

Personalized Health Information Technology (pHIT) Task Force Pilot Study

Volume II: Appendices



California Council on Science and Technology
May 2011

**California Council on Science and Technology
Personalized Health Information Technology (pHIT) Task Force
Pilot Study
Summary Update and Status Report
May 2011**

Volume II: Appendices

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**CALIFORNIA COUNCIL ON SCIENCE AND TECHNOLOGY
PERSONALIZED HEALTH INFORMATION TECHNOLOGY (pHIT) TASK FORCE
PILOT STUDY
SUMMARY UPDATE AND STATUS REPORT
MAY 2011**

Volume II: Appendices

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Appendix A: Stakeholder meeting agenda, 9/19/08



Exploring the State's Role in Personalized Medicine

September 19, 2008
10 – Noon

Location: 980 9th Street, 4th Floor, Suite 480
Sacramento, CA 95814

DRAFT AGENDA

SUBJECT	LEAD	TIME:
Introductions and Framing Assumptions	Kathryn Lowell , Deputy Secretary for Life Sciences and Health Systems, BTH	10:00 – 10:10
Overview of Personalized Medicine	Dr. David Martin , President, Avidbiotics; Chairman, Board of Directors, Bay Bio	10:10 -10:20
Discussion of State Barriers and Opportunities in Personalized Medicine	ALL	10:20-11:20
Moving Forward	Dr. Susan Hackwood , Executive Director, California Council on Science and Technology	11:20-11:40
External Direction and Participation	Dr. David Martin , President, Avidbiotics, Chairman and Board of Directors, Bay Bio	11:40 – 11:50
Conclusion	Kathryn Lowell , Deputy Secretary for Life Sciences and Health Systems, BTH	11:50-12:00

Appendix B: Letter from BTH to CCST, 10/16/08

STATE OF CALIFORNIA

ARNOLD SCHWARZENEGGER
Governor

Department of Alcoholic Beverage Control
Department of Corporations
Department of Financial Institutions
California Highway Patrol
California Housing Finance Agency
Department of Housing & Community Development
Department of Managed Health Care
Department of Motor Vehicles



DALE E. BONNER
Secretary

Office of the Patient Advocate
Department of Real Estate
Office of Real Estate Appraisers
Office of Traffic Safety
Department of Transportation
California Film Commission
California Office of Tourism
Infrastructure and Economic Development Bank

BUSINESS, TRANSPORTATION AND HOUSING AGENCY

October 16, 2008

Dr. Susan Hackwood
Executive Director
California Council on Science and Technology
1130 K Street, Suite 280
Sacramento, CA 95814-3965

Dear Dr. Hackwood,

Personalized medicine is an emerging group of industries in California with possible opportunities for economic development as well as improving the quality and cost of the state's healthcare system. We are seeking to build a partnership with the California Council on Science and Technology (CCST) that will assist the state in assessing the economic impact of personalized medicine on our state.

We would like to create task forces in the areas of macroeconomics, regulation, and information technology. These task forces would provide us with: (1) the design for a pilot study characterizing the economic impacts of personalized medicine in California; (2) guiding principles for lowering any regulatory burdens on emerging companies involved in personalized medicine; and, (3) an assessment of how the state's HIT infrastructure effort can facilitate inter-institutional sharing of information and materials necessary for biomarker validation.

We appreciate the work CCST has done to date in providing the state with critical background information about our technology-based industries. Personalized medicine is another area in which the expertise of your members could be utilized to provide the state a solid understanding of the pertinent issues faced by this group of industries and their relative impact on the economic future of California.

Sincerely,

Dale E. Bonner
Secretary

**Personalized Medicine/HealthCare
MOVING FORWARD PROPOSAL**

Revised: December 5, 2008

California Council on Science and Technology

Personalized Medicine is a rapidly evolving field with significant opportunities for economic development as well as significant implications to the State's healthcare system. However, the role of the State government has not yet been defined.

In general, Personalized Medicine (PM) refers to the tailoring of prevention and medical treatment to the personal characteristics of each individual. It does not literally mean the creation of drugs or medical devices that are uniquely suited to each patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific prevention or treatment. Appropriate preventive or therapeutic interventions can then be applied to those who will benefit, sparing expense and side effects for those who will not.

It is pointed out in a recent report from the President's Council of Advisors on Science and Technology (PCAST)¹, that the current high level of interest in PM from a policy perspective can be attributed not only to the promise of improved patient care and disease prevention, but also to the potential for PM to positively impact two other important trends – the increasing cost of health care and the decreasing rate of new medical product development. This is true at the state as well as the federal level.

Recognizing the business implications to California both as home to the emerging industries and the state government as a purchaser of healthcare services, the Business Transportation and Housing Agency (BT&H) has convened key stakeholders from the public and private sectors to solicit their input. Initial discussions amongst State agencies involved directly or indirectly with healthcare have highlighted the need to know more about how PM will affect the delivery and management of healthcare in California.

BT&H held a meeting of industry and academic leaders in PM from the public and private sectors on September 19, 2008, in Sacramento. Participants at the meeting expressed that a mechanism for informing State government representatives of emerging risks, benefits and opportunities afforded by PM was needed. California could lead the nation in PM policy as it has in climate change and energy.

Based on the discussions at the above meeting, a "Moving Forward" implementation plan and mechanism of operation is proposed below to allow policymakers and implementers to make informed decisions.

¹ Priorities for Personalized Medicine", Report of the President's Council of Advisors on Science and Technology, September 2008.

Appendix C: Moving Forward Proposal, 12/5/08

CCST Proposal:

We propose to create an agile, outcomes oriented advisory group that would be tasked to identify the issues to be addressed by the State, define principles and make specific, actionable recommendations to the responsible entities in the State government. Although this work will be documented, this group would provide product in real time; the output would not rely only on a report being produced.

The proposal is to create a PM Advisory Group comprised of approximately 20-24 S&T/PM leaders, mostly from the private sector, but including the state government and academia. The group would be divided into three Task Forces to focus on topic areas that were identified in the September 19th meeting. Task Force topics include:

- Task Force 1: Macroeconomics
- Task Force 2: Regulation
- Task Force 3: Information Technology

The Task Forces, meeting twice each, would discuss, debate and define guiding principles and make recommendations in their areas of expertise. Initial recommendations would be made at the first Task Force meetings and final recommendations approved at their second meetings. The whole Advisory Group would then meet once again to amalgamate the Task Force outputs and provide the State with guiding principles along with recommendations designed to meet or satisfy those principles. If project commences in January 2009 The work of Task Forces would be completed within six months and the whole effort completed by **October 2009**. This process is diagrammed below.

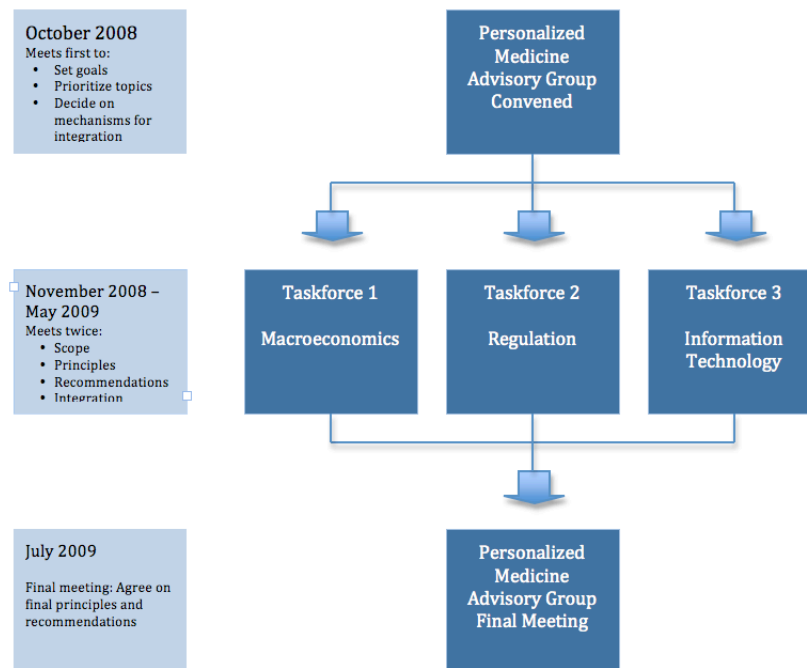


Figure 1. Personalized medicine project process

The California Council on Science and Technology (CCST) would organize this project. It is CCST's statutory mandate from the State to serve in such an advisory capacity. CCST will nominate members of the PM Advisory Group and Task Forces. BT&H would appoint the advisory members and coordinate the liaison with other State agencies and departments. Total cost for this project will not exceed \$195K.

Meetings will be scheduled to maximize the attendance of members. To optimize the productivity of the sessions CCST would provide to all members in advance of the meetings extensive background information relevant to PM and the tasks at hand. This is not another study, but rather a product consisting of defined principles and specific recommendations targeted to the agents of change.

PCAST states that the benefits of personalized medicine are threatened by an array of obstacles including:

- Methodological and logistical challenges in validating apparent correlations between disease and genomics-based biomarkers, which are being generated at an accelerating rate through the latest genomic and molecular technologies
- Regulatory and reimbursement systems that were not designed to accommodate complex genomics-based diagnostics that have the power to sway high-stakes medical decisions
- Absence of the electronic medical record-linked decision support tools needed to effectively integrate the results of genomics-based diagnostic tests into routine clinical practice
- Intellectual property laws and practices that may present barriers to investment in genomics-based diagnostics
- Privacy concerns that may limit patient acceptance of genomics-based diagnostics
- Education of patients and physicians on the proper use and limitations of new genomics-based diagnostics

We shall build on this analysis and that of others such as reports being produced by the Personalized Medicine Coalition and a Deloitte report on "Where is the ROI for Targeted Therapies? Assessing the barriers and incentives for adopting personalized medicine,"² especially focusing on specific issues of California and California State government.

Task Forces

The project will be accomplished by a series of 8 meetings. Recommendations will begin to emerge immediately from the first meeting and will continue to evolve during the project process. During deliberations, pilot programs that could be initiated promptly by the State government will be suggested.

Note: Revise timelines here.

Project Steps:

1. Formation of PM Advisory Group – February, 2009

² Where is the ROI for Targeted Therapies? Assessing the barriers and incentives for adopting personalized medicine" scheduled for release in January 2009.

To ensure neutrality and balance, Task Force members will be nominated by CCST and appointed by BT&H. Approximately 20-24 members will be selected based on their competencies in areas that represent industry, academia, non-profit and state agency leaders in fields that represent the various interests in personalized medicine. Members will serve pro bono, but meetings costs will be covered, and CCST staff will provide the background work and support to enable efficient and productive use of time. The whole group will meet once for a 4-6 hour meeting to agree on goals, Task Force priority topics and mechanisms for integration.

2. Task Forces – March 2009 - July 2009

Three Task Forces will be created comprised of 6-8 members of the Advisory Group. Each Task Force as a group will meet twice for a half-day. The first meeting, held between October and January, with appropriate preparation by each member will scope the issues and make preliminary recommendations. The second meeting, held approximately one month later, will be to review, refine and confirm the principles and recommendations. The 3 Task Forces will work in parallel, a total of 6 meetings. BT&H will invite appropriate state agency participation in all meetings.

3. Integration of Recommendations – September 2009

The PM Advisory Group will meet one last time to integrate the outputs of the focused Task Forces. Recommendations will be targeted to the State government, as provided through the convener, BT&H.

4. Principles and Recommendations – October 2009

After a confidential peer review from within CCST (timeline: within approximately two weeks) and endorsement by CCST, a summary will be transmitted to BT&H.

The proposed Task Force model described above was used in a prior CCST project entitled *Shaping the Future: California's Response to Rising Above the Gathering Storm*.³ In that case, the creation of four high-level Task Forces operating in parallel to address a well defined set of topics created a mechanism for providing agile, real-time feedback and recommendations to the State government on critical issues of economic competitiveness. Task Forces produced recommendations, and members then oversaw the production of a single, consolidated set of recommendations. As a fairly large group of people is involved, this method has the advantage of getting key stakeholder buy-in during the project execution.

Task Forces topic areas identified at the September 19 Public/Private Collaborative Meeting include Macroeconomics, Regulation and Healthcare Information Technology. The Task Force members will prioritize the issues to be addressed in order to ensure a focused deliberation.

Task Force 1: Macroeconomics

Charge is to design a pilot study of the short- and long-term economic impacts of PM in California including a disease specific, real world example of a prospective pilot where health outcomes and cost implications will be determined.

³ More information for the CCST project and final publications can be found at <http://www.ccst.us/publications/2006/2006gatheringstorm.php>.

Work will involve recommending a focused, prospective macroeconomics analysis of personalized medicine as applied to one or a few specific diseases or disorders of significant health and fiscal impacts in California. This will be accomplished through in-depth discussion with economists, medical and industry experts and possibly a new analysis that will provide reasoned assessments of the macroeconomics of PM and the involved industries over a five- and ten-year period.

Candidate Topic Areas:

- Macroeconomic impact of personalized medicine to CA state government as a health care purchaser – as costs and savings are shifted. Where are the potential impacts as applied to, for example, diabetes, maternal-fetal medicine, breast cancer or AIDS? Which agencies and California businesses as employers will be affected?*
- The cost effectiveness of generating in California a more attractive business climate supporting innovation and development of advanced technologies for PM.*
- The macroeconomics of uniform policies on payer coverage and reimbursement.*

Possible Outcomes

Guiding principles, scope and specifics of possible pilot programs the State could readily initiate related to MediCal and CalPERS populations, e.g. including recommended use of drugs, therapies, etc. with measureable outcomes. Determine nature of prospective pilot study, parameters to be used, and projected time period required for completion. Potential measureable economic outcomes may include lost work days and tax revenue implications, costs of hospitalization, diagnostics and therapeutics, etc.

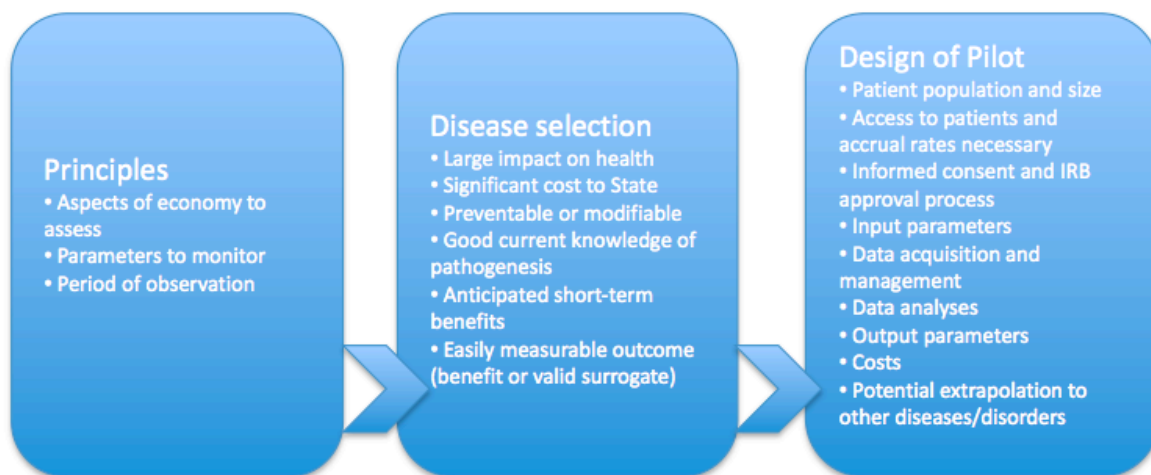


Figure 2. Development process for pilot

Task Force 2: Regulation

Charge is to explore need, and propose guiding principles and make specific recommendations to promote innovation and mitigate the State's regulatory burden on emerging companies involved in PM.

Candidate Topic Areas:

- a. Develop principles of early regulatory consistency and clarity between federal and state laws, with particular attention to CLIA (Clinical Laboratory Improvement Amendments)⁴*
- b. Investigate and develop principles for rational adjudication*
- c. Evaluate the need to improve regulatory certainty in payment reimbursement*
- d. Investigate any regulatory impediments to accelerating innovation to the marketplace*
- e. Propose regulatory system modifications to promote disease prevention.*

Possible Outcomes

Specific principles the State should adopt and recommendations on State regulations that should be added or removed.

Task Force 3: Health Information Technology

Charge is to examine the HIT infrastructure goals for the state in the context of PM, especially looking at archiving and sharing of information and materials necessary for biomarker validation.

Candidate Topic Areas:

- a. Examine and recommend specific improvements to data storage and management infrastructure at present*
- b. Recommend policies on and means of **Archiving and Sharing of Materials**. At the present time, there are no clear guidelines for the sharing of collected materials that both protect the patient's privacy and allow researchers access to vast amounts of information necessary to validate biomarkers and supporting technologies and to improve health and medical care. Inter-institutional mechanisms of storing, sharing and protecting materials and data need to be created, taking into account the significant legal and policy issues.*
- c. Assessing impact of GINA⁵ and of non-genetic biomarker-based information as it relates to archiving and sharing of materials.*

Possible Outcomes

Recommendations to the State and to the Privacy and Security Advisory Board⁶(PSAB) for validating and sharing (inter-institutional) information, tools and materials of PM (e.g. EMR, archiving images and pathology specimens).

⁴ Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed. <http://www.fda.gov/CDRH/clia/>.

⁵ Genetic Information Nondiscrimination Act: 2007-2008, to prohibit discrimination on the basis of genetic information with respect to health insurance and employment. <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493>.

⁶ California Privacy and Security Advisory Board (CalPSAB) charged with making recommendations on privacy and security standards for State. <http://www.chhs.ca.gov/INITIATIVES/HEALTHINFOEX/Pages/CalPSAB.aspx>

Scoping of potential prospective pilot for archiving and inter-institutional sharing of information and materials of PM.

In addition to the recommendations being developed by the Task Forces, CCST will undertake an examination of the existing or needed workforce development to support the shift of healthcare systems to PM practices.

Workforce analysis will:

- a. Identify options for building a personalized medicine-informed health care workforce through collaboration among personalized medicine industry experts and education/training providers to target needed workforce skills and critical education pathways.
- b. Explore education/workforce training needs among medical personnel as well as development of appropriate continuing education programs. Include exploration of need to infuse personalized medicine concepts and tools into medical school curricula.
- c. Investigate need to develop a consumer education program regarding the benefits of personalized medicine and engaging consumers in the personalized health care process, including dialogue with providers and payers.
- d. Examine public policy needs supporting education and workforce development required by this emerging industry.

Appendix C: Moving Forward Proposal, 12/5/08

BUDGET ESTIMATE

	<u>BUDGET</u>
Project Management	
CCST Staff and Consultant Salaries*	\$125,060
Benefits based on 32%	\$40,020
Meetings and Travel	
Staff Travel	\$4,400
Task Force & Advisory Group	\$12,000
Meeting Costs	
Refreshments/Lunch	\$3,960
Report	
Writer	\$6,500
Production, Design, Publication of report	\$500
Supplies and Office Expenses	
Misc. expenses (postage, supplies, telephone expenses, etc.)	\$1,200
	<hr/> <hr/>
Total Costs	\$193,640

Does not include indirect cost recovery of 19.2%

*Includes:	Executive Director - 1 day per month	5%
	Project Director	100%
	Project Associate	70%
	Administrative Support - 4 days per month	20%

Appendix D: Task Force meeting notes, 5/27/09

CALIFORNIA HEALTH INFORMATION TECHNOLOGY TASK FORCE

DRAFT ONLY

MEETING: WEDNESDAY, MAY 27, 2009

3:00 – 7:00 P.M.

HYATT REGENCY HOTEL

SEQUOIA ROOM

SACRAMENTO, CALIFORNIA

MEETING SUMMARY:

Attendees:

Charles Kennel, Chairman, California Council on Science and Technology

Susan Hackwood, Executive Director, California Council on Science and Technology

Ramesh Rao, Director, UC San Diego Division, California Institute for Telecommunications
and Information Technology

David Martin, CEO, AvidBiotics

Alex Kam, Office of Information Integrity, Health and Human Services Agency

Kathryn Lowell, Deputy Secretary, Health Systems and Life Sciences, Business, Transportation and
Housing Agency

Jeffrey F. Moy, M.D., Medical Consultant, CalPERS, Health Benefits Branch

Richard Sun, M.D., MPH, CalPERS, Health Benefits Branch

Ellen Badley, MHA, Division Chief, CalPERS, Health Benefits Branch

Robert MacLaughlin, CCST

Diana Rude', CCST

Lora Lee Martin, CCST

By conference call:

Alfonso Cardenas, UCLA Professor, Computer Science Department

Steve Shak, M.D., Chief Medical Officer, Genomic Health

Jay (Marty) Tenenbaum, Founder and Chair, CollabRX

Guest: Charles Kennedy, Well Point, Inc.

Charles Kennel, Chairman, California Council on Science and Technology, welcomed the Health Information Technology Task Force and noted he would like to share CCST's enthusiasm and commendation for the valuable work the HIT Task Force is doing. Charles Kennel noted he has directed the Scripps Institution of Oceanography.

Susan Hackwood (an electrical engineer), Executive Director of CCST, noted that CCST is equivalent to the National Academies or the National Research Council in Washington but for the State of California,

Appendix D: Task Force meeting notes, 5/27/09

and serves to advise and provide scientific and technical expertise to State government. CCST has an extraordinary group of experts committed to working on issues related to public policy, such as energy, climate change, health care, education, etc.

Other participant introductions followed.

Task Force Chair, Ramesh Rao opened the meeting noting he is an electrical engineer by training. His Involvement in the California Institute for Telecommunications and Information Technology – has led him to become involved in projects related to information technology, telemedicine, etc. Much of the Institute's involvement is centered around data.

Kathryn Lowell noted she and BT & H have been involved with this collaborative HIT Task Force effort with CCST for a number of months. It originally began with three separate task forces (i.e. Macroeconomics, Regulation and Health Information Technology). What has now emerged is the result of the opportunity around the Federal Stimulus dollars, i.e. the role of Health Information Technology and specifically electronic medical records – i.e. the role that HIT plays in the advancement of personalized medicine. Unless we can collect appropriate data, store it and share it, personalized medicine will not see its potential as an industry. This effort has focused now on Health Information Technology as a platform.

Kathryn noted that, over the last month, other task forces have been created in State government (i.e. through the State Health and Human Services Agency). A newly appointed Deputy Secretary for Health Information Technology at Health and Human Services Agency (HHSA), Jonah Frolich and Kathryn have talked and determined what the CCST Personalized Health Information Technology Task Force (pHIT) is accomplishing here will contribute to the work of the HHSA's Health Information Exchange (HIE) Workgroup process.

Kathryn stated the question will be how this HIT Task Force will be integrated into the larger State effort. This Task Force is not a policy committee or regulatory making body, but rather -- to separate us from other efforts going on in the State – it is a real live deliverable – a real world pilot that can be tested out, i.e. that these are the data elements for an Electronic Health Record that make personalized medicine a reality. Example: This is the way a personalized health record platform will need to be changed or added to make personalized medicine a reality. Kathryn suggested renaming this Task Force to further distinguish it from other efforts and suggested adding personalized health to the task force name. Following discussion, “ Personalized Health Information Technology Task Force (**pHIT**)” was suggested as the new task force name.

Ramesh Rao stated a first goal will be to fine tune the charter of this Task Force leading to the design of a pilot. Our goal will be to design a pilot with expected outcomes that a pilot will bring clarity to.

Susan Hackwood added that Robert MacLaughlin is also working on workforce development focusing on the health care workforce of the future. It will be a parallel effort to the work of the **pHIT** Task Force.

Appendix D: Task Force meeting notes, 5/27/09

Susan also noted there are funds currently available to do the planning phase of this work. As customary for CCST projects, each Task Force member's work is pro-bono. David Martin queried whether there are skills that the Task Force is missing. We may decide we really need a particular skill base and the list of CCST Council Members and CCST Fellows is large enough that we can tap that resource to identify what skills we may be missing. Ramesh Rao noted that how we structure our pilot – i.e. depending on who our partner is -- we may need someone else to assist in effectively doing that piloting.

Kathryn suggested our charge is how do we enable personalized health through an electronic platform.

Charles Kennedy of Well Point, Inc. noted there is a data architecture problem. In many of the health information exchanges Charles has observed is a messaging model where the effort is to send a message from Point A to Point B but never achieves a single representation of a patient that everyone contributes to and becomes a longitudinal effort. What is needed is a single record of a patient that follows a patient wherever they go over time. Many of the health information exchanges won't give you that tracking mechanism. Kathryn added what kind of data (including genomic data) do we need to collect and track that we aren't tracking now that will result in further personalizing that single record.

David Martin added identification of obstacles – i.e. whether they be technical, legal, regulatory or privacy issues that impact trying to enable personalized trackable information allowing a patient to improve his/her own health and allows researchers to gather the data to improve those inputs.

Ramesh queried what will be the outcomes.

Kathryn noted it depends on who client is. In the case of CalPERS, could identify some disease states noted earlier – i.e. diabetes. A goal would be improving patient health outcomes and cost, i.e. can we improve health and reduce costs? The ability to collect -- over a period of time -- data on an individual – including certain genomic data.

David Martin suggested a pilot study question would be: How does the collection of data and knowledge about an individual patient affect the outcomes of that individual and other individuals with similar predispositions and/or disorders? How can we benefit the patient, the provider and the reimbursor?

Alex Kam, HHS, noted one of the outcomes to consider measuring is the new package of information must be treated differently by the provider system. If you send new, richer information into the same provider system mode, there is no guarantee they can absorb it, integrate it or apply it to the benefit of patients. Who are the right types of people to use this information?

Alex Kam further noted we could bring the California Privacy and Security Advisory Board collaborative process to help be involved in the pilot in terms of testing certain controls and standards. What unique

Appendix D: Task Force meeting notes, 5/27/09

types of issues will need to be considered in terms of privacy and security issues. What regulatory changes will be needed? Identify potential red flag issues in the design stage.

David Martin noted folding the regulatory issues in as a deliverable of this task force, i.e. identifying regulatory issues that would constitute barriers. Ramesh Rao noted that if there are regulatory issues or privacy concerns that would impact the architecture of what we are doing, it would be important to identify that up front.

Charles Kennedy reported on the work of Well Point, Inc. in exploring pilot implementations of electronic health records, etc. Dr. Kennedy reported he and his company have been involved in several RHIO'sⁱ nationally and have also run pilot projects, i.e. in St. Louis. Dr. Kennedy serves on the federal HIT Policy Committee, a body endeavoring to come up with a framework to spend federal stimulus funds correctly. (Note: American Recovery and Reinvestment Act directs Federal Stimulus funds to HIT; also Title IV on Health Information Technology is contained in current pending legislation in Congress)ⁱⁱ It was noted the Health Information Technology for Economic and Clinical Health Act is a key element of the House-Senate economic stimulus bill, proposing to invest \$36 billion in new funds in Health IT infrastructure along with Medicare and Medicaid incentives to encourage doctors and hospitals to use HIT to electronically capture and exchange patient health information.

Dr. Kennedy notes a vast majority of data systems can't deal with variations of health care data. There is no current system to track a patient over time. He noted an ontology is needed to effectively store all data relevant to a patient. Doctors are not data entry clerks but are data entry consumers.

Kennedy noted Well Point, Inc. (a health claims processing company) is seeking a partner or partners to roll out an innovative Health Information Technology pilot. The initial results have indicated a positive impact on care in ways not possible before. Dr. Kennedy has met with the University of California – which has an RFP out that Well Point has responded to. Presentations have been made to Cal PERS, Medicaid, and commercial entities as well. This will take collaboration.

Well Point's partnering vendor is CentriHealth (headed by Dr. Ralph Cortman, an oncologist at Loma Linda). Dr. Cortman has built and sold about 7 companies. Cortman's Chief Medical Officer, Dr. Anthony Knowland, was the architect of a British Health Care Initiative. Centri Health has been working on their health information technology platform system since 2002. The CentriHealth equipment is produced by SUN and the technology is high quality and designed to track a patient over time. Dr. Kennedy invited the Task Force to meet with Centri Health, if there is interest. He noted there are not a large number of vendors to choose from, but Well Point conducted a review of vendors and found Centri Health to be the most high quality option. The Centri Health system is a custom object oriented box, normally hosted at a hospital or another hosting facility. Centri Health conducts training to utilize the system.

In a Kettering Health Network proof of concept pilot with this technology, 70% of employees who logged on used the system at least once and 45% used it 3 or more times. 10,000 members and 300 doctors

Appendix D: Task Force meeting notes, 5/27/09

participated in the Kettering pilot. Additional pilots are being launched by Well Point commencing in June 2009.

Dr. Cardenas asked if Well Point has looked at a system called Tolven? Cardenas noted the Tolven system appears closer to the infrastructure Well Point appears to be seeking.

Jeffrey Moy, CalPERS indicated the Health Plans and payers are interested in how we can facilitate a stronger relationship between the doctor and the patient.

Charles indicated a PHR disease management system for the patient could be rolled out within a region. Data could be collected to be made available to members and also may be made available to a health coach. An IHR integrates all clinical and financial data on a regional basis creating a comprehensive, shared clinical and financial record for the patient and the doctor. Improvements in physician productivity have occurred via real time patient data.

Dr. Ramesh Rao presented the following as a **proposed work plan and timeline for the Personalized Health Information Technology Task Force (pHIT)**:

PERSONAL HEALTH INFORMATION TECHNOLOGY TASK FORCE – (pHIT)

(Health Information Technology Task Force)

CONFERENCE CALL – JUNE 5th

To Do List/Next Steps:

- Finalize Charter
- Outline Pilot
 - Target Disease/Conditions
 - Centri System Feasibility
 - Clinical/Genomic data
- Finalize Architecture Study Topics
 - Open Access
 - Research Opportunities

Assignments

Ramesh Rao

Richard Sun, Jeff Moy, CalPERS
Ramesh Rao, Alfonso Cardenas
Steve Shak

Ramesh Rao
Susan Hackwood/Alfonso Cardenas
Kathryn Lowell, B T & H

MEETING #2 -- Late July

- Launch/Finalize Pilot

Appendix D: Task Force meeting notes, 5/27/09

- Scope
 - Metrics to assess
- Invite Centri Health/Well Point, Inc. description
 - What are the system issues, if any
 - What are the regulatory issues, if any
- Enlist other participants (**i.e. QUALCOMM and other candidate companies**)
- In September, approach the CalPERS Board during their meeting.
 - HIT Workgroup (**Health and Human Services Agency**)

MEETING #3 -- October

- Monitor Progress
 - System
 - Outcomes

MEETING #4 -- November

- Review
- Hand off

ⁱ Regional Health Information Organization – defined as a Health Information Organization that brings together health care stakeholders within a defined geographic area and governs health information exchange (HIE) among them for the purpose of improving health and care in that community. (Source: Wikipedia)

ⁱⁱ Title IV, Health Information Technology as contained in S.350 in the US Senate and H. 598 in US House of Representatives as of May 2009, containing incentives and guidelines for development and use of HIT.

Appendix E: Steven Shak memo to Task Force, 7/30/09

DRAFT ONLY

DRAFT ONLY

TO: Members, pHIT Task Force

FROM: Steven Shak, MD, Genomic Health

**RE: TARGET DISEASE(S) CONDITION(S) CANDIDATES OF GENOMIC TESTS
TO BE INCLUDED IN pHIT PILOT STUDY**

DATE: July 30, 2009

I have been working with Richard Sun and David Martin on a summary of our initial ideas raised at the last teleconference concerning target diseases/conditions for pilot study.

Two teleconferences were held to evaluate and select target disease(s)/condition(s) candidates of genomic tests to be included in the pHIT Pilot Study.

The criteria for selection were reviewed, and were based on the proposed CHARGE and MISSION of the Personalized Health Information Taskforce. Some of the key criteria included:

1. Genomic test available and reimbursed as standard care recommended by current guidelines with direct relevance to important health outcomes/costs.
2. Clear potential for personalized health information to provide value to patients, providers, and payors.
3. Capable of delivering pilot results within one year.
4. Potential for showing cost-effectiveness.
5. Overlap with CalPERS priorities.
6. Key data sources available and amenable to the available health IT “solutions.”
7. Will result in progress on regulatory issues related to personalized health information.

More than 10 candidate diseases and genomic tests were reviewed. Genomic tests in cardiovascular conditions (e.g., Warfarin metabolism test), cancer, liver disease, neuropsychiatric disease, muscle and bone disorders, and respiratory disorders were considered and compared with CalPERS priorities.

Appendix E: Steven Shak memo to Task Force, 7/30/09

Most of the candidates did not meet our key criteria.

However, our evaluation identified two individualized genomic tests in cancer – Oncotype DX, a test of acquired individual genomic signatures in the tumor that is recommended to guide who should be given chemotherapy at the time of breast cancer diagnosis, and BRAC Analysis, a test of inherited genetic alterations that are recommended to guide use of strategies that would prevent breast and ovarian cancer. A detailed overview and background information for each are provided in the attached documents. Both Oncotype DX and BRAC Analysis appeared to have very high potential to meet all the above criteria and our CHARGE:

1. Propose hardware infrastructure and software services goals for the State in the context of Personalized Health [\[1\]](#) (pH). Evaluate technologies for and obstacles to archiving and sharing of information and knowledge based materials necessary for personalized health including biomarker validation, outcomes measurements, and patient and clinician access to broadband electronic personal health record (PHR).
2. Develop a pilot that can be tested for purposes of evaluating the use of personalized health data in an appropriate personal health record platform with a goal of offering in an open electronic format a comprehensive record of a subject (patient) that tracks the individual over time while protecting privacy.
3. Include as a deliverable a limited assessment of regulatory issues anticipated or confronted in the pHIT Task Force pilot in the context of potential impacts on system architecture and on data-information accessibility and sharing.
4. Include as a deliverable a list of potential Federal Stimulus funding opportunities for pHIT.

<<Overview of BRCA Analysis DM revised.doc>> <<Overview of Oncotype DX DM revised.doc>>
<<ASCO Tumor Marker Oncotype Guidelines JCO 2007.pdf>> <<Lyman Health Economics Oncotype Cancer 2007.pdf>> <<NEJM 2004 Paik NSABP B-14 Oncotype.pdf>> <<ASCO SSO Review Risk Reducing Surgery 2006.pdf>> <<ASCO policy genetic testing 2003.pdf>> <<Rebbeck NEJM BRCA Article 2002.pdf>>

Overview of Oncotype DX®

Summary

Oncotype DX

Oncotype DX is a commercially available multi-gene expression test that has established clinical utility to guide the use of chemotherapy for patients who are diagnosed with invasive early-stage breast cancer. The clinical utility is based on well controlled clinical studies which support its ability to predict the likelihood of chemotherapy benefit as well as recurrence. Oncotype DX has been evaluated in multiple independent studies with evidence obtained in more than 4,000 breast cancer patients, including a large validation study published in *The New England Journal of Medicine* and a chemotherapy benefit study published in the *Journal of Clinical Oncology*.

The Oncotype DX test is a genomic test which examines the acquired abnormalities that are found only in the tumor tissue. These tumor acquired abnormalities cannot be passed along to one's offspring. Genetic counseling is not a component of Oncotype DX testing.

To date, 7,500 physicians have ordered more than 100,000 tests, and both Medicare and private health plans covering over 90 percent of U.S. insured lives provide reimbursement for Oncotype DX through contracts, agreements and policy decisions. Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network recommend the use of Oncotype DX for patients with node- negative breast cancer that is estrogen-receptor positive and/or progesterone-receptor positive. Technology assessments from the Blue Cross/Blue Shield Technology Evaluation Center (BCBS TEC) and the Agency for Healthcare Research and Quality (AHRQ) and economic analyses of the Oncotype DX-guided therapy compared with tamoxifen alone demonstrate greater efficacy with substantial cost savings with the use of the multi-gene assay to guide therapy.

Patients have reported great interest in knowing the results for the individual biology of their tumors. A small number of studies have been performed to document the changing patterns of care and treatment that accompany the use of Oncotype DX. The individual and societal impact of this application of personalized medicine has not been evaluated in California.

Unmet Need in Breast Cancer Care that Led to the Development of Oncotype DX

In 2008, the National Cancer Institute estimated that approximately 200,919 new cases of invasive breast cancer are expected to be diagnosed in the United States. It is a high priority to provide the optimal treatment at the time of initial diagnosis. Treatment at the time of initial diagnosis of localized disease (cancer confined to the breast and/or regional nodes) has traditionally been based on evidence provided by large clinical trials and clinical guidelines. In contrast, treatment of metastatic breast cancer, that is, cancer that

Appendix F: Overview of Oncotype DX

has spread to the lung, liver, bone, etc. is often empiric and many palliative treatment regimens are offered.

Almost half of the new cases are lymph node-negative (LN-), estrogen receptor positive (ER+) tumors.¹ Approximately 17% (tumor size 0.1-1.0 cm) to 34% (tumor size 2.6-3.0 cm) of women with node-negative, ER-positive tumors are at risk of distant recurrence within 10 years with no adjuvant therapy. The landmark NSABP B-14 study indicated that tamoxifen has clear efficacy and can reduce that distant recurrence rate to 15%.² A later study conducted by Paik et al found that in a group of 651 tamoxifen-treated patients, the proportion of patients without distant recurrence at 10 years increased just 4.4%, from 87.8% to 92.2%, with the addition of chemotherapy to the treatment regimen.³

For each patient, this benefit must be weighed against the risk of adverse events. Chemotherapy-related adverse events occur in almost all patients and more than 1 in 10 women experience a serious or life-threatening event.⁴ Between 1 in 100 to 1 in 500 women actually die from side effects related to the administration of chemotherapy. Other adverse effects include ovarian failure, cardiotoxicity, nausea, and hair loss. As Paik et al concluded, "The likelihood of 10-year distant recurrence in patients treated with tamoxifen alone is about 15%, at least 85% of patients would be over-treated with chemotherapy if it were offered to everyone."²

Clinical guidelines exist (based on clinical markers such as tumor size, age of the patient, and tumor histology) to guide the decision of who should undergo chemotherapy. Guidelines define most women with node-negative, ER-negative breast cancer as having higher risk of recurrence than ER-positive women, thus more than 60-70% of women receive adjuvant chemotherapy and at least 1 in 2 women receiving adjuvant chemotherapy are subject to the risk of early and late adverse events without a clearly defined sub-group for which benefit is ascribed.⁵

Large clinical trials, such as the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) trials (B-14 and B-20), have demonstrated the benefit of tamoxifen and adjuvant chemotherapy in women who have node-negative, ER-positive breast cancer.^{2, 6} Because the likelihood of distant recurrence in patients treated with tamoxifen alone after surgery exceeds 10% at 10 years, the results from these trials have supported a treatment trend toward use of adjuvant chemotherapy across this population.

A more reliable method of identifying those patients due to receive benefit from chemotherapy could provide both better treatment outcomes and potentially save many from the adverse effects of chemotherapy.

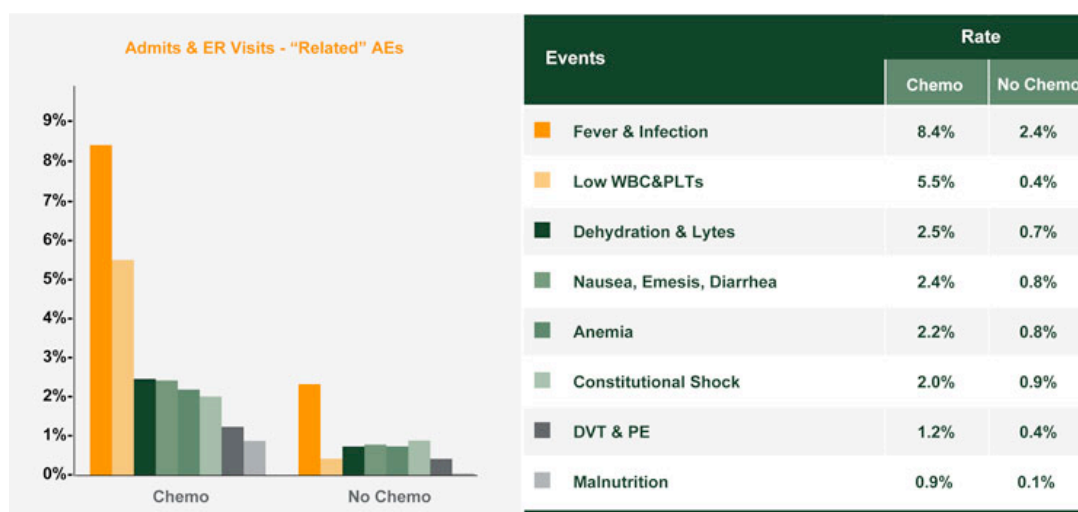
Risks of Adjuvant Chemotherapy

Chemotherapy is associated with serious early and late adverse events (AEs).³ In the following Figure 1, Hassett and colleagues displays the difference between hospital admission and emergency room visit rates among breast cancer patients with and without

Appendix F: Overview of Oncotype DX

chemotherapy.⁷ Chemotherapy-related adverse events were more common among chemotherapy recipients (infections, neutropenia, thrombocytopenia, anemia, nausea, emesis, diarrhea, malnutrition and dehydration) whereas chemotherapy-unrelated adverse events (hip fractures, etc.) were not, after adjusting for age, co-morbidities, metastatic status and other factors. Approximately 51% of chemotherapy patients visited the ER or were admitted to the hospital within the first 6 months of treatment compared to 23% of women not receiving chemotherapy. Chemotherapy-related adverse events occur in almost all chemotherapy patients and more than 1 in 10 women experience a serious or life-threatening event.⁴

Figure 1. Hospital admissions and Emergency Room visits among breast cancer patients, grouped by chemotherapy usage.



From Hassett et al. 2005

When the absolute benefits of chemotherapy are small, the associated toxicities of chemotherapy may outweigh any potential benefit. Therefore, accurate and reliable information is needed to help physicians and their patients weigh the potential benefits and risks of adjuvant chemotherapy.

Addressing the Unmet Need: Oncotype DX® Assay Node Negative Overview

Oncotype DX is a validated genomic test that predicts the likelihood of breast cancer recurrence, the likelihood of patient survival within 10 years of diagnosis and the likelihood of chemotherapy benefit in early-stage, node-negative, ER-positive breast cancer. The Oncotype DX assay uses a reverse-transcriptase (RT) polymerase chain reaction (PCR) process to quantify the presence of specific mRNA for 16 cancer-related genes and 5 reference genes in paraffin samples obtained from a breast cancer biopsy, combining the expression results into a single score called the Recurrence Score™.

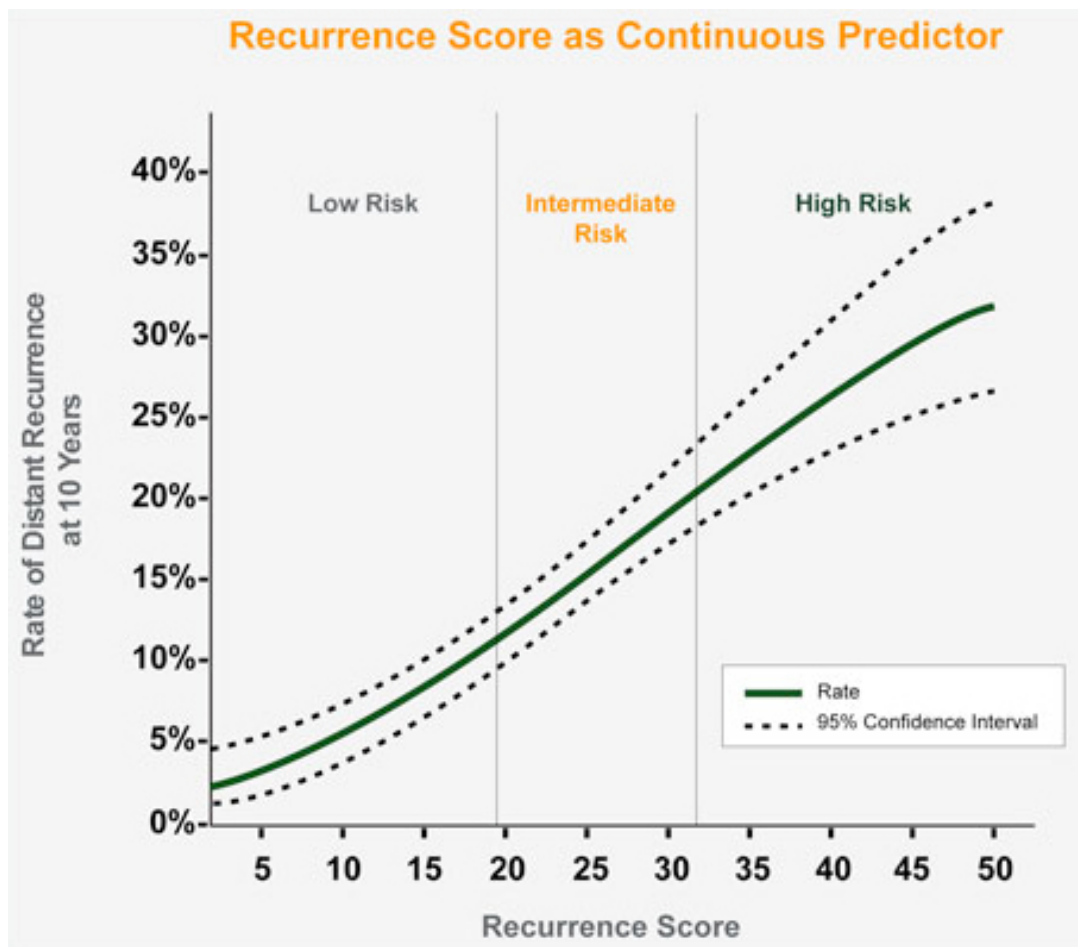
Clinical Validation

In order to clinically validate the Oncotype DX® assay, prospectively designed trials of archived tissue from the two NSABP studies mentioned above were performed with the Oncotype DX assay. The results of the NSABP B-14 trial supported the prognostic value of the assay while the NSABP B-20 trial supported the predictive value of the assay in determining the magnitude of chemotherapy benefit.^{2, 6} The 2007 ASCO (American Society of Clinical Oncology) Guidelines Committee recently stated that although performed retrospectively, the validation of the Oncotype DX assay may be considered Level of Evidence I.⁸

Figure 2 below shows the performance of the Recurrence Score™ as a continuous predictor of distant recurrence at 10 years; 50% of patients are found to have scores <18 ("Low Risk"). From the Oncotype DX NSABP B-14 Study, Figure 3 below shows the ability of the assay to stratify women with node-negative, ER positive breast cancer who were treated with 5 years of tamoxifen by risk of distant recurrence. The prognostic value of the Oncotype DX assay has also been evaluated in a community hospital setting, in a large case-control study by Habel et al among Northern California Kaiser Permanente patients, with consistent clinical results.⁹

Figure 2. Recurrence Score as a continuous predictor of distant recurrence at 10 years in a Node-negative, ER-positive population.

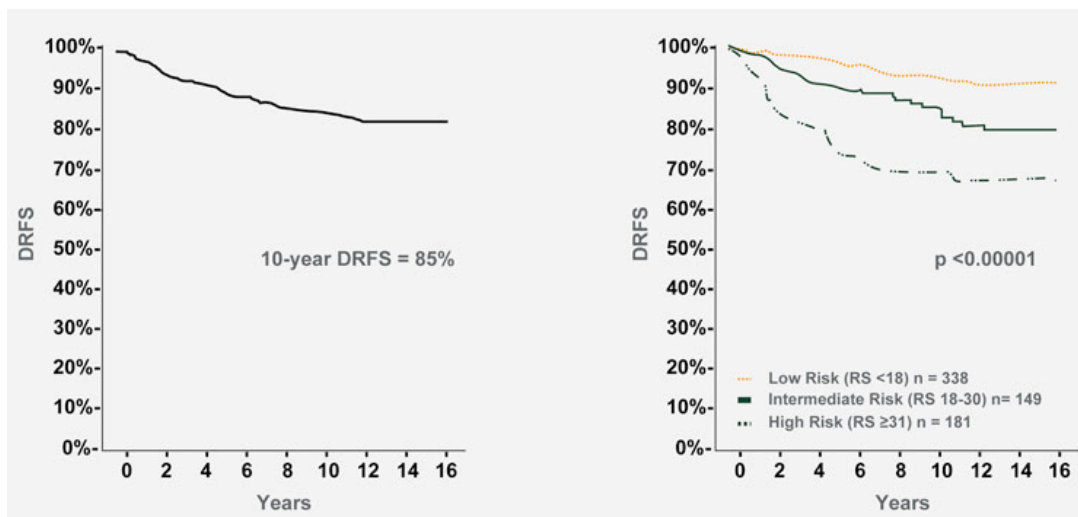
Appendix F: Overview of Oncotype DX



From Paik et al 2004

Figure 3. B-14 Overall 10-year DRFS for the whole group (left) and Recurrence Score groups (right).

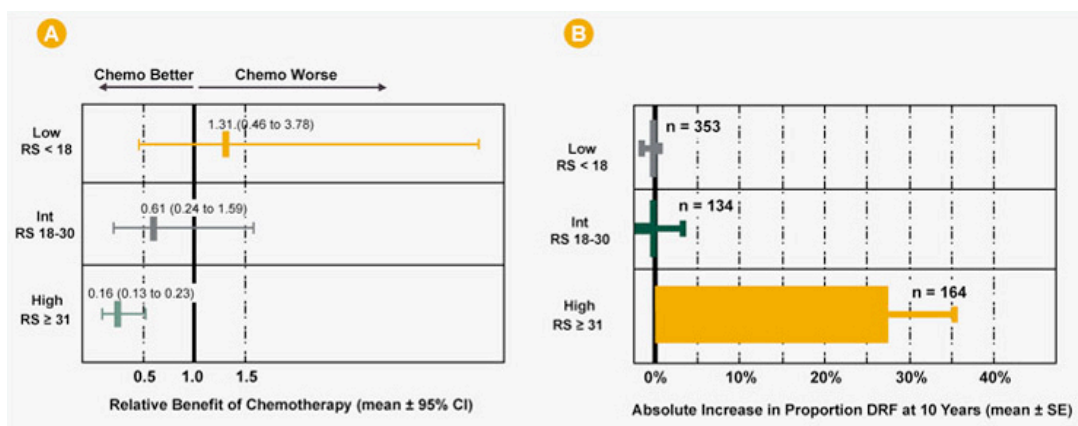
Appendix F: Overview of Oncotype DX



From Paik et al. 2004

Figure 4 below shows that Low Risk Recurrence Score patients (Scores <18) are found in the NSABP B-20 study to have minimal, if any, benefit from chemotherapy, whereas those with Recurrence Score results >31 ("High Risk") have clear and significant benefit (75% relative benefit, 28% absolute benefit). It is important to note that not all prognostic tests or measures are predictive of chemotherapy benefit; each must be independently tested to determine whether it has this ability.

Figure 4. Chemotherapy absolute benefit stratified by Recurrence Score risk.



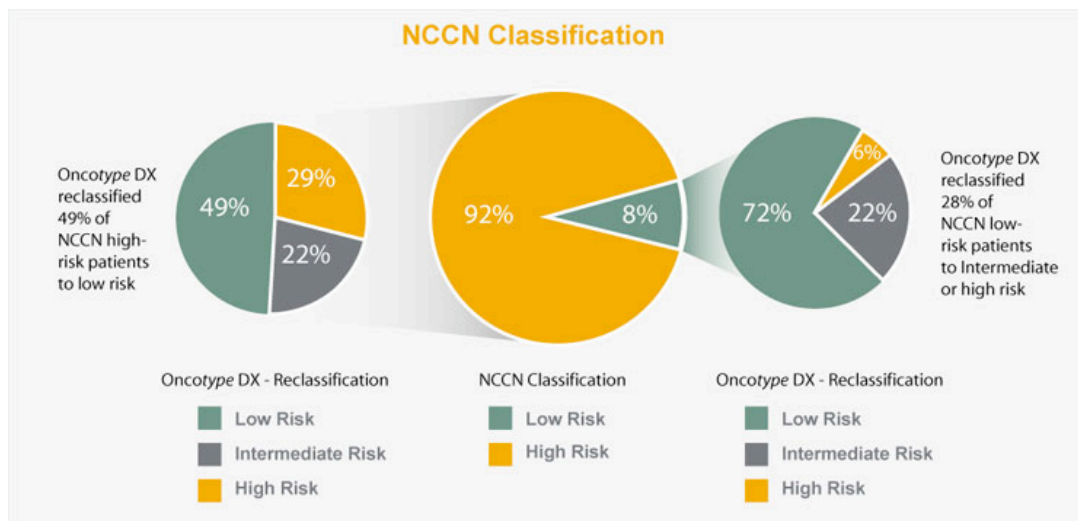
From Paik et al. 2006; DRFS = Distant recurrence-free survival

Benefit Beyond Established Measures

Appendix F: Overview of Oncotype DX

In a comparison of the distribution of patients by Recurrence Score and by older standard treatment guidelines from NCCN, 668 patients from NSABP B-14 were assessed by Oncotype DX (RSlow, RSint, RShigh) and NCCN guideline criteria for tumors (Nlow, Nhigh).¹⁰ In Figure 5, Oncotype DX reclassified 28% of NCCN low risk patients as intermediate or high risk (and thus high likelihood of chemotherapy benefit), and 49% of the NCCN high-risk patients showed a low Recurrence Score with low risk of 10-year distant recurrence and minimal if any benefit from chemotherapy. In total, about 50% of patients were reclassified from NCCN risk groups by the Recurrence Score. Results from this analysis illustrate that the Oncotype DX multi-gene assay offers additional, quantitative evaluation of recurrence risk beyond the NCCN guidelines, which rely on age, tumor size, and tumor grade.⁶

Figure 5. Recurrence Score reclassification rates from NCCN guidelines.



From Paik et al 2005

Similar results were obtained in the analysis which examined the treatment based on St. Gallen guidelines. The Oncotype DX multi-gene expression assay offers additional, quantitative evaluation of recurrence risk beyond that observed with St. Gallen guidelines.

Another established measure to quantify risk of distant recurrence is Adjuvant!Online. Adjuvant!Online, an established on-line breast cancer model, is a validated computer-based model that estimates 10-year disease-free and overall survival with and without adjuvant chemotherapy using standard measures such as patient age, tumor size, tumor grade and lymph node status as inputs. A recent analysis conducted by Goldstein et al. showed that Oncotype DX predicted recurrence more accurately than the Adjuvant! risk prediction algorithm adjusted to 5-year outcomes. Recurrence Score was a highly significant predictor of recurrence for node-negative and node-positive disease ($P < 0.001$).¹¹

Incorporation into National Guidelines

Appendix F: Overview of Oncotype DX

In a 2007 ASCO update on the use of tumor markers, the ASCO committee recommended that "...the Oncotype DX® assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high Recurrence Scores™ appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from Tamoxifen."⁸

In its 2008 update, NCCN commented on the validity and usefulness of molecular classifiers to further improve the prediction and classification of risk for women with early-stage breast cancer. Oncotype DX is recommended for Her2-negative, node-negative (pN0) patients characterized as 0.6-1.0 cm (if moderately/poorly differentiated or unfavorable features) or >1 cm tumors or node positive patients with micrometastatic disease (pN1mi, tumors <2mm).¹²

Inclusion of Oncotype DX into both ASCO and NCCN guidelines indicates that the oncology community does consider prospective studies of archival tissue sufficient to establish clinical utility and indicates that new large long-term prospective trials are not needed.

The TAILORx trial, currently underway (total accrual goal ~10,000 patients), is designed to obtain greater information of the benefit of chemotherapy, if any, for women with mid-range Recurrence Scores. This trial will determine disease recurrence outcomes of Recurrence Score intermediate patients (RS 11-25, ~44%) in particular by randomizing ER- and/or PR-positive, lymph-node-negative (by current methods) patients with intermediate-risk Recurrence Score results to hormonal therapy (either tamoxifen or AI-based) plus chemotherapy versus hormonal therapy alone. Low-risk patients (RS<11, ~29%; treated only with hormonal therapy) will also be followed and compared to a prespecified target of no more than 5% recurrence at 10 years. The high-risk group (RS>25, ~27%) is assumed to benefit from chemotherapy. However, the TAILORx protocol uses more conservative cutoff values to define low- and high-risk patients than used in assay validation studies, in order to help define optimal cutoff values.

Clinical Utility

Experience from several university and community-based groups has shown that the Oncotype DX® assay does change the decision to undergo chemotherapy. The Oncotype DX results are likely to most affect women re-classified as low risk (originally thought to be at indeterminate or high risk of recurrence with unclear benefit from chemotherapy) who can forego chemotherapy and affect a relatively smaller percentage of women who are re-classified as high risk (previously thought to be at a lower risk of recurrence) who now have a substantial likelihood of benefiting from chemotherapy. On average, studies indicate that, despite the widespread use of Adjuvant! Online, guidelines, and other tools which integrate traditional measures to aid treatment decisions, women and clinicians are impacted by Oncotype DX results and change treatment decisions, with the net effect in

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studies of a reduction in the use of adjuvant chemotherapy by 17-36%. (See Tables 1-3. Complete references for the table are contained in the clinical utility section of the dossier. Table 3 shows the four studies with patients re-classified into a higher risk group with Oncotype DX, and consequently changing from hormone therapy to chemotherapy. This group represents a percentage of women for whom the test provides clear-cut benefit from a risk re-classification by the assay.)

Table 1. Changes in treatment associated with Oncotype DX.

FIRST AU	CITATION	DESIGN	ENDPOINT	NO	DISTR.			CT GIVEN			CT GIVEN, STRATIFIED BY RS			CT GIVEN AND/OR RECOMMENDED			NCCN LOW			NCCN HIGH		
					Low	Int	High	Pre	Post	Net	Low	Int	High	Pre	Post	Net	Low	Int	High	Low	Int	High
Hornberger	AJMC 2006	X-sectional	Comparison with NCCN criteria	668	51%	22%	27%										6%	2%	0%	45%	21%	27%
Erb	30th SABCS - #3082	Pre-post test	Chemotherapy usage by era	123	51%	37%	12%	40%	22%	-18%	2%	38%	86%	56%	26%	-30%	12%	6%	1%	34%	30%	17%
Liang	30th SABCS - #2061	X-sectional	Comparison with NCCN criteria	260	46%	36%	18%				2%	45%	92%									
LO	ASCO 2007	Pre-post test	MD recommendation pre and post Oncotype	89	43%	47%	10%									-19%						
Mumby	30th SABCS - #1092	Pre-post test	Patient decision pre- and post- Oncotype	89	43%	47%	10%			-2%												
Oratz	JOP 2007	Pre-post test	Physician treatment recommendations before and after RS knowledge (Table 3)	74	51%	22%	27%									0%						
Oratz	JOP 2007	Pre-post test	Physician treatment recommendations before RS knowledge and actual adjuvant treatment administered (Table 4)	74	51%	22%	27%			-17%												
Ben-Baruch	ASCO 2007 - #11008	Pre-post test	CT given before and after Oncotype	313	41%	45%	15%	55%	27%	-27%	0%	33%	87%									
Thanasoulis	ASBS - 2008	Pre-post test	CT given/ recommended before and after Oncotype	78	37%	51%	12%							49%	13%	-36%						
Asad	ASBS - 2008	X-sectional	Comparison with NCCN criteria	66																		33%

Note: CT given = the proportion of patients actually receiving chemotherapy; CT given, stratified by RS = the proportion of patients actually receiving chemotherapy stratified by Recurrence Score group; CT given and/or recommended = the proportion of patients recommended and treated with chemotherapy; NCCN low = the proportion of patients in the NCCN low risk group; NCCN high = the proportion of patients in the NCCN high risk group.

Table 2. Net change in treatment decisions from CHT to HT.

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NET	
CT given	-20.3%
CT recommended	-22.5%
Based on NCCN	-41.2%
All criteria	-34.4%
<i>Note: CT given = the proportion of patients who ultimately received a treatment (i.e., chemotherapy or no chemotherapy) that differed from the original physician recommendation; CT recommended = the proportion of patients who received a change in physician recommended treatment; Based on NCCN = the proportion of patients re-classified into a different NCCN risk group than previously classified prior to Oncotype DX.</i>	

Table 3. Net change in treatment decisions from HT to CHT.

FIRST Au	STUDY GP	n	PROPORTION
Liang	Pitt	260	0.19%
Oratz	NYU, Rocky Mountain CA	68	1.47%
Ben-Baruch	Clalit, Israel	313	1.28%
Thanasoulis	Bryn Mawr	78	2.56%
Total		719	
Average			1.04%

CHT = combination chemotherapy and hormonal therapy; HT = hormonal therapy.

Health Economics

In a 2005 economic analysis of the Recurrence Score in node-negative, ER-positive patients receiving tamoxifen, Hornberger et al. performed a cost-utility analysis using a decision analytic model.¹³ Using a Markov model, they forecasted overall survival, costs, and cost effectiveness of using the Recurrence Score in patients classified as having low or high risk of distant recurrence based on 2004 National Comprehensive Cancer Network (NCCN) clinical guidelines. Given the reclassification rates noted above, among a hypothetical cohort of 100 patients, Recurrence Score was predicted on average to increase quality-adjusted survival by 16.3 years and reduce overall costs by \$155,128.

Instead of using this hypothetical reclassification model, economic benefits can now be assessed from the published clinical utility of the test described above (change in treatment decisions from Table 2). For example, in a 2 million member plan,

approximately 2000 women will present each year with node-negative, ER-positive early-stage breast cancer. If half receive the test, given the high and increasing cost of adjuvant chemotherapy, supportive care, and management of adverse events, the use of the Oncotype DX is estimated to save approximately \$1,930 per woman tested (given the 34.4% average reduction in chemotherapy use). Please refer to the Economic Validity section of this dossier for additional information on this analysis.

Conclusions

Oncotype DX® is a clinically validated test that provides clinical utility for identifying the many women with invasive breast cancer who are subject to serious adverse events with limited benefit and in identifying a smaller number of women who will clearly benefit from adjuvant chemotherapy. These findings supported the inclusion of Oncotype DX into the ASCO and NCCN guidelines. The public health and economic implications have applicability to commercial health plans, Centers for Medicare Services (CMS), and the oncology community as a whole.

References

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Appendix F: Overview of Oncotype DX

⁹ Habel LA, Shak S, Jacobs MK, et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res* 2006;8(3):R25.

¹⁰ Paik S SS, Tang G. Risk classification of breast cancer patients by the recurrence score assay: comparison to guidelines based on patient age, tumor size, and tumor grade [Poster presentation]. Poster presented at the 28th Annual San Antonio Breast Cancer Symposium, December 2005; San Antonio, Texas.

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¹³ Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. *Am J Manag Care* 2005;11(5):313-24.

Appendix G: Overview of BRAC analysis

Overview of BRAC Analysis®

Summary

BRAC Analysis is a genetic test that requires only a blood sample to determine whether a patient has a BRCA1 or BRCA2 gene mutation, indicating a predisposition to hereditary breast and ovarian cancer (HBOC). Once genetic risk is identified, there are specific management strategies that can be employed for early detection, risk reduction and possible prevention of these cancers.

Genetic tests involve examination of DNA that is inherited and finds mutations that can be passed along to one's offspring. Genetic counseling is often an important component of genetic testing.

Patients have reported great interest in knowing the results for their individual cancer risk. A number of studies have been performed to document the changing patterns of care and treatment that accompany the use of the BRCA analysis. The individual and societal impact of this application of personalized medicine has not been evaluated in California.

Benefits of Genetic Testing

Not only does BRAC Analysis genetic testing enable the physician to take a proactive management approach with clearly identified at-risk patients, but it can also enable clinicians to:

Avoid unnecessary interventions in family members who have not inherited a known familial mutation

Target increased surveillance and other interventions to individuals with a BRCA1 or BRCA2 mutation - maximizing patient care while increasing clinical efficiency

Counsel patients and family members on the underlying cause of cancer.

Finally, if cancer does develop, patient outcomes are likely to be significantly improved and medical costs reduced by early diagnosis and treatment.

The Myriad Genetic Laboratories Advantages

Myriad Genetic Laboratories offers the most accurate clinical test available to detect BRCA1 and BRCA2 gene mutations, including:

Proprietary automated robotics systems that decrease the chance of human error in the analysis and ensure specimen integrity

Appendix G: Overview of BRAC analysis

The Myriad Reimbursement Assistance Program (MRAP) that assists patients in maximizing their payment options for genetic testing

Professional support specialists who are available via e-mail and telephone to answer clinical questions.

Etiology and Clinical Features of HBOC

The genetic basis of hereditary breast and ovarian cancer (HBOC) is a germline mutation in highly penetrant cancer susceptibility genes such as BRCA1 and BRCA2. Normally the proteins encoded by BRCA1 and BRCA2 genes prevent cells from becoming malignant by helping to repair mutations that occur in other genes - making them "tumor suppressor genes." But an inherited mutation within either of these tumor suppressor genes greatly increases the probability of malignant transformation and cancer.

The reason that mutations in BRCA1 and BRCA2 are associated primarily with cancers of the breast and ovary is not yet fully understood, but is thought to be related to the expression of estrogen receptors in these tissues.

Specifically, approximately seven percent of breast cancer cases and 10 percent of ovarian cancer cases are thought to be associated with an autosomal dominant pattern of inheritance of BRCA1 and BRCA2 gene mutations (4). When assessing hereditary cancer risk, a patient's comprehensive family history remains an essential part of investigating the risk of HBOC. However, genetic testing provides the most accurate risk assessment profile for HBOC.

Identifying Patients at Risk for HBOC

Increasingly, direct genetic testing for germline mutations in the BRCA1 and BRCA2 genes is used to identify patients at risk for hereditary breast and ovarian cancer (HBOC).

Genetic testing for germline mutations in BRCA1 and BRCA2 is indicated for:
Individuals with a personal or family history of breast cancer before age 50 or ovarian cancer at any age

Individuals with two or more primary diagnoses of breast and/or ovarian cancer
Individuals of Ashkenazi Jewish descent with a personal or family history of breast cancer before age 50 or ovarian cancer at any age

Male breast cancer patients

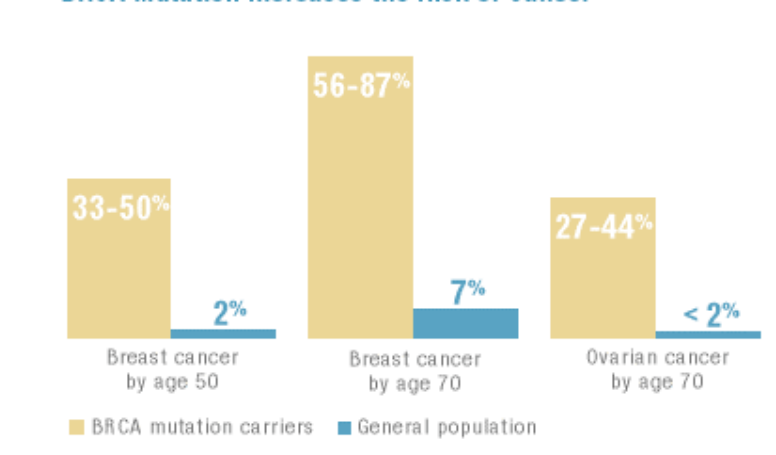
Genetic testing will allow an accurate assessment of the patient's BRCA-based hereditary cancer risk and enable appropriate patient management.

Appendix G: Overview of BRAC analysis

HBOC Cancer Risks

BRACAnalysis is the genetic test for determining a patient's risk of developing hereditary breast and ovarian cancer (HBOC). Patients testing positive for a BRCA1 or BRCA2 mutation have up to a 92 percent risk of developing breast or ovarian cancer or both, by age 70 (1, 2, 3). Mutation carriers previously diagnosed with cancer have a significantly increased risk of developing second cancers (9).

BRCA Mutation Increases the Risk of Cancer



Managing Patients with HBOC

Mutations associated with hereditary breast and ovarian cancer (HBOC) significantly increase the probability of developing these cancers. If BRACAnalysis test results for a patient show an increased risk for breast or ovarian cancer, the following medical management options can help reduce that risk, and either prevent or detect cancer at an early, treatable stage.

Risk Reduction

Increased Surveillance

Monthly breast self-exams starting at age 18 to 21 and annual or semiannual clinical breast exams, beginning between ages 25 to 35 (10).

Yearly mammography beginning between ages 25 to 35 (10).

Annual or semiannual transvaginal ultrasound and testing for serum CA-125 to detect ovarian cancer beginning between the ages of 25 to 35 (10).

Consideration of investigational surveillance techniques, such as magnetic resonance imaging.

Appendix G: Overview of BRAC analysis

Chemoprevention

Drugs such as tamoxifen may significantly reduce the risk of breast cancer in women with BRCA mutations (5).

Oral contraceptives have been associated with up to a 60 percent reduction in the risk of ovarian cancer in women with BRCA mutations when taken for six or more years (6).

Prophylactic Surgery

Prophylactic mastectomy reduces the risk of breast cancer by at least 90 percent in women with BRCA mutations (7).

Prophylactic oophorectomy reduces the risk of ovarian cancer by up to 96 percent and simultaneously reduces the risk of breast cancer by approximately 50 percent in women with BRCA mutations (8).

Family Matters

Genetic testing for HBOC may have significant meaning not only for the individual initially tested, but also for his/her family members. Gene mutations in BRCA1 or BRCA2 causing HBOC are passed on in families in an autosomal dominant pattern. This means that an individual with a BRCA1 or BRCA2 mutation has a 50% (or 1 in 2) chance of passing that mutation on to each of his or her offspring. Most of the time, an individual inherited their mutation from a parent. Knowing if the mutation came from the mother or father is helpful, because other, more distant family members on that specific side of the family (aunts, uncles, cousins, etc.) may also carry the mutation.

It is important to share genetic test results with family members. For example, a positive result indicates that other family members may also carry the mutation. Relatives have the option of being tested for the identified mutation so they can make informed decisions about screening and management that can help them prevent cancer or identify cancer at an earlier, more treatable stage. Undergoing genetic testing is a personal decision and individual family members may differ in their viewpoints and reactions to genetic testing.

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Appendix G: Overview of BRAC analysis

5. Narod SA, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study." *Lancet*. 2000;356:1876-1881.
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8. Rebbeck TR, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations." *N Engl J Med*. 2002;346(21):1616-1622.
9. Verhoog LC, et al. Survival and tumour characteristics of breast cancer patients with germline mutations of BRCA1. *Lancet*. 1998; 351:316-21.
10. Burke W, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II BRCA1 and BRCA2. *JAMA*. 1997;277:997-1003.



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December 15, 2009

AGENDA ITEM 3c

TO: MEMBERS OF THE HEALTH BENEFITS COMMITTEE

- I. SUBJECT:** California Personalized Healthcare Information Technology (pHIT) Pilot Study - Phase I
- II. PROGRAM:** Health Benefits
- III. RECOMMENDATION:** Information Only
- IV. BACKGROUND:**

The U.S. Department of Health and Human Services defines "personalized health care" as "medical practices that are targeted to individuals based on their specific genetic code in order to provide a tailored approach." In September 2008, the California Business, Transportation and Housing Agency (BTH) partnered with the California Council on Science and Technology (CCST) to convene a stakeholders' meeting on personalized health. As a result of that discussion, a roadmap was created addressing the identified lack of Health Information Technology (HIT) infrastructure in the area of personalized health and genomics. A partnership has evolved to include leaders in policy, academia and industry. A twelve-member Personalized Healthcare Information Technology (pHIT) Task Force was established in Spring 2009 by CCST in partnership with BTH with a goal to develop a pilot study utilizing a health information platform containing genetic and genomic health information designed to improve health care quality and patient outcomes.

The pHIT Task Force proposes a one-year "Phase I" pilot study to demonstrate how information technology enables integration of genomic information into an electronic health record system and improved decision-making by individuals and their care providers. The project activities would include:

- Integrating information from genetic/genomic medical tests with an existing Electronic Medical Record (EMR) system in a manner useful to individual patients and their healthcare providers and reimbursers.
- Developing a protocol for integrating genetic/genomic test data with EMRs, with assistance by an interdisciplinary team of experts.
- Generating a new knowledge-based Individual Health Record (IHR) system capable of offering support to the individual and the physician-provider by enabling shared decision-making informed by test data.

This study (see Attachment 1) will integrate standard-of-care genetic and genomic information with clinical and behavioral information to make them useful to the individual and her/his healthcare providers. The pilot proposes to build the pHIT system deploying retrospective de-identified medical records and personalized healthcare data of a selected population of patients with breast cancer. Breast cancer is recommended as the target disease focus for this pilot study, as there are at least two genetic/genomic tests currently used by physicians as standard of care.

Strict attention will be given to security of personal health information and protection of patient privacy. No identifiable personal health information will be exchanged with entities not already in possession of these data.

The pilot study will be overseen by CCST and led by Dr. Ramesh Rao (Director of the California Institute for Telecommunications and Information Technology at the University of California at San Diego) and Dr. Nate Heintzman (University of California Discovery Fellow). Current pilot study partners include Anthem-WellPoint, CentriHealth and Genomic Health.

V. ANALYSIS:

As stated at the November 2009 Committee meeting by Mr. Jonah Frohlich, Deputy Secretary of HIT at the California Health and Human Services Agency, CalPERS could play a significant role in advancing HIT efforts in California. This pilot project is consistent with the Health Benefits Program Vision Statement which states in part that CalPERS will "be a leader for health care reform both in California and nationally."

The results of Phase I of the pilot project should be available by early 2011. Upon successful completion of Phase I, subsequent phases will present added opportunities to focus on specific conditions, health and economic outcomes, and statistically meaningful findings on patient populations. The project could lead to improved quality of health care, reduced burdens of "disease care," and reduced costs of health care. Furthermore, establishing the feasibility of a new HIT resource may provide new opportunities for economic growth and innovation for California business.

Strategy

Staff plans to do the following:

- Continue to work with BTH, CCST, and its partners in the implementation of the study. This work would include the retrieval of data from the Health Care Decision Support System.
- Report to the Committee early in 2011 on the results of the project.

Members of the Health Benefits Committee
December 15, 2009

Page 3

VI. STRATEGIC PLAN:

This item supports Goal XII: "Engage and influence the health care marketplace to provide medical care that optimizes quality, access and cost."

VII. RESULTS/COSTS:

Costs to CalPERS associated with this item are minimal and will be absorbed in the current Health Benefits Branch budget.

John Rice, Interim Chief
Office of Health Plan Administration

Ellen Badley
Interim Assistant Executive Officer
Health Benefits Branch

Attachment



CALIFORNIA COUNCIL ON SCIENCE AND TECHNOLOGY

Sustaining Members

*University of California • California State University
California Community Colleges • California Institute of Technology
Stanford University • University of Southern California*

Laboratory Affiliate Members

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Lawrence Livermore National Laboratory • Sandia National Laboratory
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January 11, 2010

**Roxana Killian, Administrator
Committee for Protection of Human Subjects
Office of Statewide Health Planning and Development
400 R Street, Ste. 369
Sacramento, CA 95811**

Dear Ms. Killian:

In response to your request of Thursday, January 7, 2010, this letter is to convey to you information about an innovative new project, “Personalized Healthcare Information Technology (pHIT) pilot study,” and to respectfully request a determination of whether our project qualifies as research. This study addresses the ongoing need for greater utilization of information technology (IT) resources in health care in California and beyond.

The principal investigator of this study is Dr. Ramesh Rao (Professor, Electrical and Computer Engineering, UC San Diego; Director, California Institute of Telecommunications and Information Technology (Calit2), UC San Diego division). Additionally, two co-PI’s have been designated for this project, Dr. Hope Rugo (Clinical Professor, Medicine; Director, Breast Oncology Clinical Trials Program, UC San Francisco) and Dr. Nate Heintzman (UC Discovery Fellow, UC San Diego). The study is conducted under the auspices of the California Council on Science and Technology (CCST) (www.ccst.us), in partnership with the California Business, Transportation and Housing Agency (BTH), and is further advised by an interdisciplinary task force convened by CCST. A representative from the California Health and Human Services Agency (CHHS) has been on the pHIT advisory team throughout the development of the pilot study and will remain on the advisory team through the study’s execution.

The study aims are two-fold: (1) to assess the feasibility of integrating personalized health data, namely genetic/genomic test result data, into an electronic health record (EHR) system; and (2) to develop a breast cancer care decision support model that includes these test results as part of the computerized ontology. The study is retrospective in nature, as all of the data to be used in the study have already been collected in the course of care, and no new data will be generated. All data used in this study will be provided in a de-identified format to the investigators and our data management partner, CentriHealth. EHR data will be provided by CalPERS via Anthem-WellPoint, and test result data will be provided via Genomic Health. These de-identified data will be employed to demonstrate the technical feasibility of integrating genetic information with the EHR, and as the basis for the development of a decision support model under the guidance of panels of physicians.

There is no intervention in patient care in this study, nor is there any contact with patients. Only de-identified patient data will be used, and no patient identifiable data will be obtained by any entity that does not already possess these data.

Appendix I: Letter from CCST to CPHS, 1/11/10

Roxana Killian, Administrator
January 11, 2010
Page two

The results of this pilot study will be published in a full report by the investigators and CCST, in cooperation with CalOHII, to inform the development of plans for broader deployment of health care IT solutions in California and the nation. The technical platform in which the study is conducted, managed by CentriHealth, may then serve as the basis for subsequent studies.

It is our understanding that our study would not be considered human subject research. We respectfully request your guidance on this matter.

Sincerely,



SUSAN HACKWOOD
Executive Director



RAMESH RAO
Chairman, pHIT Task Force

Appendix J: Letter from CPHS to CCST, 1/26/10

STATE OF CALIFORNIA - HEALTH AND HUMAN SERVICES AGENCY

ARNOLD SCHWARZENEGGER, Governor

COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

400 R Street, Suite 369
Sacramento, California 95811
916-326-3660 FAX 916-322-2512



January 26, 2010

Ramesh Rao, PhD
California Council on Science and Technology
5005 La Mart Drive, Suite 105
Riverside, CA 92507

Project Title: "Study of the Personalized Healthcare Information Technology (pHIT)
Task Force"

Dear Dr. Rao:

The California Health and Human Services Agency's Committee for the Protection of Human Subjects (CPHS) received your exemption request, dated January 19, 2010, for the project listed above. The aim of this study is to demonstrate the feasibility of integrating personal genetic/genomic information into an electronic health record system and to develop a personal decision support model of breast cancer care. You requested an exemption based on 45 Code of Federal Regulations (CFR), 46.101(b)(4)(ii) as the existing personal health information was collected retrospectively and will be de-identified before being provided to the study investigators.

Based on the information provided in the request, CPHS has determined that this project is exempt because the existing data will be de-identified. This study qualifies for an exemption from CPHS review based on 45 CFR, Section 46.101(b)(4)(ii) because the data is recorded in such a manner that it cannot be linked to individuals.

If the parameters of your project change, or are reasonably expected to change, so that the project might no longer meet the federal requirements for exemption, you must submit a protocol of your project to CPHS for approval. The protocol must describe the changes occurring or expected to occur in your project. Information is available on the CPHS website, www.oshpd.ca.gov/boards/cphs, to assist you in assessing whether your project might no longer meet these research exemption requirements. If such a protocol is submitted, you should not implement any changes until you receive either CPHS approval of the project or written confirmation from this office that your project either does not constitute research or is exempt from CPHS review.

If you have any questions, please contact our office at (916) 326-3661.

Sincerely,

A handwritten signature in blue ink that reads "Roxana Killian".

Roxana Killian
Administrator

Appendix K: pHIT use cases, 7/14/10

pHIT use cases July 14, 2010

1: Patient-centered decision-making

A 53 y/o postmenopausal patient with a new diagnosis of invasive ductal breast carcinoma is seen by an oncologist. She had surgery one week earlier revealing a 2 cm tumor that had intermediate histologic differentiation, two negative sentinel nodes, and tumor cells positive for estrogen and progesterone receptor and negative for Her2neu receptor over-expression. She has no major co-morbidities and is open to the possibility of chemotherapy if recommended. The clinician uses information from existing evidence-based guidelines, decision aides and genomic profiling to discuss with the patient the advantages and disadvantages of chemotherapy in addition to hormonal therapy for adjuvant treatment.

2: Test pre-authorization

A physician receives a referral of a patient who has had an abnormal mammogram followed by a biopsy and carries a diagnosis of breast carcinoma. The oncologist is making a decision whether or not to proceed with testing for BRCA-1 mutation analysis and genomic profiling of the tumour specimen at resection. At the time of the patient visit, the patient's electronic record is available for review by the oncologist. It includes a recommendation to move forward with the testing based on algorithmic outputs from a rules engine interacting with the patient's record to date. When the physician decides to proceed with the study, the CPOE process results in an automatic authorization due to the algorithms being accepted by the insurance company as appropriate medical management. It also includes an authorization number from the health insurance company which is attached to all submitted claims for payment. On the basis of the information provided by the treating physician proceeds with their clinical practice and treatment of this patient. These data are then collated used in a process of quality improvement for the labs, as well as conduct "virtual" Phase 4 clinical trials.

3: Recording and audit of care and outcomes.

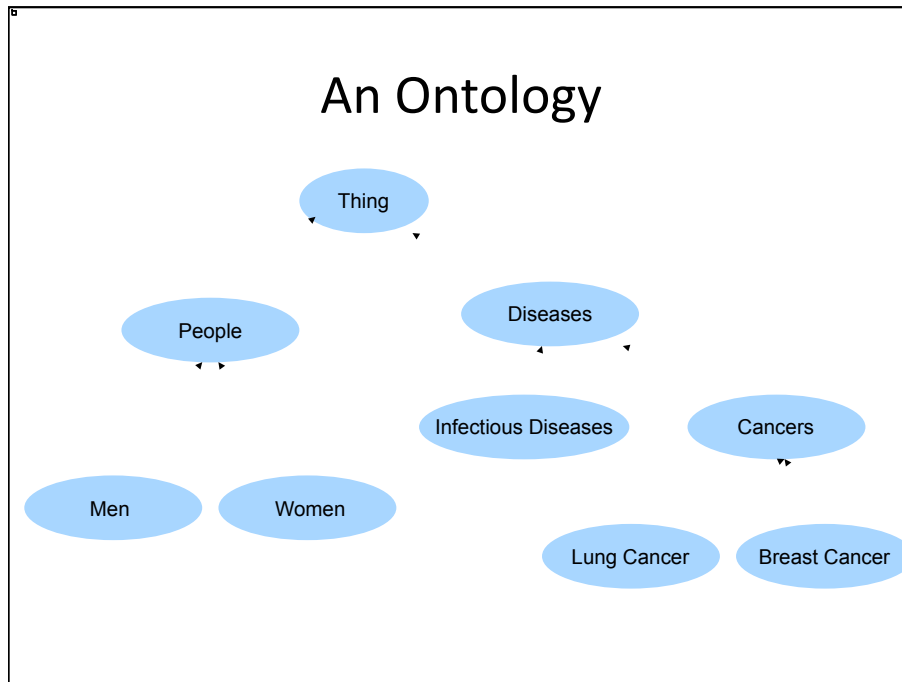
A large health insurance provider reviews the results of several different breast cancer genomic profiling tests and centers. They are able to track test use, results and uptake of further diagnostic and therapeutic procedures. On the basis of this, they are able to perform ongoing quality assurance on tests and treatments, as well as monitor trends in patient decision-making. The tool allows them to integrate this data, but the analysis is done in a separate environment.

Ontologies vs. Decision Support

Matt Williams
Notes for July 14th 2010

Some Clarity of terms

- An ontology is a:
 - “specification of a conceptualisation”
 - A MODEL of the world
 - The things in it
 - How they relate to one another
- A Decision Support System is:
 - a workflow plus decision-points with rules



Why use an Ontology

- Common Terms
 - Your idea of “Breast Cancer” is also mine
- Control of granularity
 - Diseases/ People
 - Men/ Breast Cancer
- Background Knowledge
 - A Breast Cancer is a Cancer is a type of Disease

Decision Support

- Constrained choices, and a method of choosing between them
- Pros:
 - Standardisation (Better for non-experts)
 - Documentation of care/ Audit
- Cons:
 - Capturing knowledge is difficult
 - Often seen as inflexible

Ontology and Decision Support

- The ontology provides the “language” for the domain
- The DSS makes the choices
 - Over terms in the domain
- The ontology allows for data integration
 - Potentially allows multiple data sources to be used with one DSS

Practical Ontology

- Standards for language
- Tools for building and reasoning
- Some reference ontologies
 - (e.g. NCI Thesaurus)
 - Not many deployed application ontologies
 - - N
 - eed to strike a balance between purity and utility
 - Ontology engineering – with a practical purpose

PERSONALIZED HEALTH INFORMATION TECHNOLOGY TASK FORCE

pHIT Task Force Ontology Panel Meeting: Wednesday, July 14, 2010

MEETING SUMMARY

Revised July 22, 2010

OFFICES OF AVID BIOTICS, 300 UTAH AVENUE, SOUTH SAN FRANCISCO, CA

1:00 – 5:00 P.M.

MEETING PARTICIPANTS:

Ramesh Rao, Chair, pHIT Task Force, CalIT2, UCSD. pHIT Task Force PI
Nate Heintzman, UC Discovery Fellow, UCSD, Co-PI
Hope Rugo, M.D., Medical Oncologist, UCSF, Co-PI, Ontology Panel
David Martin, M.D., CEO, AvidBiotics
Cindy Post, Vice President, Product Strategy and Management, CentriHealth
W. Randal Clegg, Chief Technical Architect, CentriHealth
Alfonso Cardenas. UCLA Professor, Computer Department
Diana Rude'. Consultant, CCST/pHIT Task Force
Matt Williams, M.D., UCL, Member. Ontology Panel (by conference call)

SUMMARY:

Ramesh Rao opened the meeting. A discussion ensued on three clinical use cases developed based on recommendations of the July 7th meeting of the Ontology Panel at UCSD in San Diego.

Cindy Post. CentriHealth noted it's important to know what your process is. You can put things on a screen but it can be unusable. It has to make sense to the clinicians.

Ramesh Rao commented on the importance of including the kinds of things that touch on how the oncologists actually reason. Even though they don't have a background in this (ontology development), they understand it. If you don't do this, the system comes back with recommendations and they ignore it. We have to produce something that is more useable.

Nate Heintzman noted we rely on Hope Rugo, M.D. and Barbara Parker, M.D. to advise on the process, but we will use NCCN guidelines, which will govern a large portion of the ontology. NCCN policies are on line and the standards are referenced in that data base.

Appendix M: Task Force meeting notes, 7/14/10

NCCN does not directly refer to Oncotype DX, but only indirectly does so. NCCN does not refer to MammaPrint.

If a doctor wanted to order MammaPrint, he/she would have to see if it follows the NCCN guidelines.

Matt Williams noted we have to know what we are talking about – we’re talking about choosing an ontology, and we must know how the academic and business community would be viewing it.

An ontology is a model of the world describing individuals or groups of things. It starts by saying everything is a “thing” -- that is a list of categories we have; differences between people and diseases; between men and women and between subdivisions of cancers. There is not a right or wrong answer but the ontology provides a means to control granularity regarding the topic. We want to talk about people who have been diagnosed with breast cancer and the kinds of knowledge we expect the system to provide to the oncologist and patient. Matt noted it (the ontology) simply provides names/words and points to differences regarding breast cancers and people. Matt emphasized this is different and distinct from a decision support system.

Dr. Williams pointed out a decision support system offers a decision point and some methodologies. It is very clear. A decision support system is different from an ontology in that it needs to make decisions based on adjudication and showing differences between things in the world. When we come up with the system rules, you can become more parsimonious in description and can use ontological structures to capture the information (i.e. bringing data in and layering rules on top of it).

Ramesh Rao pointed out that since the data will come in from multiple sources, the extraction of the data can be confusing. Having a common ontology is important.

Alfonso Cardenas commented we have an advantage of having CalPERS as a major data source, along with three reference labs.

David Martin emphasized we don’t want to limit the data solely to those sources. David also commented the information contained, i.e. in Use Case I (titled “Patient-centered decision making”) is very superficial. Dr. Hope Rugo would not take action (i.e. regarding a clinical decision) based only on the data in this use case. We will have to build a larger data base before we can test our ontology. How do we go beyond a superficial use case to build an ontology?

Dr. Rugo concurred that this use case is superficial and is not based on NCCN guidelines.

Appendix M: Task Force meeting notes, 7/14/10

Dr. Williams noted there are large bodies of information contained in the NCI Thesaurus and within NCCN guidelines. Various bodies are drawing up what they consider to be breast cancer ontologies. We can't keep building ontologies but will benefit from drawing on appropriate ontologies from other sources.

Matt commented that we may be interested in a class of diagnostic data regarding breast cancer in women who are post menopausal. The NCI Thesaurus does not contain that information.

Matt emphasized there is a difference between a reference ontology and an applications ontology, which is much smaller and more complex. In this project, if we are going to position ourselves, we would be developing an applications ontology and would ensure a large amount of data would come from a reference ontology. Matt commented that SNOMED started out as a lexicon of terms, but is now a decision logic based ontology.

Ramesh Rao asked how do use cases inform an ontology?

Dr. Williams responded that it comes down to building a bridge. We need to do this by references to general specific concrete example of the domain. Use cases assist in defining the scope of the domain and in general terms, what we want the system to do and also to make clear that we don't want the system to do "x." Parts of the ontology can be taken from the NCI Thesaurus and bits from other ontologies in order to satisfy the domain. The use cases help define which part of the NCI Thesaurus we want to use.

Hope Rugo, M.D. pointed out the many variables in patient centric diagnosis and decision support, e.g. whether a cancer was initially detected by imaging or palpation; whether a patient is pre- or post-menopausal. Dr. Rugo suggested the possibility of including Ki 67 expression data as well as factors such as types of surgery and types of chemotherapy.

Matt Williams emphasized if we are trying to design something that will fill a need over a 5 to 10 year period of time, this would require a great deal of time. This pilot study needs to demonstrate certain properties; we need to demonstrate this approach works and use things that contain the identified priority fields. There may be things we want to include and we need to make sure the ontology is covering most of the domain. There cannot be a way of ensuring a decision, but there is value in cross-bridging of data.

Hope Rugo noted that means we have to set up boundaries to make it work. She suggested looking at gene expression, proteomics, node size, etc. If the patient is menopausal, make sure to test to see if they should have Tamoxifen.

Matt noted in three to five years there may be more genomic assays. What is more work is having to add an entirely new type of test. If you have categories of tests, you can add

Appendix M: Task Force meeting notes, 7/14/10

within the category easily at a later time. If you “change your world,” you have to also change the ontology.

Dr. Rugo noted if you want to decide whether to recommend BRCA I or BRCA II testing, that does get you to a management plan. If you want to talk about those tests, you have to make sure they are in the ontology; the same is true for Tamoxifen.

David Martin cited the importance of having a place in the ontology where those data are integrated.

Hope Rugo further suggested incorporating such things as risk and morbidity in order to use the genomics (i.e. risk of use of chemotherapy.) Hope also noted there should be a classification for male cancer patients.

Other possible clinical data discussed:

- GI microbiome
- CYP variants
- Bone density
- Gene expression and genomic data

Ramesh Rao noted bone density belongs to a certain class. Hope asked if we want to include ethnicity. David Martin stated there are socio-economic issues related to clinical care (i.e. ability of a patient to travel (i.e. by bus/car) to receive clinical care. Other considerations noted: a) obesity; b) cigarette smoking and c) alcohol use.

Matt Williams emphasized we should be able to specify use for each added data item. If we can't specify use, the data item should not be included. An ontology provides language to aid in making decisions. The process of measuring risks and benefits belongs to decision support. Dr. Williams further emphasized the importance of not designing an ontology to cover everything we want to do. If we decide to include certain things, we can build them in, but cannot include everything.

Dr. Williams concluded we can have an ontology with sufficient domain to cover links between clinical and genomic data over a 5 – 10 year time period; and once we have done that, a decision support system can be layered on top of it. Our collective decision last week (i.e. July 7th meeting of Ontology Panel) was to base our ontology on NCCN guidelines because these represent a standard most people agree with. We can say we based this on NCCN guidelines with “x” number of additions.

Appendix M: Task Force meeting notes, 7/14/10

In a discussion of Use Case 2 on “Test pre-authorization,” Cindy Post (CentriHealth) noted Anthem/Well Point’s guidelines for BRCA analysis were used in this use case. Hope Rugo queried the goal of Use Case 2. Ramesh Rao responded that right now Use Case II is the pre-authorization process that adds costs to the system.

Cindy noted Charles Kennedy (Well Point) was consulted on that payer’s authorization guidelines. Charles indicated if it is included in NCCN guidelines, then it is approved. Cindy again noted that MammaPrint is not included in NCCN guidelines, but the Ontology Panel has been discussing inclusion of this genomic test. This use case discusses the procedure in authorization of payment of claims.

Ramesh Rao cited the need to determine the type of supplemental information that will be required to determine the end result in Use Case 2. Hope Rugo, M.D. asked what is to prevent a physician from ordering 2 or 3 genetic tests?

David Martin noted family history will assist in determining what underlying mutation existed that led to the tumor.

It was noted the bulk of the work for Use Case 2 will look to the NCI Thesaurus data base to assist in determining the ontology for looking at inherited mutations.

Following discussion of this Use Case, a list of proposed revisions to Use Case 2 were suggested:

- Add Ki 67
- Refer to “BRCA mutation” rather than “BRCA I” (Can say “inherited mutations” or “inherited genetic predisposition”.)
- Add reference to family history, age, ethnicity (Potential influence of religious – or cultural affiliation was also mentioned.)
- Cost reduction potential

Randy Clegg (CentriHealth) noted CentriHealth spends a lot of time listening to potential customers asking what they want. It’s a trade off on how you tailor to an individual vs. how you tailor to the average. It’s a trade off on what you guess the average will look like vs. using cards for everyone in systems. You have high speed tech savvy physicians who get into tailoring it and then older physicians who don’t want the tool to get in the way.

Matt described Use Case 3 on “Recording and Audit of Care and Outcomes.” He noted this use case is more about collecting data and analyzing the process of care. Examples: the

Appendix M: Task Force meeting notes, 7/14/10

insurer looks at all patients who have had a BRCA test done. The insurer looks at patients' uptake of prophylactic mastectomy.

Follow up to this meeting:

Ramesh Rao suggested the need for preparation of a written document summarizing use cases & presentation. (Note: Matt will put together an ontology and decision support.)

Ramesh indicated he wanted to share where we are now. Matt & Maryann can work on the ontology piece and work on rules and will want this group's expert opinion on whether this framework is effective.

Dave Martin inquired on the status of Mike Hogarth. People at ATHENA were asking that Mike participate. Nate Heintzman indicated he would make contact with Mike.

Ramesh Rao noted there is desire to make sure the ontology discussion is representative of use cases and that consideration be given to how well NCI plays with ATHENA. This is part of the ontology discussion.

Hope Rugo, M.D. emphasized use of existing NCCN guidelines.

Matt Williams suggested that in Use case I, instead of just doing an Oncotype DX, make a decision on using one or several genomic tests and when results of those come back, show how we may incorporate those in the decision support tool.

It was noted that MammaPrint can't come from NCCN guidelines because NCCN doesn't include this form of genetic testing. It will be necessary to add more guidelines. This pilot study is to demonstrate it's possible to do these things. The existing CentriHealth system will be used because this system has ability to include ontological models.

Ramesh Rao queried if CentriHealth can share customization?

Centri Health will provide relatively minimal, but functional, decision support system in these few areas. Ramesh Rao noted we as a group will need to provide additional data.

The following questions were raised:

- 1) How will we integrate Oncotype DX and MammaPrint and 3, 4 and 5 (i.e. other possible genomic tests)?
- 2) In Use Case 2, how will we do guidelines for preauthorization?

Appendix M: Task Force meeting notes, 7/14/10

In a clarifying discussion on Use Case 3, Ramesh Rao noted the intent of Use Case 3 is to provide clinically realistic scenarios over five or so years, with a goal of having easier to use mechanisms.

Matt Williams, M.D. pointed out that one of the things about integrating data is that it allows the system to take patients from California and Massachusetts, and take patients from other different areas. That allows you to look at results from national experiments, i.e. looking at the experience the patient had followed and looking at the resulting outcomes.

Matt Williams also discussed looking at different routes of referral for diagnosis, noting the idea was to think about how we would be able to describe pathways of care. Every time someone makes contact to a provider, sum up the cost of that event. We were thinking we could use that as Use Case 3. Matt noted he does not know if sufficient data will be available to do that but, if we do this, it will be interesting to observe results.

Ramesh Rao and Alfonso Cardenas noted the intent is to have a framework, i.e. this is how you do it and this is the framework used to do it.

Matt noted we could do this with sham patient data. We could come up with something for that.

Matt suggested this above-noted data can be added to Use Case 3: Move away from monitoring of single or oligo data points. Determine whether individual patients have had a BRCA test and show the cost of six months before diagnosis of breast cancer and two years after that. Does that cost vary, depending on routes into care and places care is delivered?

Cindy Post noted if we were taking a case, we (CentriHealth) could write a query on patients who have had a mastectomy.

Ramesh Rao queried if this data category would go into Use Case 3, or does it go into decision support?

Matt Williams noted he sees this residing in the decision support side of things. Ramesh clarified that in San Diego's meeting of the Ontology Panel the analytical component was a separate thing. It wasn't decision support.

Hope Rugo, M.D. asked, "Do I want to know this?"

Matt Williams, M.D. emphasized there are different patterns of cost leading up to a diagnosis that are probably broken down by socioeconomics, access to care. Hope Rugo, M.D. asked what this type of data has to do with genomics?

Appendix M: Task Force meeting notes, 7/14/10

Matt stated it has nothing to do with genomics and maybe should drop it; but in a sense it does, i.e. the use of genomic testing influences patient pathways. Therefore, we should be able to see areas of high use of Oncotype DX vs. low use. It does require a timeline analysis.

Dave Martin, M.D. commented that PAMF is interested in the patient and has developed a framework to allow determination of patient outcomes years down the road, etc.

Matt stated that every event in an ontology has a timestamp. The information included in the ontology makes assembling a timeline from the data easy.

Matt Williams suggested in follow up to today's meeting we should add into use case the few things mentioned here, including more complex timeline-based patient journey..

The following next steps were discussed:

- 1) Matt will discuss with Maryann the planned scope of ontology development. There is need to provide a figure for a budget. Matt e-mailed Maryann some approximate and reasonable figures.
- 2) There is need to obtain patient data. The data is at a high level; at a minimum we need to handle the patient data that we receive. A recent e-mail suggests patient data will be arriving any time soon.
- 3) Producing an ontology is not that helpful. We also need to document it, test it and write some use cases and sample code surrounding it, in order to make it useful to other people

Matt Williams further noted he expects to be receiving information back from Maryann Martone and until that is received he cannot say for sure regarding timings and costing for the ontology.

Cindy Post asked what is our deliverable at end of year? (Note: It was discussed by Diana Rude' that a commitment has been made by the pHIT Task Force to CalPERS that the final outcome report of the pHIT pilot study will be submitted in early 2011.)

Nate Heintzman noted he will obtain Maryann Martone's input on the timeline.

Matt Williams commented that realistically we will not get an ontology built and properly tested by the end of this year. There is a way of achieving much of that, however. We would build the ontology and be doing testing of it. Once we are happy with internal testing, potential users could start using it while Matt writes rules surrounding it.

Cindy Post noted we are not installing a clinical system but doing a proof of concept.

Appendix M: Task Force meeting notes, 7/14/10

Matt noted there is a clinical data set available that comes from Lubjana. One approach would be to look at headings and data items in a sample data set, and then mock up the data ourselves. One disadvantage is that when we come to discuss it, we haven't done it with real patient data.

Cindy Post stated CentriHealth needs data to start working on this and suggested we ask Marc Gottlieb or Charles Kennedy of Anthem/Well Point, noting they can provide a sample of the data. Nate Heintzman will follow up with Charles and Marc and with Matt to make sure we are on the same frequency.

Matt Williams will e-mail Randy Clegg information on large data bases.

David Martin commented ATHENA will get back to us on whether we will be invited to present the pHIT project at an ATHENA strategy meeting on August 5 or 6th.

Nate will follow up with Kathy Hajopoulos of ATHENA and will contact Mike Hogarth.

It was noted that Jeff Belkora, UCSF School of Medicine, is ATHENA's contact for decision support.

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RESEARCH PLAN

Introduction and Hypotheses:

This Personalized Health Information Technology (pHIT) [CCST 2011] pilot study will apply cutting-edge information technology resources to the integration of molecular and genetic/genomic data with health records of breast cancer patients, thus enabling rapid adoption and meaningful use of new information in the course of decision-making and clinical care of breast cancer patients, across socioeconomic boundaries, in all care settings. With emphasis on truly rapid translation of knowledge into practice, the first releases of our new online decision support tool and dynamic knowledge resource will occur in Year 1 of the project period. This project addresses multiple Priority Issues set forth by the California Breast Cancer Research Program (CBCRP), in particular: eliminating the unequal burden of breast cancer and accelerating the translational potential of diverse basic and clinical research, as described below. Our work will provide a means of keeping California at the forefront of world-class breast cancer care and research.

Information technology (IT) is becoming increasingly embedded in all aspects of society, including healthcare. Innovations enable digitization of patient medical records, secure management and exchange of healthcare information, and greater connectivity between patients and their physicians. Simultaneously, advances in biomedical sciences provide an expanding array of molecular diagnostics and genomic tests to inform personalized care for patients, from indicating familial disease predisposition to predicting benefit of therapeutic treatment regimens. Whole genome sequencing for patients is on the horizon, presenting both significant opportunities and challenges in healthcare information management, security, and interpretation.

Although a number of genetic/genomic tests are currently available to patients with or at risk for breast cancer, the current healthcare system lacks a standardized means of assimilating information from these tests into the patient health record in a manner that is meaningful and useful to the individual and the care provider. The emergence of new genetic/genomic tests, whole genome sequencing, and new discoveries in clinical and basic research only aggravate this problem—the patient and physician are poised to be overwhelmed by exponentially increasing amounts of data.

The pHIT pilot study will develop a system to translate clinical and basic research results into comprehensible information for use by both patients and clinicians to support their decision-making in the midst of the data deluge. The pHIT study will develop an ontology, or knowledge representation, for breast cancer care in the context of molecular and genetic/genomic information. This ontology will be open-source, publically available, and developed such that it can easily scale up to include additional sources of information (new tests, emergent findings from clinical and basic research, new treatment guidelines, new resources, etc.). In partnership with CancerCommons,[CancerCommons] we will develop the first Molecular Disease Model (MDM) for breast cancer, creating an interactive “living” online document that shares the entirety of breast cancer knowledge from basic research to clinical trials, updated regularly by a national council of experts. The breast cancer MDM and ontology will be published and freely accessible to any patient, clinician, researcher, or other interested party with access to the Internet. Cancer Commons has developed an example of such a resource (for melanoma) and has recently published an overview.[Vidwans, 2011] CancerCommons.org is developing as a rapid-learning community for all cancers, enabling cross-pollination of discoveries and therapies between diverse cancer types. Based in California, they are pursuing the development of MDMs with collaborators across the country, including this project. The results of this proposal—a breast cancer MDM developed by experts at University of California medical and technology centers—will solidify California’s leadership in innovation for breast cancer care.

In addition to generating new, accessible knowledge resources, our study goes further to extend these resources into decision-support tools that interpret diverse sources of data, providing patient-centric knowledge to the individual with breast cancer and clinicians alike. One such tool is the “Targeted Therapy Finder” (TTF) application (“app”),[CollabRx] which enables a patient or clinician to identify expertly-informed, personalized treatment options based on key features of the individual’s breast cancer, including available molecular and genetic/genomic tests, recommended therapies, and relevant ongoing clinical trials. In addition to a widely-

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accessible internet app, our work will produce an analogous module for seamless integration into electronic medical record (EMR) workspaces, focusing initially on the EpicCare EMR and its Beacon Oncology Information System.[EpicCare EMR] With these different resources, the latest breast cancer decision support will be equally accessible to state-of-the-art academic medical centers and rural clinics alike.

With the availability of our free, online MDM and apps, breast cancer patients will benefit from the appropriate use and interpretation of molecular and genetic/genomic tests and clinicians will be supported in exploring diverse personalized therapeutic options. This has the potential to improve the overall quality, and equality, of care. Importantly, such use of our app(s) will also potentially reduce cost burdens, financial and otherwise, across the state of California and beyond. With an estimated 23,640 new breast cancer diagnoses expected in California alone in 2011, the resources requested for our efforts represent a small \$32 investment per newly diagnosed patient for improved decision-making and outcomes, not even taking into account current patients, care providers, advocates, and researchers who will use these tools.[American Cancer Society 2010] We believe this is a sound investment.

Specific Aims:

Specific Aim 1: Generate open-source, rapid-learning breast cancer knowledge resources including (1) a breast cancer ontology (BCO) that integrates molecular and genetic/genomic information with breast cancer patient records in the context of the breast cancer care knowledge domain, and (2) a breast cancer Molecular Disease Model (MDM) that shares the entirety of breast cancer knowledge from basic research to ongoing clinical trials. These resources will be scalable to include emerging molecular and genetic/genomic tests, capable of rapidly integrating new findings from clinical and basic research, developed according to accepted technical and clinical standards, and freely, publicly available.

Specific Aim 2: Extend the knowledge resources into rules-based decision-support tools that provide meaningful, patient-centric information to individual patients and their care providers. These tools will be developed as (1) web-based apps and (2) seamlessly integrated modules within the EMR workspace.

Specific Aim 3: Broadly disseminate these free resources and tools to patients, care providers, breast care advocates, and all interested parties by developing interfaces with complementary breast cancer care projects, including the ATHENA project, [ATHENA] Stanford and Palo Alto Medical Foundation (Stanford-PAMF),[Stanford-PAMF] and others; presenting at regional and national breast cancer conferences; and partnering with diverse clinical, advocacy, and education groups in the breast cancer space.

Background and Significance:

In the past, estimation of breast cancer prognosis and choice of treatment were based on TNM staging and histopathologic features.[Early BCTCG 2005; Goldhirsch, et al. 2007] More recently, the trend is toward the use of biologic, molecular, and genetic features to individualize treatment.[Paik et al. 2004; Goldstein et al. 2008; van 't Veer et al. 2003; Knauer et al. 2010a, 2010b; Mook et al. 2009; Perou et al. 2000] These features not only stratify patients into risk categories, but also predict response to therapy. Selection of appropriate therapy reduces risks of unnecessary treatment, thereby reducing emotional, physical, and financial costs of breast cancer treatment. Examples of tools used in making these decisions range from standard biochemical or genetic measurement of estrogen receptor (ER), progesterone receptor (PR), and Her2neu to the diagnostic test Oncotype Dx (Genomic Health), which is used to decide whether or not to administer adjuvant chemotherapy to patients with resectable breast cancer.

As a result of expanding molecular and genetic information breast cancer is increasingly recognized as a very heterogeneous disease. Treatment options have correspondingly multiplied. Faced with this growing complexity, both breast medical oncologists and breast cancer patients undertake increasingly more intricate decision-making. There is also a growing and valuable trend towards patient involvement in the decision-making process. An easy to use way of synthesizing available data into a clear and understandable format will greatly facilitate this process. We aim to create such a system.

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Currently, there is no standardized system to support the use of molecular and genetic/genomic test results in breast cancer care. Indeed, even within popular EMR systems such as EpicCare, there is no discrete data field to collect/store the results of such tests in a codified manner (for example, the Oncotype DX Recurrence Score). These data are therefore not codified and may be lost or misunderstood and, importantly, such data are inaccessible for computational clinical analyses. In light of the growing complexity of ever increasing numbers of molecular and genetic tests and the advent of whole genome sequencing, resources to provide meaningful information and decision support to physicians and patients, at the individual and population levels, must be developed.

The system developed by the pHIT pilot project promises to provide more personalized care for breast cancer patients through better informed decision-making. This work will positively impact individual breast cancer patients as well as the larger community by enhancing physician/patient communication, improving breast cancer resource distribution, optimizing therapy, and minimizing the negative impacts of inappropriate/ineffective therapies. Our breast cancer ontology (BCO), molecular disease model (MDM), and Targeted Therapy Finder (TTF) app will be developed according to open-source standards and made freely available to any individual, clinician, researcher, or other interested party, enabling significant impact across broad communities and populations affected by breast cancer within California and beyond. This is true regardless of socioeconomic status—any patient with access to care and/or the internet can benefit from this work, and indeed the greatest impact may be realized in clinical settings that currently do not have consistent access to knowledge about molecular and genetic/genomic tests.

Preliminary Results:

This integrative study spans the disciplines of information technology, ontology development, genetics/genomics, and breast cancer care. Our team, in development since 2008, includes leaders in each of these areas and is advised by a Task Force with representatives from academia, industry, and policy.

Briefly, advances in computer programming and information technology have enabled the development of rapid-learning, scaling IT architectures that can be beneficial in the healthcare setting. Our system will be built upon a computational knowledge representation, or “ontology,” which models the domain of breast cancer care and the use of molecular and genetic/genomic information therein. Ontological development has been the focus of a great deal of work over the past five to ten years. There are now major ontologies in diverse areas including medicine, genetics, and other research areas; examples include, respectively, NCIT [National Cancer Institute (NCI) Thesaurus], GO [Gene Ontology], and model organisms [*C. elegans* Development]. many of which can be found at Stanford’s BioPortal.[Noy et al. 2009] However, the development of a clinically useful ontology requires close cooperation between computer scientists, clinicians, and scientists to accurately capture the knowledge of the experts and the rules for applying that knowledge.

The use of ontologies allows the integration of data from diverse and disparate sources, spanning both clinical and genetic/genomic domains in the context of our work. Within our breast cancer ontology (BCO), we focus initially on integrating data from two representative genetic/genomic tests, BRACAnalysis and Oncotype DX, as well as a clinical data source, with the capability to expand to other tests and sources of clinical, molecular, and genetic/genomic information. These two tests were chosen because they have been widely used and retrospective data is readily available for many hundreds to thousands of patients. We have established partnership agreements with the vendors of these two tests, Myriad Genetics and Genomic Health, respectively, to obtain de-identified test data for our project.

Our BCO is implemented using widely-accepted international standards (including OWL2) and is based on existing large reference ontologies, such as those produced by NCI, in order to construct a more focused domain-specific ontology which still contains over 8000 concepts. The BCO captures diverse concepts including age, tumor stage, antineoplastic agents, and therapeutically important markers (for example, ER and HER2). The BCO’s main contribution is to provide a much more concise and applied model than the reference ontologies, but one that is also much richer because of the large number of definitions that have been added.

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This allows the BCO to draw far more inferences than would result from only using a reference ontology. We are now in the process of refining the BCO with reference to a real breast cancer dataset in order to ensure that we can accurately capture and reason about clinically relevant breast cancer information and so provide a suitable format for clinical and genomic information.

The BCO provides a common language that the next stage of the work, the molecular disease model (MDM), will use as its basis. For example, whereas the MDM may describe in text the influence of a genomic marker on disease response, the BCO provides the underlying computational language to systematically define and describe the genomic markers and disease response and to integrate relevant data from different sources for use in individualized decision support. The knowledge base for the breast cancer MDM is already under development under the leadership of Drs. Hope Rugo, Barbara Parker, and Matt Williams, all key personnel in this proposal.

The project PI, Prof. Ramesh Rao, is a renowned leader in information technology and the director of the UC San Diego Division of the California Institute for Telecommunications and Information Technology (Calit2). At the Moores UCSD Cancer Center are clinicians Dr. Barbara Parker, esteemed breast medical oncologist and Medical Director of Oncology and Dr. Teresa Helsten, breast cancer expert, expert in the EpicCare EMR system, and representative of UCSD's institutional review board (IRB). Also at UCSD are Prof. Maryann Martone, an expert in large-scale systems and ontology development and Prof. Nate Heintzman (project co-PI), an expert in genomics and translational technologies both at Calit2 and the Division of Biomedical Informatics at the UCSD School of Medicine. Project co-PI Dr. Hope Rugo at UC San Francisco is also a renowned breast cancer clinician and an expert in molecular diagnostics. Also integral to the team is Dr. Matt Williams, whose medical practice in breast cancer care is complemented by a Ph.D. in computer science and deep expertise in ontology, and his colleagues at CollabRx who have developed the established melanoma MDM and app (Drs. Tenenbaum, Shrager, Gobbel, and Vidwans).

Our team is in regular conversation with (and shares personnel with) other breast cancer projects including ATHENA and the collaboration between Stanford and the Palo Alto Medical Foundation (Stanford-PAMF). The pHIT pilot study has been supported thus far in part by the California Council on Science and Technology (CCST), Calit2, Anthem-WellPoint, and other project collaborators.

Research Design and Methods:

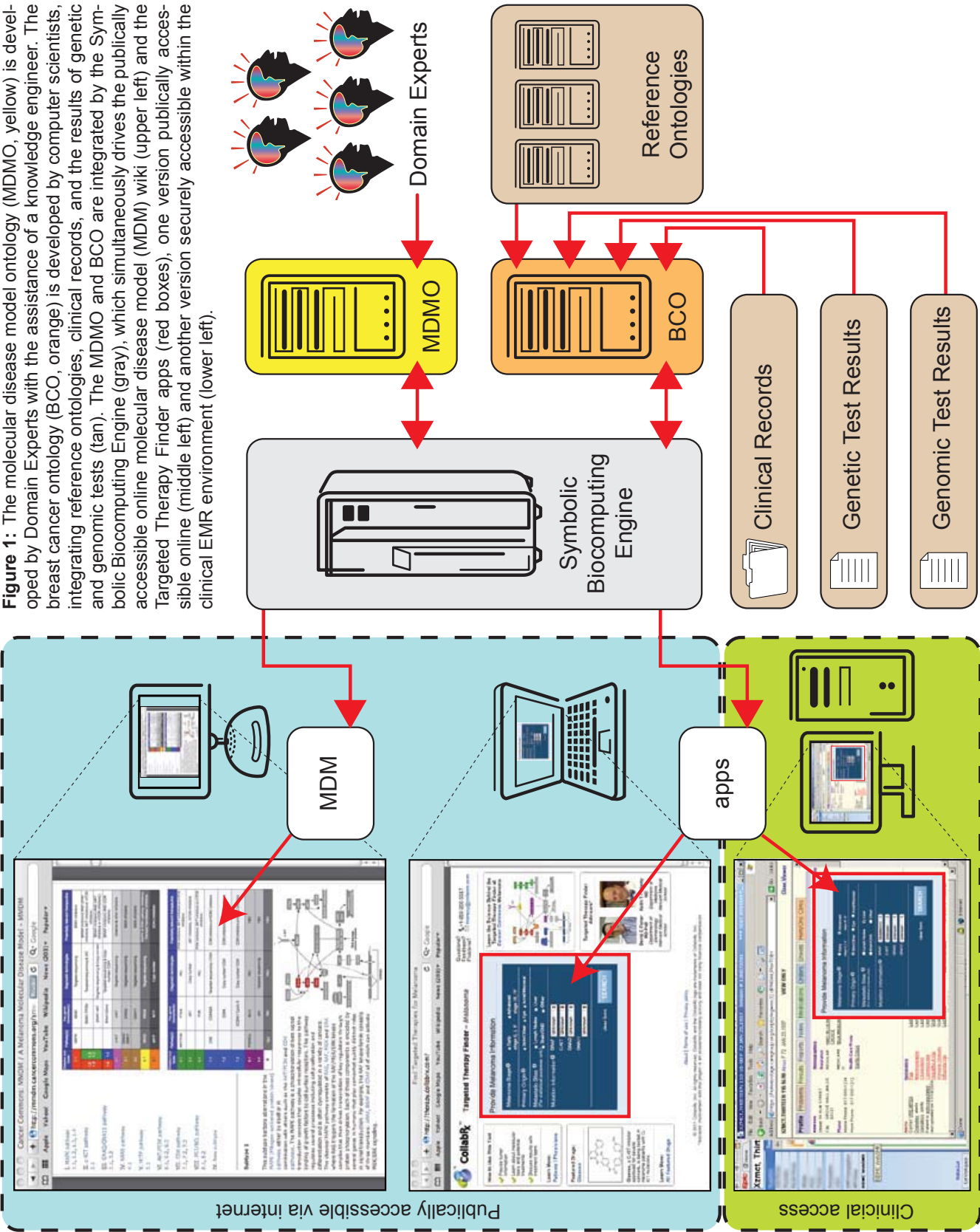
Our project will rapidly generate and broadly propagate new, easily accessible breast cancer resources for patients, advocates, clinicians, and researchers. In the first year of the project, we will produce a breast cancer ontology (BCO), a breast molecular disease model (MDM) with specific cancer subtype foci, and a web-based online Targeted Therapy Finder (TTF) app for breast cancer patients. Year 2 will see the development of a clinical TTF app that is integrated seamlessly into an electronic medical record (EMR) system, as well as further development of the BCO, MDM, and the online TTF app. In Year 3, we will continue to expand the scope of these knowledge resources while focusing on their dissemination through conference presentation, partnerships with other organizations, and promotion via a vast online community presence including informational webinars.

Please note that while this study has a direct impact on quality of care for patients, because we initially employ only anonymous, de-identified patient data in a retrospective fashion, the study has thus far been classified as non-human subject research by the Committee for Protection of Human Subjects of the California Health and Human Services Agency (CHHS), and was thus granted an exemption from Institutional Review Board (January, 2010). Subsequent prospective applications of the resources generated by this project may involve human subjects in a clinical setting, at which time appropriate action will be taken to ensure the privacy, safety, and consent of participants (explained further in attached document). Dr. Teresa Helsten will coordinate the IRB process at UCSD and beyond.

Please refer to Figure 1 throughout in order to visualize the integration of the various components of our knowledge resource framework.

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Figure 1: The molecular disease model ontology (MDMO, yellow) is developed by Domain Experts with the assistance of a knowledge engineer. The breast cancer ontology (BCO, orange) is developed by computer scientists, integrating reference ontologies, clinical records, and the results of genetic and genomic tests (tan). The MDMO and BCO are integrated by the Symbolic Biocomputing Engine (gray), which simultaneously drives the publically accessible online molecular disease model (MDM) wiki (upper left) and the Targeted Therapy Finder apps (red boxes), one version publically accessible online (middle left) and another version securely accessible within the clinical EMR environment (lower left).



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Specific Aim 1: Generate open-source, rapid-learning breast cancer knowledge resources including (1) a breast cancer ontology (BCO) that integrates molecular and genetic/genomic information with breast cancer patient records in the context of the breast cancer care knowledge domain, and (2) a breast cancer Molecular Disease Model (MDM) that shares the entirety of breast cancer knowledge from basic research to ongoing clinical trials. These resources will be scalable to include emerging molecular and genetic/genomic tests, capable of rapidly integrating new findings from clinical and basic research, developed according to accepted technical and clinical standards, and freely, publicly available.

Specific Aim 1.1: Breast Cancer Ontology (BCO)

The BCO development is informed by the team's previous experience with biomedical ontology development, [Bug et al. 2008; Williams & Hunter 2007] as well as the scientific literature. Although we aim to remain compliant with existing reference ontologies (including NCI Thesaurus, ICD-10, and HL-7) where possible, our focus is on providing a clinical ontology that enables us to deliver the functionality that clinicians and biomedical researchers expect. To do this, the pHIT team consulted with experts to develop a set of three use cases, then used these use cases to extract the relevant areas of the reference ontologies. Our focus will be on using test-driven development to verify that the BCO can both represent and reason with the clinical data available to us. We currently are using both a small in-house data set and a publicly available breast cancer dataset, the UC Irvine Machine Learning Repository, [Frank & Asuncion 2010] and anticipate further revisions as more clinical data become available.

Much of the ontological development literature is concerned with questions of ensuring ontological correctness. [Guarino et al. 2002; Smith 1996] Although we support the rigor that these approaches bring, we are keen to preserve the ability to align our work with existing reference ontologies (to allow for further data integration) rather than to substantially change the underlying structure of the reference ontologies. For this reason, we have adopted a limited version of the OntoClean approach, accepting the underlying structure of the reference ontology, and verifying only that our work does not add any errors or inconsistencies.

As noted earlier, we are well underway with the development of the BCO. We started with the integration of clinical data, as this represents the bulk of the work. We are currently able to describe the concepts in our two test datasets, and are developing definitions of new classes to allow reasoning and mappings between data and ontology using XLWrap. [XLWrap] Major weaknesses of existing reference ontologies include their lack of definitions and multiple trees for unique diseases. For example, the NCI thesaurus has extensive sets of classes for "breast cancer," "breast adenocarcinoma," "invasive breast carcinoma," and "female breast carcinoma," despite the fact that a typical breast cancer would belong to all of those classes. Our focus has therefore been on identifying areas of redundancy and overlap, so that we can use logic-based definitions to link similar concepts in the BCO (such as "an invasive adenocarcinoma of the breast in a woman," to use the example above).

We have already received sample datasets from both of the clinical tests on which we are focusing in the first stage of this work (Oncotype DX and BRACAnalysis), and we are in the process of obtaining fuller datasets to allow mapping of molecular and genetic/genomic with clinical data into the BCO. Both sample datasets are smaller than the clinical datasets (as they tend to focus on just a few factors), and so should be easier to integrate.

We will assess the functionality of the BCO using two approaches. First, we will use a validity assessment of the basic structure and relations (from a clinical perspective), which will be allied with a theoretical approach to ontological structure based on OntoClean as mentioned earlier. Second, we will use a data-based, test-driven approach similar to that used in other branches of software engineering, where we will verify that queries to the ontology give expected answers based on similar queries run on the raw data.

The first version of the BCO will be completed early in Year 1 of this project and made immediately available via hosting on our website and pursuit of publication in a peer-reviewed journal.

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Specific Aim 1.2: Breast molecular disease model (MDM)

The molecular disease model (MDM) is essentially a “dynamic review paper” that presents the breast cancer knowledge domain in a comprehensive, interactive online document. The MDM is driven by the BCO and a related MDM ontology (MDMO) (see Figure 1), in effect translating the computational knowledge domain of the ontology into a format familiar to the typical reader (discussed further below). An example of a fully developed and published MDM for melanoma can be seen on the CancerCommons website.[Vidwans] The melanoma MDM was written by Cancer Commons’ esteemed panel of expert contributors and editors over the past year. We will proceed similarly with an initial panel of four breast oncologists (Drs. Rugo, Parker, Helsten, and Williams), which will expand over time. While some face to face meetings will be required initially in the course of the technical development and knowledge sharing, much of the subsequent work will be accomplished using electronic communications including tele/videoconferencing, online discussion platforms, and email, representing significant cost-savings as the expert panel grows to a national scale.

Recognizing that breast cancer is a heterogeneous disease with complex decision-making requirements, in Year 1 we focus on developing our MDM for two key breast cancer subtypes that are well recognized in the clinical setting, identifiable using currently available technology, and can be treated with either clinically proven therapies and/or very promising emerging therapies. The initial two subtypes are estrogen sensitive breast cancer (ER and/or PR positive) and Her2neu positive, described in detail below.

Estrogen Sensitive Breast Cancer (ER and/or PR positive): This is the first recognized and the most common subtype of breast cancer, affecting approximately two thirds of all breast cancer patients. Measurement of estrogen receptor (ER) and progesterone receptor (PR) is considered the standard of care for all breast cancers. [Hammond et al. 2010] They can be measured qualitatively or quantitatively by standardized immunohistochemical or gene expression techniques that are commercially available (including Oncotype DX). More importantly, differential expression of ER, PR, or both is directly proportional to predicted benefit from (response to) several anti-estrogen therapies, including: tamoxifen, selective aromatase inhibitors, other selective estrogen receptor modulators, GNRH agonists, steroidal antiestrogens, progestins, and even oophorectomy. [Early BCTCG 2005; Dowsett et al. 2008; Stendahl et al. 2006] Incorporation of this subgroup into our breast cancer tool will be immediately applicable to very large numbers of breast cancer patients, but it represents only the first stage of our efforts.

Our subsequent efforts will focus on the fact that hormone receptor positive breast cancer still represents a very heterogeneous group of cancers. Further separation of this group into more specifically defined subtypes can be accomplished using other molecular and genetic markers. For example, increased Ki-67 expression (measured by immunohistochemistry or gene expression, as in Oncotype DX testing) is an indicator of increased proliferative rate, which maybe used to identify subgroups of patients who would benefit from specific therapies.[Viale et al. 2008] in contrast to tumors that have low Ki-67 expression. Gene expression profiling is also used to further subdivide hormone receptor positive breast cancer into luminal A and luminal B subtypes.[Perou et al. 2000] At this point in time, there are not distinct therapeutic options for these subtypes, but continued clarification of estrogen (and other) signaling in breast cancer may define new/different therapies for each subtype. We anticipate incorporation of this more granular data into our model in subsequent versions.

Endocrine therapies are well tolerated and highly effective, but resistance remains a highly relevant clinical problem, eventually affecting nearly all with advanced breast cancer. There are currently several approaches being tested that are aimed at preventing, delaying, or overcoming endocrine resistance. These include, for example, mTOR inhibition, EGFR inhibition, anti-IGF-IR antibodies, combinations of therapies, and others.[Johnston 2010] As our understanding and prediction of endocrine resistance improves and as therapeutic options increase, future expansion of our breast cancer tool can easily incorporate any number of estrogen pathway components or markers of endocrine resistance.

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Her2neu positive (amplified or overexpressing): Her2neu represents the first and best characterized target of anti-cancer immunotherapy: trastuzumab (Herceptin). [Slamon et al. 2001; Vogel et al. 2002] Her2neu is overexpressed or amplified in about 15-20% of all breast cancers. [Slamon et al. 1987] It is a marker of aggressive cancer behavior, higher risk of recurrence, and increased risk of brain metastases. Measurement of Her2neu is considered standard of care for all breast cancers at diagnosis and at recurrence. [Wolff et al. 2007] Her2neu can be measured by immunohistochemistry, FISH, or gene expression techniques (including Oncotype DX). Her2neu overexpression or gene amplification is also predictive of response to trastuzumab and lapatinib, [Slamon et al. 2001; Vogel et al. 2002; Geyer et al. 2006] as well as several other emerging Her2neu-targeting agents, including pertuzumab, trastuzumab-DM1, neratinib, and others. [Roy & Perez 2009; Burris et al. 2011; Baselga & Swain 2010] In fact, the use of adjuvant trastuzumab has dramatically changed the epidemiology of Her2neu positive breast cancer, significantly reducing recurrence risk and mortality for this subset of patients. [Romond et al. 2005; Piccart-Gebhart et al. 2005; Joensuu et al. 2006] Incorporation of Her2neu measurement into our breast cancer tool will allow identification of patients eligible to receive any number of highly effective therapeutic options.

Current ASCO guidelines indicate that either Her2neu overexpression or gene amplification implies benefit from anti-Her2 therapy, [Wolff et al. 2007] but discrepancies in testing are generating more awareness of potential distinctions within this broader subtype of breast cancer. It is possible that future efforts will better define how/which testing should be used in making therapeutic choices. [Pauletti et al. 2000] Incorporation of all available forms of Her2neu testing into our breast cancer tool will allow translation of such future distinctions into practical use. This may better define not only which patients should be treated with Her2neu-targeting agents, but also which of these agents should be used. As with endocrine therapies, understanding of Her2neu resistance is increasing. A variety of agents aimed at overcoming, delaying, or preventing resistance to Her2neu-targeted therapies are currently under study, including targeting of mTOR, PI3K EGFR, and IGF-IR. [Nahta et al. 2009, 2010] Furthermore, Her2neu is currently the object of more new targeted breast cancer therapies than any other. These agents have different mechanisms of action intended to exploit differing sensitivity/resistance profiles of breast cancer and may even have enhanced benefit when used in combination. Later versions of our breast cancer tool may allow application to a very aggressive subtype of breast cancer as well as consideration of a large number of targeted therapies.

Other Breast Cancer Subtypes:

Both estrogen sensitive and Her2neu positive breast cancers represent broad breast cancer subgroups. These markers are currently used to select targeted therapies in current clinical use. We have chosen to begin with these subgroups to develop our breast cancer tool during the first year of this project. Subsequent steps will integrate more and more granular subtypes as detailed above. We will also include other breast cancer subgroups and relevant new data as they emerge. Breast cancer subtypes to be considered include BRCA1/2-associated breast cancers and triple negative breast cancers (ER negative, PR negative, and Her2neu negative). Triple negative breast cancer is also quite heterogeneous, encompassing several types of highly proliferative, aggressive breast cancers, including basal-like and claudin-low identified by gene expression profiling. [Constantinidou et al. 2010] Triple negative breast cancer has a high recurrence risk, tends to recur early, and has no targeted therapeutic options. [Foulkes et al. 2010] Since the only clinically available treatment options for this subgroup are cytotoxic chemotherapies, there is significant need for more effective and better-tolerated treatment options. There are several agents in development for triple negative breast cancer, including PARP (polyadenosine diphosphate ribose polymerase) inhibitors, tyrosine kinase inhibitors, anti-angiogenesis agents, and others. [Anders et al. 2010; De Laurentiis et al. 2010] And, though BRCA1/2-associated breast cancers represent a small fraction of all breast cancers, PARP inhibitors are also being studied for use in these cancers, [Chan et al. 2010] which have significant overlap with the subgroups delineated herein. Since we have access to genomic data from BRACAnalysis, the only commercially available test for deleterious BRCA1/2 mutations, we will incorporate these data into our model.

Staged publication of our MDM (and associated app, described below in Specific Aim 2) enables immediate benefit to patients and clinicians while a comprehensive MDM is being developed by a growing panel of contributors and editors. After publication of our focused MDM in Year 1, we anticipate incorporation of a variety of other markers/genes with therapeutic relevance to breast cancer in Years 2 and 3. We anticipate

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ongoing incorporation of additional markers, increasing separation of subgroups, increasing numbers of therapeutic agents, and increasing attention paid to markers of treatment resistance. A key goal is to ensure that our breast cancer tool will continue to evolve dynamically and rapidly with the applicable science, while remaining easy to use by clinicians and patients alike.

As noted above, the MDM draws on a related ontology, the MDMO, which represents objects and processes relevant to molecular/genetic diagnostics and therapeutic options. A unique aspect of the MDMO is that it translates knowledge in terms understood by clinical researchers (e.g., pathways, mutations, molecular subtypes of disease, drug targets, etc.) into terms needed to directly drive web applications. As a result, the MDMO enables the presentation of the underlying knowledge in two completely different ways as resources for two very different audiences. First, the knowledge is presented for the benefit of clinicians and biologists in a “dynamic review paper” format with the appearance of a typical review, but it includes numerous hyperlinks and is hosted on a web-based wiki-like portal (specifically, in the Semantic Media Wiki, an extension of the technology supporting Wikipedia). This “dynamic review” MDM is complemented by publication in a peer reviewed journal (PLoS ONE, in the case of the melanoma MDM) in more traditional, static format.[Vidwans et al. 2011] Second, the knowledge in the MDMO is presented in the form of an interactive web-based application (the “app”) that enables clinicians and patients to “execute”, so to speak, the recommendations captured in the MDM (discussed below in Specific Aim 2). It is the MDMO that keeps these co-projections aligned, so that changes in one resource are immediately available in the other with little or no engineering work.

The integration of the BCO and MDMO will be accomplished by a Symbolic Biocomputing Engine (SBE) using the open source BioBike platform (formerly “BioLingua”).[Massar, et al. 2005; Elhai, et al. 2009] BioBike has been extended with semantic reasoning in BioDeducta,[Shrager et al. 2007] which combines with the SNARK Full First Order Logic (FFOL) reasoner. FFOL power (and bulkiness) is not required for our purposes and so, as the BCO is represented in OWL2, we will utilize the RACER reasoner ([Racer link](#)), which has specialized modules for OWL2 reasoning. We will create a set of example “proof point” queries that demonstrate the correctness and power of the unification of the MDMO with the BCO. Examples of such queries include (1) “what treatments were most successful in terms of time to recurrence for patients with the same molecular profile as the present patient, in terms of model subtypes?” and (2) “what adjustments to the model subtypes (e.g., splitting or unifying subtypes) will improve the predictive power of the model in terms of the patient population at hand?”, among others. The BCO and the MDMO will be “threaded” at the BioBike layer toward the goal of these proof point queries, demonstrating their correct execution in both the MDM and app.

The first iteration of this process will occur in its entirety in Year 1 of the project, resulting in a freely accessible online breast MDM that will be substantially augmented in Years 2 and 3. The MDM will be published in a peer-reviewed journal as quickly as possible, and immediately hosted at www.cancercommons.org, an online “rapid learning” community website that already features a melanoma MDM and is developing MDMs for a variety of other cancers.

Specific Aim 2: Extend the knowledge resources into rules-based decision-support tools that provide meaningful, patient-centric information to individual patients and their care providers. These tools will be developed as (1) web-based apps and (2) seamlessly integrated modules within the EMR workspace.

Specific Aim 2.1: web-based Targeted Therapy Finder (TTF) app for breast cancer

As described above, the conceptual and computational resources needed to drive the TTF app are found in the MDMO and BCO and integrated by the Symbolic Biocomputing Engine (SBE). The app is built in Ruby/Rails over MySQL according to widely recognized web development standards, and can be easily adapted to the dynamic environment of Web2.0 and its inevitable successors. Concurrently, changes to the knowledge domain of breast cancer (for example, new results from clinical or basic research or newly available anti-neoplastic agents) are automatically reflected in the app by virtue of its real-time interaction with the underlying ontologies via the SBE, which runs combinations as needed of Lisp/Racer/Jena/R.

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Given the efficiency of knowledge incorporation “behind the scenes,” the focus of the app is chiefly on ease of user experience. We will replicate the successful process used in developing and deploying the melanoma TTF app,[CollabRx] which has already been viewed over 1500 times in its first month of being “live” on the web (released January 22, 2011). Briefly, a breast cancer TTF app user (patient, clinician, advocate or other) anonymously enters information about an individual breast cancer, such as stage, histopathologic grade, ER/PR/Her2neu results, known mutations, sites of metastases, etc., via a very user-friendly point-and-click interface. These inputs are then rapidly processed within the SBE, which draws on the underlying MDMO and BCO to present the user with a simple output of individualized knowledge including subtype classification, available diagnostic tests, recommended therapeutic options, emerging therapies, ongoing clinical trials, and more. The user thus receives a meaningful, actionable response to the query, all in a matter of seconds. The response information is hyperlinked so that a user can learn, for example, which reference labs offer particular diagnostic tests, or which sites are recruiting for clinical trials. The response can also be printed, or exported to a simple standard file format for inclusion in a patient’s personal health record.

As part of our development process, we will consult with external parties to evaluate our beta version TTF app, including clinicians, genetic counselors, patient advocates, and other breast cancer care projects such as ATHENA.

The first iteration of this process will occur in its entirety in Year 1 of the project, resulting in a freely accessible online breast TTF app that will be substantially augmented in Years 2 and 3. The app will be hosted at www.collabrx.com similar to the existing melanoma app,[CollabRx] and its usage will be tracked via standard accepted analytics and metrics. This app is freely accessible to anyone with internet access, including patients and care providers, who may adopt this resource as part of clinic visits. Even care providers who have not adopted an electronic medical record (EMR) can use this tool immediately, while care sites with an established EMR will further benefit from the integrated clinical TTF app described below in Specific Aim 2.2.

Specific Aim 2.2: integrated clinical Targeted Therapy Finder (TTF) app within an EMR system

Another novel aspect of this project is the development of a clinical TTF app that is seamlessly integrated into a clinical EMR workflow. We will focus initially on integration with EpicCare, as this EMR system is well established and in use at UCSD and beyond (all UC Medical Centers, numerous other care facilities). Our team will work with EpicCare representatives at UCSD to build a frame for the TTF app within the native EpicCare EMR environment, thereby precluding the need for a clinician to “leave” EpicCare in pursuit of the knowledge resources during the course of their normal workflow.

A simple embodiment of the integrated TTF app could be an exact reproduction of the aforementioned web-based app, allowing clinicians and patients to enter information via a series of simple clicks. Our approach intends to go beyond that, however, by virtue of the BCO that integrates clinical records with the results of molecular and genetic/genomic tests. In this manner, the relevant data can be dynamically collected directly from these sources and automatically entered into the various query fields of the app, resulting in the appearance of a customized knowledge response within the EpicCare environment (either main interface or within the Beacon Oncology Information System, a “specialty add-on” offered by Epic).

The beta version of the EMR-integrated clinical TTF app will be evaluated by the UC clinicians on our team, namely Drs. Rugo, Parker, and Helsten. We are developing a specific roadmap for broader adoption of this tool in partnership with Epic or other EMR vendors.

The first iteration of the EMR-integrated clinical TTF app will be completed in Year 2 of this project. Like the online version of the app, the clinical app will benefit from real-time updates to the MDMO and BCO as new knowledge emerges and new diagnostic tests are included in our repertoire. This entire process is facilitated by the deliberate, fundamental interoperability of our system.

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Specific Aim 3: Broadly disseminate these free resources and tools to patients, care providers, breast care advocates, and all interested parties by developing interfaces with complementary breast cancer care projects, including the ATHENA project,[ATHENA] Stanford and Palo Alto Medical Foundation,[Stanford-PAMF] and others; presenting at regional and national breast cancer conferences; and partnering with diverse clinical, advocacy, and education groups in the breast cancer space.

The very nature of our work (ie, open-source, available on the internet) will greatly accelerate the adoption and use of our MDM and apps by a broad constituency, including patients, advocates, clinicians, and researchers. Further, the prominence of our online resources will be enhanced by state-of-the-art search engine optimization (SEO) and activity on popular social networking websites and online media channels. Concomitant publication of our knowledge resources in peer-reviewed journals will firmly establish their credibility and greatly increase their visibility to the research community, both clinical and basic science. Care providers and advocates will be educated about the knowledge resources and tools via presentations at prominent conferences, as well as communication partnerships with various clinical, advocacy, and education groups (for example, email notifications). The conference environment also allows for regular face-to-face interaction opportunities for members of our expert MDM editorial panel, who are expected to number in the dozens by Year 3. While we will promote our new resources regularly online and at meetings beginning later in Year 1 of this project, the bulk of targeted dissemination will occur in Years 2 and 3 after we have established the broad utility of the MDM and the TTF apps, including preliminary uptake statistics.

Figure 2 summarizes a timeline of milestones for each of the above Specific Aims.

Figure 2: Timeline of milestones for the pHIT project, arranged by Year and Specific Aim

	Year 1	Year 2	Year 3
Aim 1	Molecular Disease Model MDM version 1 edited by Rugo, Parker, Williams, Helsten focus on initial subtypes	MDM version 2 edited by Rugo et al (expanded council) expand to additional subtypes	MDM version 3 edited by Rugo et al (expanded council) comprehensive breast cancer MDM
	Breast Cancer Ontology BCO version 1 supports integration of clinical data with results from BRACAnalysis, Oncotype DX	BCO version 2 supports additional test results, integrates data and pushes decision support to clinical TTF app	BCO version 3 supports additional test results, released with documentation for adoption by other parties
Aim 2	Targeted Therapy Finder app (online) TTF online version 1 decision support for initial subtypes covered in MDM version 1	TTF online version 2 decision support for additional subtypes covered in MDM version 2	TTF online version 3 comprehensive decision support in line with MDM version 3
	Targeted Therapy Finder app (clinical)	TTF clinical version 1 decision support for initial subtypes integrated into Epic EMR	TTF clinical version 2 decision support for expanded subtypes integrated into Epic EMR
Aim 3		Disseminate information about MDM and TTF apps at conferences, through partner- ships with advocacy groups, online, etc	Continue as in Year 2, pursue opportuni- ties for integration with other breast cancer research platforms

Summary:

The pHIT study uses cutting-edge information technology to gather the entire breast cancer care knowledge domain, organize it under expert guidance into interoperable ontologies, present it in an accessible manner via an online “dynamic review” (the molecular disease model, MDM), and extend it into easy-to-use, free Targeted Therapy Finder (TTF) decision support tools for patients with breast cancer, family members, advocates, clinicians, researchers – any member of the breast cancer community in California, and beyond. The first results of our work will be made publicly available in less than a year from the project start date, providing

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immediate benefit and translational application. Further, as new information enters the breast cancer knowledge domain or as feedback is given about our MDM and apps, these resources will be updated by the same expert team, ever increasing in number as additional clinicians and researchers participate on the MDM editorial board. In short, our system fundamentally alters the paradigm and pace of knowledge translation from research producers to research consumers, and back again.

We take very seriously the involvement of patient advocates in the development of our work. In December 2009, the pHIT study was endorsed by the CalPERS Health Benefits Committee, including breast cancer survivors and advocates, and is informed by the direct clinical experiences of our team of renowned breast cancer experts with exemplary, demonstrated dedication to patient wellbeing. Ongoing conversations with other leading breast cancer studies, including those undertaken by ATHENA, Stanford and the Palo Alto Medical Foundation, and partnerships with other patient-centered efforts including Cancer Commons, will ensure that patient-survivor experiences and knowledge are included with the utmost respect and consideration. Further, our team works with counselors and patient advocates in the genetic/genomic testing space to promote dialogue about the values and pitfalls of current and emerging tests and information, for example, Dr. Lisa Madlensky, director of the Family Cancer Genetics Program and registry at UCSD Moores Cancer Center (see letter of collaboration in Appendix).

As noted above, the results of our work will be available to the public beginning in Year 1 and with regular updates throughout the project period. Figure 2 summarizes the sequential release plan for each of our knowledge resources and decision support tools. We begin our work as “mid-level research” on the critical path, specifically “developing practical applications of previous research findings.” Over the course of the three years of proposed support by the California Breast Cancer Research Program, we will achieve and surpass “advanced studies,” that is, “demonstration projects to test and refine the effectiveness of different methods and models for the final phases of translating research knowledge into health services delivery, policy, and environmental modifications,” all the while enhancing other studies’ ability to reach translation into practice. Support from CBCRP represents a one-time investment in the sustainable translation of past, present, and future research in breast cancer care in California and beyond, and brings state-of-the art knowledge to the breast cancer community for improved quality and equality of care.

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