning", is also used by large tech companies like Google and Facebook to recognize objects in images, such as faces or animals like cats and dogs. This image recognition technology can be revolutionary for the rapid detection of emergencies such as brain hemorrhage and swelling so that physicians can be alerted for immediate action, thereby preventing medical errors from missed or delayed diagnosis. Testing for the automated detection of acute brain hemorrhage shows accuracy equivalent to that of board-certified radiologists, and performance continues to improve. The team is working with industry to implement this AI system in the "cloud" so that CT scans can be uploaded for analysis from anywhere in the world. The immediate diagnosis aided by this technology for rapid automated evaluation of head CT could greatly improve care in the Emergency Department (ED), especially rural areas, and even ambulances, intensive care units, and operating rooms that are increasingly equipped with portable CT scanners. Treatments begun early in the ambulance or ED hold tremendous promise for better outcomes in neurologic emergencies, including fewer deaths and less disability. Reducing disability and shortening hospital stays also produces economic benefits.

Furthermore, until now, it has not been practical to analyze the millions of medical images residing in research repositories worldwide because the necessary human expertise is scarce and expensive. These advanced AI techniques can cheaply and efficiently analyze these large research imaging databases to produce quantitative information about clinically important findings on the scans ("imaging biomarkers"), which can then be combined with clinical, genetic and other types of patient information for Precision Medicine research. This can lead to better clinical trials for effective treatments for TBI, stroke and aneurysmal hemorrhage, which is sorely needed because almost all such trials have failed up to now, in large part due to the lack of useful biomarkers. In the next 5-10 years, the team plans to further improve this technology developed through this CIAPM Demonstration Project and extend it to other types of medical imaging (e.g. MRI scans) and other clinical applications (e.g. cancer imaging) where rapid and automated evaluation could prove beneficial to patient care. Further progress will rely on access to larger databases of patient scans, but in a way that preserves the privacy of the individuals involved. Through cheap cloud-based delivery via the Internet, this technology has great potential to achieve more equitable health outcomes by improving the access of underserved populations to high-quality evaluation of medical imaging, a vital and growing component of modern healthcare.

4. Early Prediction of Major Adverse Cardiovascular Events Using Remote Monitoring

Principal Investigators: Brennan Spiegel; Noel Bairey-Merz, Jennifer van Eyk; Cedars-Sinai Medical Center

Partner institutions
Agilent
AliveCor*
Beckman Coulter
DocuSign
Fitabase
Fitbit
HealthLoop
Neoteryx
SCIEX
Tasso*
Thermo Fisher Scientific
University of California, Los Angeles

Funding
The project launched in January 2017, with $1.2 million in state funds and a total of $639,090 in contributions (Cedars-Sinai $200,000, Neoteryx $12,000, Cambridge Isotope Labs $19,090, Thermo Fisher Scientific $100,000, Beckman Coulter $50,000, and SCIEX $258,000). The project was awarded supplemental funds of $223,261 under "CIAPM Limited Competition for Supplemental Funds: Request for Proposals" in October 2017 with an additional $131,775 in contributions (AliveCor $53,350, SCIEX $1,445, Tasso $10,000, and Cedars-Sinai $55,782).

Project
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 major adverse cardiac events (MACE) may be prevented through treatment intensification and efforts to enhance compliance with life-saving therapy. Accurate assessment of cardiovascular risk is essential for clinical decision making in that the benefits, risks, and costs of alternative strategies must be weighed ahead of choosing the best treatment for individuals. The outcome of interest for this study is MACE, which the team defines as a composite outcome of events including death (all cause), non-fatal MI, non-fatal stroke, or hospitalization for heart failure.

The goal of this project is to use novel remote monitoring techniques to see if there are early signals that might predict who could develop a MACE. MACE includes events like a heart attack or stroke. The team has completed recruitment of around 200 Californians with heart disease who underwent remote monitoring for several months each. The remote monitoring included use of a Fitbit device to monitor step counts, heart rate, and sleep, along with a specialized remote EKG heart monitor called Kardia. Both of these sensors are manufactured by California companies. In addition, we monitored blood tests using a home-based testing kit developed by a California company called Neoteryx. Finally, patients in this study also monitored their quality

of life and symptoms using an app called HealthLoop, which is also developed by a California company.

They are now analyzing all the data to see if there are early clues to predict who could have a MACE occur. They are also evaluating whether this could be a cost-effective approach to managing heart disease. Because heart disease is the top cause of mortality in California and beyond, this study lays groundwork to evaluate more efficient, modern, and cost-effective approaches to remotely monitoring and predicting early signs of MACE, hopefully with the eventual goal of intervening sooner.

5. Full Genome Analysis to Guide Precision Medicine
Principal Investigator: David Martin, Children's Hospital Oakland Research Institute (CHORI)

Partner institutions
GenomeOne*
Human Longevity*
Illumina
University of California, San Francisco (UCSF)
UCSF Benioff Children's Hospital Oakland
University of California, Berkeley

Funding
Launched in January 2017, with $1.2 million in state funds. All personnel, except Hazel Perry and Dario Boffelli, provide their time in-kind. Computational resources in excess of the supported level are provided in-kind at CHORI, UCSF, and UC Berkeley.

Project
This project will advance precision medicine by developing methods to identify mutations that cause inborn or inherited diseases, and assembling a team of doctors and scientists who can carry out those methods. The team will eventually become part of larger international teams, with the long-term goal of creating a catalogue of all DNA variants that can cause human disease. Most inherited diseases become apparent in childhood; analysis of a patient's entire complement of DNA can often find the defective gene responsible for a disease. They use full genome analysis, a method developed by one member of the team, to provide a more complete picture of abnormalities in an individual's DNA. The project has achieved its goal of sequencing the genomes of fifty children affected by genetic disorders, and their parents. They have been able to identify genetic variants responsible for disease in 12 the 28 cases analyzed to date.

The very high identification rate directly benefits patients who receive a diagnosis, by solving medical mysteries that frequently require lengthy diagnostic odysseys with uncertain outcomes. The answers produced by full genome analysis give patients and their doctors insights that permit appropriate management of the condition and thereby reduce the costs of care. The team envisions the data generated by this project contributing to a national effort

that will produce a large-scale database and enable the effective computational identification of genotype-phenotype associations. This will progressively expand the set of actionable genetic variants, allowing more children to benefit from full genome analysis. CIAPM support has allowed them to assemble a team and develop a standardized pipeline for the acquisition and delivery of clinical genome sequence data, which will serve as the nucleus of a larger program. There is a vast assortment of cases, even if only pediatric cases are considered, that are likely to have a genetic cause; thus, full genome analysis could prove to be very broadly useful.

This proof-of-concept work has provided valuable lessons for the successful continuation of the project, and they are working to secure funds to continue the project. The work to date has given the team a clearer picture of the effort required for case recruitment and computational analysis, and the challenges of enlisting and sustaining the participation of physicians who are not familiar with genetics.

6. Personal Mobile and Contextual Precision Health (PERCEPT)
Principal Investigator: Nicholas Anderson, UC Davis

Partner institutions
iHealthLabs*
Overlap Health
University California, Berkeley
University of California, San Francisco

Funding
Launched in January 2017, with $1.2 million in state funds, iHealth contributed in-kind support of $10,000 in services and device discounts.

Project
The PERCEPT project sought to develop and evaluate an integrative personalized health system that allows patients the ability to manage their medically diagnosed chronic care conditions under the direction of their physicians, using their personally owned mobile phones, and in context of their own personal clinical data history. The goal of this project was to identify and overcome barriers for any chronic-care patient to take an active and sustained role in their personal health management, and empower them in health decision making through shared provisioning of their personal outcomes data (blood pressure, mood scales, medication compliance), as well as ubiquitous monitoring data from their phones. The project enrolled over 170 patients with medically diagnosed depression and hypertension to study of engagement, communication and behavior change on their personal Android or iPhones. The majority of patients completing the study reported enthusiasm with having the opportunity to share management of their health, with many requesting additional means to sustain engagement beyond this study, such as more dynamic goal setting capabilities, frequency of communication prompts, and enhanced application usability.

A majority of California citizens are connected - nearly continuously - through smart phones to each other, to their friends, and increasingly to their health data, yet rarely do they have the opportunity to use self-monitoring data captured through their daily activities as part of their personalized clinical health management. As the cost of health care continues to grow for chronic disease management, fewer patients will seek regular clinical expertise to coordinate their care management for reasons ranging from scheduling, transportation, or concerns relating to insurance. This pilot project can be an example of a new form of personalized precision health, where patients provide their own existing and nearly- ubiquitous technology, adopt applications developed through industry partnerships based on recommendations from their care providers or chronic care communities, and define conditions to link their personalized data to clinical data and expertise, wherever they live.

7. Precision Medicine for Early Prostate Cancer: Integrating Biological and Patient Complexity Variables to Predict Treatment Response

Principal Investigator: Sheldon Greenfield, MD (University of California, Irvine and UCI Medical Center)

Partner institutions
Cedars-Sinai Medical Center
University of California, Los Angeles Medical Center
Veterans Affairs Long Beach Healthcare
Veterans Affairs Los Angeles
GenomeDx Biosciences
Ambry Genetics Corporation*

Funding

This study was launched in January 2017, with $1.2 million in state funds and received a supplemental award of $246,205 under "CIAPM Limited Competition for Supplemental Funds: Request for Proposals" in October 2017. In-kind contributions from Health Policy Research Institute and the Donald Bren Foundation added $480,000 in support from UCI. The team has also leveraged in-kind support from two California corporations. GenomeDX Biosciences who has performed the Decipher genomic tests and Ambry Genetics Corporation who has conducted the genetic tests on prostate tissue. Both companies have agreed to absorb the costs of the tests not covered by Medicare or insurance.

Project

Prostate cancer is the most common cancer in men and is the second leading cause of cancer death in men, affecting roughly one in seven men over their lifetime. Patients diagnosed with prostate cancer can face difficult choices about treatments that may involve significant side effects. Often doctors must counsel them without adequate data to explain the likelihood that a given therapy will succeed. The goal of this project is to develop ways to predict, prior to treatment, which therapy will work best for each patient, given how far this disease has progressed and his tolerance for side effects. The project aims to employ a computational approach that considers socioeconomic, health status and other types of data, including

traditional severity indicators, and a genomic test that measures the probability of a patient's cancer spreading after surgery. The final combined prediction model will aid doctors and patients in personalizing prostate cancer treatment decisions to maximize effectiveness and minimize side effects, and choose the treatment optimal for individual patients.

In 2018, it is estimated that 15,190 men will be newly diagnosed with prostate cancer in California. Disparities in the outcomes of prostate cancer treatment persist, with African-American men in particular, at greater risk for poor outcomes. At present, physicians have only clinical information (e.g. PSA levels, tumor stage, biopsy results) to guide treatment recommendations. The goals of this project were to provide, for all men with early prostate cancer, the information on which to base their treatment decisions. More specifically, the goals were to: (1) assess the reproducibility of the risk prediction model in diverse populations and clinical settings; (2) assess the value of the addition of genomic information to the risk prediction model; and (3) build a dynamic updatable registry using the risk prediction model variables that can further add to the ability of providers and patients to personalize treatment options to optimize health outcomes. Both the outcomes of this study and the registry that is created, will provide the information needed at diagnosis to support the doctor-patient conversations that will help these men choose an optimal personalized treatment. This project could serve as the basis for a national model of personalized medicine for prostate cancer.

The team has successfully achieved and surpassed the target recruitment goal of 600 men with newly diagnosed low risk prostate cancer. They have created a database of survey (e.g. stress, resilience, quality of life, satisfaction with care), medical record and administrative data as well as genomic data. The sample has substantial variability by patient characteristics, including race/ethnicity and socioeconomic status, and by characteristics of study sites. Preliminary analyses show differences in multiple survey-based, clinical and genomic variables by race/ethnicity. The team added a new industry partner, Ambry Genetics, which has added germline data, including some rare gene variants, to the tissue-based genomic information we have collected in collaboration with GenomeDx. The addition of these variables, and their possible interactions with survey-based and clinical measures, will allow further improvement of the risk prediction models that can subsequently be used to enhance precision medicine for prostate cancer.

Building upon the state funding, the team anticipates that the registry they have created, and its encrypted data platform, will continue to be used by researchers, providers, and ultimately by patients to understand how best to further personalized treatment for prostate cancer. While they have survey-based outcomes that they will use to evaluate treatment outcomes by risk category at the conclusion of the current CIAPM funding, discovering which of the patient-reported characteristics, clinical variables and genomic data, alone and in combination, contribute to disease progression or recurrence will require them to follow the cohort of men over a longer time interval. To that end, additional funding from federal and foundation sources, in partnership with industry colleagues, is being sought.

A key lesson learned was the critical role of industry partners in the effort to conduct precision medicine research. Combining the rapidly expanding field of genomics, with survey-based, medical record and administrative data in an integrated database allowed and will allow for the examination of the interaction of these variables and subsequently to the occurrence, recurrence and progression of prostate cancer, particularly among different racial/ethnic groups. Each site had its own Institutional Review Board that raised different issues related to protection of human subjects and the creation of an integrated database with personal health information. Addressing these concerns caused delays in the start of data collection. Future multi-institutional studies would benefit from a consolidated process for human subject's protection for the purpose of conducting personalized medicine research.

8. Precision Medicine for Multiple Sclerosis: Making It Work
Principal Investigators: Project inception: Walter F. Stewart, Sutter Health; Current: J.B. Jones, Sutter Health

Partner institutions
Genentech*
Jordan Research and Education Institute
National Multiple Sclerosis Society
University of California, San Francisco

Funding
Launched in January 2017, with $1.2 million in state funds. Early discovery work was supported by $100,000 from the Conrad N. Hilton Foundation, as well as funds from Sutter Health Philanthropy (i.e., $75,000). Efforts to implement a mobile application pilot will be supported with $250,000 from Genentech. Finally, the Genentech Foundation provided $400,000 in additional funding to explore the use of quantitative image analysis for developing cohorts of MS patients within health system that could serve to inform treatment guidance.

Project
Sutter Health and UCSF partnered to take precision medicine for multiple sclerosis (MS) from "the bench to the bedside". MS affects people in the prime of their lives. While patients vary widely in how they experience symptoms, MS can have a major impact on their ability to work, move, and perform other roles. As research speeds up how quickly medical knowledge grows, it's harder and harder for doctors and patients to keep up.

Sutter Health and UCSF built the neuroSHARE application ("app") to combine the latest medical knowledge and data with input from patients, in a single place. 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 neuroSHARE app supports doctors' efforts to keep pace with the latest knowledge so they can provide tailored treatment to each patient they see. It brings precision medicine to the patient – whether that is at a top-ranked UC medical center or in a small rural clinic in the Central Valley.

The team worked closely with patients and doctors to learn what was needed to provide the most precise MS care along with the best patient experience. This input was integral to the development of the final app that was launched at the test-sites. The app collects and combines the latest precision medicine data in real time, and displays it during the patient's appointment. One of the major features is the electronic questionnaire. The team started with a valid but complex MS survey tool. After much time and effort, the team developed it into a questionnaire that patients can complete from home. Patients' answers flow right to the app so they can be used during appointments to guide shared decisions about care and treatment. The final effort – still ongoing – is testing the app with doctors and patients in three neurology clinics.

Basic app design was made possible by philanthropic seed funding; however, the CIAPM funding from the state allowed the team to take the app from a concept to a reality. Continuing forward, more features and MS data sources will be added over the next couple of years based on user feedback and requests. Additionally, the app will be implemented at more clinics beyond the initial three pilot sites. The challenges solved in designing the neuroSHARE app are common to most medical specialties. Over the next decade, the research team will seek additional funding to expand the app beyond MS. This may include headache and other movement disorders.

Translational research involves learning how to solve problems in real world settings. This can be a challenge when it involves adding new technology, partners, and data sources. New ways to doing things require current processes to be modified, and these modifications require early and frequent engagement with legal, privacy, and data security teams. When it came to creating the app, IT teams needed to partner with expert outside vendors. This requires a level of documentation that can be at odds with agile development. The team learned that you have to include the effort required to merge these approaches into your management plan. As healthcare systems evolve to meet the demands of their changing market, research must be ready to adapt.

California's National and International Impact

California continues to have a role in the national and international dialogue in precision medicine. Partners are presenting at academic and policy-oriented conferences nation-wide and internationally with multiple publications in process in the academic and policy literature (see Appendix 1 and Appendix 2). California's role to advance precision medicine serves as a model for other states as well as enables the partnerships needed across sectors and expertise to realize precision medicine. This work is important so that California continues to be a global leader in technological innovation, health promotion, and health care.

Several of the demonstration projects have generated intellectual property that is steadily making progress into the health care market, while others have had their work featured in the news or at popular talks. The "Artificial Intelligence for Imaging Brain Emergencies" project has

secured a licensing agreement to develop a cloud-based application of their neural network for detecting and classifying traumatic brain injuries for worldwide deployment. Developments such as these will continue to develop as the projects and partnerships mature.

Governor's Precision Medicine Advisory Committee

The Governor appointed a sixteen-member Precision Medicine Advisory Committee in October 2017. The projects have been an excellent way to demonstrate precision health and medicine applications and yield tangible health outcome results in the near-term through collaborative, multi-institutional partnerships. Yet, the projects themselves, although important to highlight policy considerations, did not address the larger policy framework necessary at the state and federal level to provide a supportive policy context.

Governor Brown convened the committee through OPR to make concrete recommendations on actions to improve health and health care through precision medicine. The actions were not limited to state actions, but also included federal, local, public, private or private nonprofit sectors. The committee included several academic institutions, non-profits, and for-profits. Expertise spanned the spectrum from health systems, patient engagement, health disparities, economics, education, data, innovation, public health, and much more. The committee hosted six meetings, including virtual and in-person as well as public meetings. In addition to the expertise of the committee, guests were invited to share expertise on specific topics.

The Governor asked the committee to consider some specific areas to guide their thinking including by not limited to:

- 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 health care 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?

The committee released, Precision Medicine: An Action Plan for California in December 2018.[2] This report provides recommendations to address 1) Data in the Context of Precision Medicine;

[2] Available at: http://opr.ca.gov/news/2018/12-26.html

2) Californians as Partners in Care and Research; 3) Education and Workforce; 4) Regulatory Challenges; 5) Finance and Cost Models; and 6) Overarching Considerations.

Next Steps for Precision Medicine

As the program has grown, OPR, through many discussions with stakeholders, examined components of CIAPM that were working well and areas that could work better to advance precision health and medicine in California given the national and international context. Subsequent to those conversations, the Governor proposed an additional $30 million for OPR in FY2018-2019 to establish a non-profit corporation named the California Institute to Advance Precision Health and Medicine. The plan for the institute was to create a board of directors including the OPR director, directors professionally active in precision health and medicine from across California, with directors appointed by the Senate Rules Committee as well as the Speaker of the Assembly. This board would have had fiduciary responsibility and would have represented precision health and medicine efforts statewide, beyond any one institution. The proposed statutory changes allowed the board to fundraise as a non-profit corporation, maintain ties with the state (similar to Visit California), continue to support the competitive-peer reviewed demonstration projects at a statewide level, allow for longer funding cycles, and transition to more policy implementation to further support a policy environment to position California to continue its leadership role. The funding for FY2018-2019 was supported by the Senate, but ultimately did not pass with the new structure in the budget to create the institute. The $30 million was passed in OPR's budget for FY2018-19 with OPR's current statutory authority. OPR, especially in light of the tremendous input and participation through the Precision Medicine Advisory Committee, is investigating the best way to continue to move this important work forward that is reflective of the cutting edge work happening across the state – including the many institutions– as well as ways to continue to support and foster the network of cross-sector, cross-institution partners leading precision health and medicine efforts in California.

Conclusion

Science, technology development, data processing, and storage capacity are all advancing at a rapid pace. California, given its unique ecosystem is poised to continue its leadership role. At the heart of precision medicine is collaboration – across disciplines and institutions – to improve health and health care for all Californians.

Appendix 1: Presentations from Demonstration Projects in 2018

The project partners have shared their cutting edge work with collaborators across the nation and internationally. Key presentations are listed below.

California Kids Cancer Comparison:

- David Haussler gave a PMWC Silicon Valley 2018 talk entitled, "The Human Genome Variation Map" (Jan. 22-24, 2018)
- David Haussler gave a plenary keynote at the Molecular Med Tri-Con in San Francisco as a recipient of the Diagnostics World Early Innovator Award Program (Mar. 10-15, 2018)
- David Haussler and Olena Morozova Vaske presented at the Biden Cancer Community Summit for the city of Santa Cruz centered around "Demystifying Cancer Research at UCSC" (Sep. 21, 2018)
- Ted Goldstein gave a TEDxSanFrancisco talk entitled, "Cancer: Who Lives? Who Dies?," which discussed a case related to the CKKC1 project (Oct.9, 2018)
  Link to video: https://www.youtube.com/watch?v=p5TLbO1wvSM
- Ted Goldstein, Olena Morozova Vaske, and Alenjandro-Sweet Cordero will all be speaking at PMWC Silicon Valley 2019

Precision Diagnosis of Acute Infectious Disease

- Charles Chiu presented a poster at the NASA Human Research Program Investigators Workshop in Texas on "Nanopore DNA sequencing for Microbial Detection and Genome Assembly on the International Space Station" (Jan. 24, 2018)
- Charles Chiu was an invited speaker at the American College of Medical Genetics Annual Meeting in Charlotte, NC (Apr. 13, 2018)
- Charles Chiu presented at the St. Jude Hospital Grand Rounds on Clinical Metagenomics (Apr. 29, 2018)
- Charles Chiu presented at the Pew Foundation/ CDC Meeting on New Technologies in Public Health giving a talk on "Clinical Metagenomic Sequencing for Pathogen Detection" (May 8, 2018)
- Charles Chiu presented at the IPFA/PEI 25th International Workshop on Surveillance and Screening of Blood-borne Pathogens in Athens, Greece on "Bloodborne Pathogen Screening using Metagenomics" (May 17, 2018)
- Charles Chiu presented at the Boston Children's Hospital Grand Rounds in Boston, MA (July 2018)
- Charles Chiu presented at MetaSUB International Conference in Brazil (Aug. 14, 2018)
- Charles Chiu presented at the Next Generation Dx Summit in Washington, DC during a session focused on "Advances in NGS for Infectious Disease Diagnostics" (Aug. 22, 2018)
- Charles Chiu presented at the International Conference of Emerging Infectious Diseases in Atlanta, GA (Aug. 29, 2018)
- Charles Chiu presented at Cornell University Grand Rounds in New York, NY (Sep. 2018)

- Charles Chiu presented at University of Arizona Bioengineering Grand Rounds (Sep. 2018)
- Charles Chiu presented at Infectious Disease Week (IDWeek) in San Francisco, CA (Oct. 2-7)
- Wei Gu presented at the International Conference on Clinical Metagenomics in Geneva Switzerland giving a talk entitle, "Pathogen Detection Using Cell-free DNA in Body Fluids" (Oct. 18, 2018)

Artificial Intelligence for Imaging Brain Emergencies

- Pratik Mukherjee gave a PMWC Michigan 2018 talk entitled, "Precision Imaging of the Human Brain Connectome" (Jun. 6-7, 2018)
- Pratik Mukherjee presented at the Silicon Valley Big Data Science AI in Healthcare Meetup giving a talk entitled, "Artificial Intelligence in Medical Imaging" in Mountain View, CA (Jun 15, 2018)
  Link to video: https://www.youtube.com/watch?v=ejgscF9VvJM
- Weicheng Kuo presented a poster at the 21st International Conference on Medical Image Computing & Computer Assisted Intervention (MICCAI) in Granada, Spain entitled, "Cost-sensitive Active Learning for Intracranial Hemorrhage Detection" (Sep. 18, 2018)

Early Prediction of Major Adverse Cardiovascular Events Using Remote Monitoring

- Jennifer Van Eyk presented at the Mass Spectrometry: Applications to the Clinical Lab in Palm Springs, California giving a talk entitled, "Data on the comparison of Apo B/Apo A-1 ratios from plasma and corresponding Mitra tips showing a linear correlation" during the Plenary Panel: The Future of Clinical Mass Spectrometry (Jan. 23, 2018)
- Kelly Mouapi gave a poster presentation at the American Society for Mass Spectrometry 2018 Meeting in San Diego, CA on "Mitra® microsampling devices in remote, longitudinal monitoring of apolipoprotein B/apolipoprotein A-I in patients at risk for cardiac events" (Jun. 6, 2018)
- Kelly Mouapi gave a research talk at the Human Proteome Organization World Congress in Orlando, Florida entitled, "Evaluating Mitra® Microsampling Devices for Remote Monitoring of Apoliproteins in Patients at Risk for Cardiac Events" (Oct. 1, 2018)
- Abstract for oral presentation was accepted for the 2019 Western Medical Research Conference in Carmel, CA entitled, "Early Detection of Atrial Fibrillation-Atrial Flutter Using Remote Patient Monitoring" (January 2019)

Personal Mobile and Contextual Precision Health

- Nick Anderson presented a poster at the American Medical Informatics Association (AMIA) Summit in San Francisco, CA entitled, "Linking Clinical Events to Patient Reported mHealth Data" (March 13, 2018)
- Meghana Gadgil presented a poster at the Society for General Internal Medicine National Meeting in Denver, CO entitled, "Using Patient-Reported and Mobile Health Data in Practice: Focus on Hypertension and Depression" (Apr. 12, 2018)

- Nick Anderson presented PERCEPT at UCSF focusing on the mental health aspect of the study
- Precision Medicine for Early Prostate Cancer: Integrating Biological and Patient Complexity Variables to Predict Treatment Response
- Sheldon Greenfield gave a PMWC Michigan 2018 talk entitled, "Biological and Patient Complexity Variable Integration Predicts Treatment Response" (Jun. 6-7, 2018)
- Abhinav Grover presented a poster at the American Society of Human Genetics Annual Meeting in San Diego, CA entitled, "Association of race, socioeconomic status and stress with Decipher® genomic classifier risk scores and gene expression: Implications on prostate cancer personalized treatments." (Oct. 19, 2018)

Precision Medicine for Multiple Sclerosis: Making It Work

- Stephen Hauser gave a presentation at American's Committee for Treatment and Research in Multiple Sclerosis in San Diego, CA entitled, "Ocrelizumab Safety in Patients with Multiple Sclerosis: Updated Analyses with a Focus on Infusion-Related Reactions" (Feb. 1, 2018)
- Joanna Cooper, JB Jones, Joshua Liberman, and Walter Stewart led a panel at AMIA 2018 Informatics Summit in San Francisco, CA entitled, "Can Informatics Return the Joy of Medicine? A Real World Pilot in Neurology" (Mar. 13, 2018)

Appendix 2: Publications from Demonstration Projects in 2018

Furthermore, several project teams have already published some their findings in the scientific literature.

California Kids Cancer Comparison

- Preparing a manuscript on "Barriers to Data Sharing" with a focus on pediatric cancer genomic datasets.

Precision Diagnosis of Acute Infectious Disease

- Gu W, Miller S, Chiu CY. 2018. Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection. Annual Review of Pathology: Mechanisms of Disease 14: 317-36 DOI: https://doi.org/10.1146/annurev-pathmechdis-012418-012751
- Miller S, Naccache S, Samayoa E, Messacar K, et al. 2018. Laboratory Validation of a Clinical Metagomic Sequencing Assay for Pathogen Detection in Cerebrospinal Fluid. BioRxiv. DOI: https://doi.org/10.1101/330381
- Additional manuscripts are in preparation for new advancements in the metagenomic next-generation sequencing (mNGS) pipeline and cost-benefit analysis of mNGS pathogen detection compared to conventional testing

Artificial Intelligence for Imaging Brain Emergencies

- Kuo W, Häne C, Yuh E, Mukherjee P, Malik J. 2018. PatchFCN for Intracranial Hemorrhage Detection. ArXiv. https://arxiv.org/abs/1806.03265
- Kuo W, Häne C, Yuh E, Mukherjee P, Malik J. 2018. Cost-Sensitive Active Learning for Intracranial Hemorrhage Detection. ArXiv. https://arxiv.org/abs/1809.02882
- An additional manuscript related to the performance of the neural network has been submitted for publication.

Early Prediction of Major Adverse Cardiovascular Events Using Remote Monitoring

- Speier W, Dzubur E, Zide M, Shufelt C., et al. 2018. Evaluating utility and compliance in a patient-based eHealth study using continuous-time heart rate and activity trackers. Journal of the American Medical Informatics Association 25(10): 1386-91
- Three more manuscripts have been either submitted or are accepted but not available online yet.