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Genomic Medicine VII: Genomic Clinical Decision Support
October 2-3, 2014
Bethesda North Marriott Hotel & Conference Center, Bethesda, MD

Welcome, Introductions, and Expectations – Marc Williams, Blackford Middleton

The National Human Genome Research Institute (NHGRI) Genomic Medicine Working Group welcomed experts convened to address a diverse set of topics related to genomic clinical decision support (GCDS) that will be important in moving genomics into the implementation space. In bringing together a broad array of stakeholders, the major objectives of Genomic Medicine VII (GMVII) are to: compare the current state with the ideal state of genomic clinical decision support (GCDS) to define gaps and strategies to close the gaps, identify and engage US and international health IT initiatives that would support recommended strategies coming out of GMVII, and define a prioritized GCDS implementation research agenda. Marc Williams (Geisinger) and Blackford Middleton (Vanderbilt) proposed possible outcomes of GMVII, which include development of a national steering group and working groups, consideration of collaborations or pilot projects related to GCDS, and identification of potential funding models for these efforts.

Overview of Survey Results – Blackford Middleton

Blackford reviewed results of the survey instrument circulated to GMVII attendees prior to this meeting. The survey was based on the 14 key recommendations from the Masys *et al* technical desiderata on integrating genomic data into electronic health records and the Welch *et al* technical desiderata on integrating genomic data into clinical decision support. Attendees were asked to rank each of these elements by importance in implementing GCDS in the current state and by proximity to ideal GCDS capabilities. Blackford highlighted four desiderata that clustered on a graph of mean importance in the current GCDS state vs. mean difference from the ideal GCDS state and were also ranked in the Top 5 priorities in achieving the ideal GCDS state:

1. Maintaining separation of primary molecular observations from clinical interpretations of those data (Masys desideratum #1),
2. Simultaneously supporting human-viewable formats and machine-readable formats in order to facilitate implementation of decision support rules (Masys #5),
3. Leveraging current and developing CDS and genomics standards (Welch #12), and
4. Supporting a CDS knowledge base deployed at and developed by multiple independent organizations (Welch #13).

Blackford proposed that the group use these prioritization insights to frame discussions and plans for potential outcomes from this meeting.

Tales of Tenerife and Three Mile Island: Lessons from Other Industries for Genomic Clinical Decision Support – Dan Masys

Dan Masys (University of Washington) delivered the keynote speech, explaining the basis and rationale behind his seven desiderata for genomic sequence data in electronic health records (EHRs) and drawing lessons from the aviation and nuclear power industries to suggest essential "building blocks" for an ideal state of GCDS.

To address the challenges of integrating genomic data into EHRs, Dan's seven desiderata state that EHR systems must have the ability to: 1) compress without losing data as it moves in and out of the clinical environment, 2) adopt changing annotation methods over time while also carrying previous annotations, 3) represent clinically actionable subsets in accessible ways, 4) be represented in human-

viewable and machine-interpretable formats, 5) separate primary sequence data and clinical interpretations, 6) hold multiple genome-scale databases for each individual over their lifetime, and 7) be used in individual care as well as discovery science. To extend the Masys *et al* technical desiderata for integration of whole genome sequencing (WGS) with CDS, Welch *et al* created seven additional desiderata that suggest that CDS systems will: 8) have the potential to incorporate multiple genes and clinical information, 9) keep CDS knowledge separate from variant classification so that annotations can be updated, 10) support multiple EHR platforms, 11) support a large number of gene variants while simplifying CDS knowledge to the extent possible, 12) leverage current and developing CDS and genomics standards, 13) support a CDS knowledgebase deployed at and developed by multiple independent organizations, and 14) access and transmit only the genomic information necessary for CDS. Dan Masys cautioned that GCDS developers run the risk of exceeding the bounds of human cognition if too much information is presented to clinicians.

Dan presented the aviation and nuclear power industries as paradigms for how industries can reinvent their operational strategies in new and effective ways. In responding to the 1977 Tenerife tragedy resulting from a captain's disregard of protocol, the aviation industry rapidly adopted a system of checks and balances among teams to replace its hierarchical model. Following the 1979 Three Mile Island nuclear meltdown, nuclear power companies formed international networks to communicate and make real-time decisions in dealing with "rare variant" situations. Learning from these industries' mistakes, GCDS developers can take similar approaches in implementing GCDS in a standardized, group-thinking way. Dan presented evidence from the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) project, which uses a regulated team-based approach to implementation to conduct discovery research through EHRs, present real-time pharmacogenomic alerts, and follow decision support outcomes. Introducing computerized provider order entry (CPOE) through CDS led to significant reduction in providers' medication prescribing errors.

Dan identified key elements of the ideal GCDS user interface. The ideal GCDS system would always be updateable; have content that can be (re)purposed for different types of users; be sensitive to different users' health and genomics literacy and numeracy; explain all its actions and recommendations; and adaptively learn what each user knows with use over time. From the perspective of healthcare organizations, the ideal GCDS would have a systems infrastructure to improve quality and consistency by autonomous individual entities; track decision support events and provide basis for correlating subsequent clinical course with guidance provided; and contribute to local continuous process improvement to a shared national learning healthcare system.

Dan offered several "building blocks," or knowledge representation standards, for an interoperable electronic decision support package. Essential components would include recognition logic for conditions of interest as represented in EHR systems (both genotype and phenotype); guidance for all target users; and recognition logic for "closed loop" decision support, or the ability to monitor process or outcome measures and track uptake of decision support advice by clinicians. A CDS Public Library or Information Commons managed by a neutral, trusted organization such as the National Library of Medicine (NLM), the Clinical Decision Support Consortium (CDSC), or a Wikipedia-like group, would allow local users to submit de-identified outcomes data to the Public Library to inform a national learning healthcare system.

Ideal State for Genomic CDS – All

Responding to Dan's definitions, the group discussed the level of robustness that GCDS should achieve before launch in the clinic, as standards of practice for GCDS do not currently exist. GCDS developers

should establish metrics to determine whether a GCDS system is ready to be implemented in the clinic. Professional societies and other institutions can form committees to create standards and guidelines for GCDS. GMVII attendees should identify where there is a lack of consensus across institutions implementing GCDS and have each organization involved decide what elements they do and do not agree on.

Pooling data about all implementation experience across the healthcare industry would increase power for this kind of research and the likelihood of being useful to the FDA and other agencies. In a competitive hospital environment, a strategy in building a national knowledgebase might be to focus on one particular area, i.e. aggregating experiences with antibiotic resistance and tracking cases of foodborne illnesses. A root cause of not having scalable GCDS support is a lack of actual business cases demonstrating the value of GCDS. Healthcare industry incentives are patient safety, as well as reimbursement and demonstration of savings. GMVII attendees might align with business-oriented stakeholders to create use cases around this. Linking with discovery science companies would also generate incentive for healthcare systems to share their knowledge. Another driver for healthcare systems is enthusiasm from patients and motivation to be involved in the GCDS initiative. GCDS developers should consider what aspects of GCDS knowledge patients should be exposed to and determine how this information affects physician-patient interactions. GCDS should have the ability to extend knowledge of risks for monogenic diseases to family members. Decision support resources might include advice on family planning and how to deliver this information to family members.

Alert fatigue is an issue. Users will mistrust the system if the alert is not based on correct evidence or not presented in the right context. GCDS developers should think about building systems that filter out information that is useful to different users, giving consideration to the tension between paternalism and open access. Workflow is not standardized for all specialties and physicians use CDS in a variety of ways. There is an opportunity to create an adaptive CDS system that can gauge what different user groups need from CDS in their workflow.

Developing a shared infrastructure between disparate EHR systems would help with transportability and interoperability. Vendors should be engaged to see if and how GCDS components and data can be transferred to different systems.

GCDS would lead to a shift in medical training culture from a hierarchical to a systems-based model. Vanderbilt uses highly automated work station-based care, allowing students to learn from their own data as well as from supervisors. When clinicians make mistakes, CDS systems can capture relevant information about why decisions were made to help others understand the cause of errors. Systems are needed that separate reporting from blame so systems can learn and improve, as the vast majority of errors are system-wide/compounded errors, not individual errors.

Panel Discussion 1: Key Question #2 – *What are the data issues that impact genomic CDS?*
Moderators: Robert Freimuth, James Ostell

GCDS systems should share and maintain individuals' genomic information and its interpretations as patients move through different healthcare systems. Beyond the patient's lifetime, and consistent with consent and privacy regulations, relevant information should also be shared with immediate family members and descendants. Vast uninterpreted data containing variants of unknown significance information should remain external to EHRs.

Creating metadata around CDS rules would track what physicians are looking at. To avoid overloading clinicians, new knowledge could be made available to them on demand rather than through a push model. It might also be possible for active and passive CDS mechanisms to operate on the same set of data in different ways.

The types of knowledge represented in GCDS vary by the CDS rule. Regardless of the data type, representations should be shareable and presented in a structured, unambiguous form. Each CDS rule should understand specific elements, both present and missing. The Standards & Interoperability (S&I) Framework initiative, with input from Office of the National Coordinator (ONC) and Centers for Medicare & Medicaid Services (CMS), has drafted language for how to represent content in CDS systems. Attendees can consider working with ONC and CMS to create a GCDS use case.

Individuals' germline genome, in an ideal GCDS system, would be sequenced at birth and stored in a central repository. Reads would be reassembled and realigned with every new set of references. Barriers to this are standardization issues and technical limitations of CDS rules. GMVII attendees should define standard trigger events to stimulate GCDS engine to fire. New knowledge can be adopted into a healthcare system based on recommendations from standing research committees who evaluate best practices periodically. Some, but not all, institutions have management teams with the appropriate expertise to interpret and implement incoming knowledge. ClinVar, a public database that stores and make publicly available information on sequence variants and phenotype associations, could share knowledge to influence standard interpretations for variants. As classifications change, GCDS developers should determine best approaches for identifying patients to which the reclassification applies and for re-alerting clinicians about these patients. Legal obligations should be considered for re-interpreting genomic data. It was agreed that not all calls or interpretations are made in the same level of confidence, and the same level of rigor may not be required in all clinical contexts.

GCDS developers should bear in mind that the sociological and political landscape of genomics is changing. Short-term advances in the present may not be applicable in the near future.

Panel Discussion 2: Key Question #3 – *How do we manage knowledge for genomic CDS?*
Moderators: Atul Butte, Josh Peterson

Funded GCDS projects, especially in pharmacogenomics (PGx), should exchange knowledge and best practices to achieve interoperability. Experts from these groups should define standard exportable methods, develop use cases for knowledge representation, and potentially identify top priority genes to create standards for specific variant representations. One (or more) central, interoperable repository(-ies) could be assembled to store encoded genomics knowledge. It would be useful to establish consensus gradation for levels of confidence, i.e. high confidence vs. intermediary confidence variants, and assess uptake of particular associations into CDS across different institutions. Levels of confidence could then be promoted or demoted as evidence on uptake and impact emerges. The Agency for Healthcare Research and Quality (AHRQ) plays a key role in disseminating knowledge and should be invited to join this initiative.

A major challenge for WGS/WES in the clinic is this data's high dimensionality. A potential deliverable might be a pilot to assess how WGS/WES should be represented in EHRs, develop methods for extracting specific variants, and demonstrate the clinical value in incorporating this kind of information into EHRs. A working group forming out of GMVII can produce use cases in collaboration with other groups in this area to determine how to feed WGS/WES information to CDS at the appropriate time across a heterogeneous set of clinical questions. NHGRI projects could be involved to test these use

cases and see what works in their clinical environments. These projects can also submit use cases appropriate for an end-to-end knowledge study. Aggregating PGx data from funded PGx projects would accumulate sufficient numbers to assess outcomes. Insights and experiences from other fields, like pathology and radiology, in developing CDS for their specialties would be helpful. Direct-to-consumer services might also be involved.

The IOM Genomics Roundtable has discussed creating a passive CDS component to provide links to educational resources on genomics (e.g. Infobuttons, Just in Time content) to give context for alerts. GCDS developers should consider creating standards for incorporating passive GCDS into EHRs as this is part of Meaningful Use standards. Several infobutton projects, like the U.S Department of Veterans Affiars (VA) OpenInfobutton and the University of Maryland infobutton study, are evaluating impact. Another idea would be to create gene information sheets that can be tagged into EHRs and link these to public resources like GeneReviews and Genetics Home Reference.

Panel Discussion 3: Key Question #4 – *What are the implementation issues surrounding genomic CDS?*
Moderators: Kensauku Kawamoto, Casey Overby

In approaching EHR vendors, GCDS developers can work with vendor systems to assess their capabilities and perhaps identify inefficiencies. GMVII attendees can consider collaborating with standards developing organizations (SDOs) like Health Level Seven (HL7) and the Independent Evaluation Group (IEG) and open source efforts to work with their rules. Institutions should be engaged to ask them what their priorities and incentives are and present the potential value of implementing GCDS systems. In demonstrating return on investment, problems can be defined using financial metrics. It will also be important to assess whether this should be performed in a research or quality improvement environment. There was interest among the group in assessing how genetic tests are ordered in different contexts and the role for GCDS in guiding test ordering (e.g., when to order genome vs. single-gene tests) and avoidance of duplicate testing.

CDS systems in the current state are not designed to re-contact users when new variant associations are discovered. The return on investment for providing CDS alerts for the 1-2 people a year who are affected by the new variant discovery does not create a large enough need to create decision support. However, if this is implemented across multiple institutions, rare situations could become collectively common and addressing them might be cost effective. Re-analysis is also not a part of the current billing system. Considering possible reimbursement models will be important in looking at the current GCDS landscape.

Challenges to scaling are a lack of communication between the knowledge creator and knowledge user. Though physical storage of whole-genome sequences is presently not ready to support scaling up of WGS work, the consensus was that the group should look at opportunities to implement WGS CDS. Developers should establish a mechanism for moving information in a validated and lossless way. Lossless data compression cannot happen unless a reference genome is agreed upon.

The group examined several methods to involve patients and motivate them to interact with GCDS. To understand more about what kind of information patients want from genetic testing, developers can set up patient portals allowing patients to choose from a pick list of information they want or do not want to receive. Patient portals can also provide data on patients' readiness to change based on this information. Mobile computing systems and personal genomics apps will also be effective in involving patients. In the Duke family history implementation project, whenever a CDS report comes up in the EHR, a simultaneous alert goes to the patient to alert them of the results' availability and inform them

on why the test/treatment was recommended. This method has been shown to activate patients as well as their clinicians. Patients at the VA can readily access their health data through the VA patient portal to engage with their own data and self-report. Literature coming out of Kaiser Permanente and GroupHealth also shows that their patients respond well to financial incentives for maintaining an online patient health portal presence. There is also the possibility to work with patient health records (PHRs) to adjust what is displayed in PHRs over time.

An infrastructure needs to be in place to test small parts of the EHR at a time and receive input from end users. Using a sandbox would allow consortium-based testing of standards for CDS processes. Cerner would be willing to test use cases in their Substitutable Medical Apps & Reusable Technology (SMART) platform as a demo. The National Cancer Institute (NCI) can help with use cases using The Cancer Genome Atlas (TCGA) data. Other possible groups to test use cases would be i2b2 (Informatics for Integrating Biology & the Bedside), which would fit in with Cerner's capabilities since it is SMART-enabled, and VA open source sandbox, which has an experimental harness, and thus might be easier than SMART to transport to other EHR vendor systems. It might also be possible to test within the National Institute of Dental and Craniofacial Research (NIDCR)-supported Practice-Based Research Network (PBRN) investment infrastructure. GCDS developers should also define the interface between EHRs and CDS in Literacy Information and Communication Systems (LINCS).

Decision support is important in developing evidence on impact of genomic medicine implementation. It might not even be possible to have an intervention without decision support in place. The strategy of using decision support to develop best practices could be used for evidence generation and adoption.

Panel Discussion 4: Key Question #5 – *What are areas that should be prioritized for the research agenda for genomic CDS?*

Moderators: Marc Williams, Blackford Middleton

Marc and Blackford synthesized key points from the first day's proceedings, listed proposed potential outcomes, and mapped possible deliverables to the key questions that guided each panel discussion.

Meeting Objective #2, to identify US and international health IT initiatives to engage in moving GCDS implementation forward, has been accomplished. Marc and Blackford extracted from discussions the following groups to potentially engage: NHGRI/NIH funded projects such as the Electronic Medical Records and Genomics (eMERGE) Network, the Clinical Sequencing Exploratory Research (CSER) program, the Implementing Genomics in Practice (IGNITE) Network, the Newborn Sequencing In Genomic Medicine and Public Health (NSIGHT) program, ClinSeq, the Clinical Pharmacogenetics Implementation Consortium (CPIC), etc.; IOM Action Collaborative; ONC/AHRQ CDS initiative, VA, CDS Consortium, Health eDecision, OpenInfobutton and OpenCDS, and SMART-on-FHIR.

Marc summarized the building blocks of ideal GCDS outlined in Dan's keynote presentation, noting that interoperable electronic decision support packages should represent genetic and genomic results related to management systems and recognition logic for closed loop decision support. To support an end-to-end project, event monitors would be embedded in EHR and PHR systems. Process or outcome measures would include user acceptance or rejection of guidance. Decision support authoring systems would involve tools to easily import, review, and implement decision support packages. System-generated alerts would present information to users at the "teachable moment" of diagnostic testing, therapy decision making, or counseling. Outcomes and user decisions would be tracked in an automated way and uploaded to a CDS Public Library.

Synthesis of Key Question 2 (KQ2 - *What are the data issues that impact genomic CDS?*) Discussion
Marc and Blackford captured key ideas addressing data issues from the KQ2 discussion. It will be important to establish a hierarchical set of knowledge representation and technical standards. A group forming out of GMVII might consider how the same set of data can be used for different CDS instances. Defining what will be the standard trigger events for GCDS engines will increase consistency across CDS systems. This group should define methods to maintain provenance of data and knowledge using metadata around data constructs and knowledge artifacts. Recognizing that patients may move among different healthcare systems, developers should assure interoperability of data elements between health record systems. These data should also be available for family members and descendants who may have interest in them. The GMVII group should also develop methods to address barriers in the current and future legal, regulatory, and policy environment and determine the public's role in GCDS implementation in different clinical scenarios (e.g. screening vs. care). Ken Kawamoto (University of Utah) recommended that GMVII attendees establish a standard mechanism to publish events. Infobutton standards are a starting point.

Synthesis of Key Question 3 (KQ3 – *How do we manage knowledge for genomic CDS?*) Discussion
The group suggested aligning with other groups to develop a standardized way to represent knowledge. The IOM Action Collaborative pilots and groups are working in portability and data sourcing. AHRQ and ONC are creating CDS systems for immunizations that could be integrated into any EHR. They might allow interested GMVII attendees to study use cases in this space. Marc proposed that, as this group learns more about what are successful GCDS elements, NIH could expect funded CDS projects to deposit knowledge in a central repository using AHRQ/ONC standards.

As more data emerge on the use of WGS/WES in the clinic, the group decided to put together use cases to test feeding information into CDS systems across heterogeneous questions. This effort could be designed to collect knowledge from and test cases with existing groups like CSER, Newborn Sequencing, eMERGE III, IGNITE PGx groups, the Undiagnosed Disease Network (UDN), somatic sequencing groups, microbial sequencing groups, and the NIH Big Data to Knowledge (BD2K) initiative.

The group suggested developing an end-to-end project based on CDS to assess current standards for data, knowledge, processes, and outcomes to inform implementation strategies and generate evidence for the economic and business value of GCDS. It will be critical to select pilots in areas where impact and patient outcomes would be seen in a shorter time frame. In defining process measures, this effort can be designed to track the firing of the alert, user's acknowledgement (or not) of the alert, and downstream recognition of alert uptake. Process measures can be captured in commercial EHRs with CDS that can make logs of the process measures. Quality measures being pulled at this time are not granular enough to track decisions, but a group of interested GMVII attendees can connect with quality assessment groups to explore using quality measures to help in tracking outcomes. Dan Masys recommended using natural language processing (NLP) descriptions to state whether or not rules were responded to in the EHR. Betsy Humphreys (NLM/NIH) urged NIH groups to come together to decide on common data elements that need to be in place to support patient safety reporting and quality measurement. The group suggested having a library of common elements. Chris Chute (Mayo) advised that dealing with similar but different standards is difficult. The research community should not create new data elements and instead adopt existing, preferably widely used, clinical elements to increase consistencies.

The group should come up with a definition for interoperability. Dan Masys made the distinction that there is a difference between interoperability and exchanging what is useful in a different context. It is

more important to exchange components that would be most useful to patients. This might require narrowing our definition of interoperability.

There are knowledge resources available like the National Center for Biotechnology Information (NCBI) Pharmacogenetics Knowledge Base (PharmGKB) that is not currently in a computable format, but could be.

Synthesis of Key Question 4 (KQ4 *– What are the implementation issues surrounding genomic CDS?*) Discussion

Actions coming out of KQ4 were proposed to tackle implementation roadblocks. To develop and test use cases, attendees discussed creating a national developmental certified EHR environment and toolkit (sandbox) potentially involving NIH, NCI and TCGA, ONC, and i2b2.

GMVII attendees participating in the business case effort should define a return on investment/business case to identify barriers to implementation beyond genomics. Research focused on workflow and user interactions, including patients, will allow this group to develop best practices based on end user needs. How data are presented to different users might depend on the type of test ordered (lab test vs. WGS results). Patients can have a role in maintaining data. There are some synergies between Patient-Centered Outcomes Research Institute (PCORI) activities and GMVII recommended initiatives. In developing a research agenda related to patient's role in GCDS, the GMVII group can connect with PCORI.

Key Question 5 (KQ5 *– What are areas that should be prioritized for the research*): Overall Synthesis and outline of a prioritized research agenda for GCDS

Marc and Blackford proposed priorities and outcomes for this group to pursue:

1. Developing a return on investment business use case for GCDS.
2. Determining a baseline for GCDS in clinical epidemiology/health services research.
3. Determining what would be the ideal presentation layer.
4. Creating standards for terminology, data, knowledge representative (hierarchical), uncertainty management, transaction, etc. in the context of data and knowledge, aligning with HL7 for synergy and concordant with existing standards through Meaningful Use (SNOMED, LINCS, etc.).
5. Establishing an end-to-end demonstration project to assess outcomes and "close the loop." A possible way to do this would be by collecting best practices from implementers (eMERGE-PGx/eMERGE-CSER.
6. Elucidating the role of public health vs. public's health with questions about screening vs. care and portability and interoperability.
7. Developing genomic CDS use cases to promote to ONC/AHRQ. Use cases would include: building on the immunization model, using HLA-B*57:01 and abacavir, and implementing American College of Medical Genetics (ACMG) Newborn Screening ACT sheets.
8. Working within a national developmental certified EHR environment and toolkit (sandbox) to test use cases.
9. Exploring the role of the patient/caregiver for genomic CDS (PCORI).
10. Exploring different types of CDS (beyond alerts) which also fit with exploration of user experience with GCDS.
11. Establishing a funded GCD center (similar to a sequencing center).

With regard to the immunization model mentioned in Priority #7, this refers to the Centers for Disease Control and Prevention (CDC) American Committee on Immunization Practices (ACIP) recommendations and translated it into XML language. It will be posted in an EHR-compatible format. Ken Kawamoto will circulate this information [***action***].

Jim Ostell (NCBI/NIH) proposed, in tying GCDS to reimbursement decisions, connecting ClinVar and ClinGen to the CDS system so that these variants and genes will be represented in CDS.

Mapping potential outcomes to key questions
The GCDS use cases proposal links to KQ1 on what would be essential in successful implementation of genomic medicine. Developing standards would address KQ2 on data issues that impact GCDS. KQ3 on managing GCDS knowledge can be targeted by creating intersections of acute care, longitudinal care, and generational considerations (public health), as well as developing knowledge management methods and establishing governance. KQ4 on identifying implementation issues surrounding GCDS would be evaluated through a study on the clinical epidemiology of GCDS, return on investment, and gathering best practices for GCDS. Demonstrating GCDS at scale, across multiple disparate EHRs, would be an ultimate goal in exploring KQ5 (identifying prioritized areas for the long-term GCDS research agenda).

<u>Presentation and discussion of Day 1 – Synthesis Mapped to Key Question #5</u>
Moderators: Marc Williams, Blackford Middleton

GMVII publications and engagement within the scientific community
Blackford and Marc will be producing a paper to summarize the outputs of this meeting. They will incorporate the data related to the survey on desiderata. Co-moderators will be encouraged to take ownership of specific content related to their key questions and become co-authors on this manuscript. It would also be possible to write two papers: one that is informatics focused and one that is genomics focused. Another aim for this paper might be to provide recommendations to specific agencies to address particular problems in the GCDS state.

Jessie Tenenbaum (Duke) is the incoming chair of the American Medical Informatics Association (AMIA) Genomics Working Group. She and current chair Bob Freimuth (Mayo) agreed to sponsor this group's proposal for a late-breaking session related to the outcomes of this meeting [***action***]. Josh Denny plans to highlight the outcomes of this meeting at his talk during an upcoming late-breaking AMIA session organized by Neil Sarkar (University of Vermont). Marc will see if he can do a separate talk at this session [***action***]. Eventually, this group will look to present at a professional society meeting. It will be important for this group to engage the genetics community to increase awareness of and begin to clarify the role of CDS in genetics.

Reviewing priorities for GMVII research agenda
Attendees voted on priorities for possible directions presented in the previous discussions. Leads were assigned to make the appropriate connections to initiate these projects. Subsequent sections are reported in order of most to least interest from the group:

GCDS use cases and sandbox
Jamie Skipper (ONC) offered to allow interested GMVII attendees to test some genomic CDS and PGx use cases in the ONC national immunization CDS repository to see if these cases can be represented in this experimental environment. The GMVII use cases group can reach out to existing informatics working groups to solicit from them a set of use cases for this effort. Participating GMVII attendees can then

select groups to test the interoperability of these use cases. Chairs of the Global Genomic Medicine Collaborative (G2MC) informatics working group should be engaged to see if it would be possible to extend this work internationally. Brian Shirts and Marc can pitch this idea during an eMERGE-CSER joint call to gauge interest and see if they would be willing to collect use cases [***action***].

Ken Kawamoto recommended starting this effort by contacting Steve Brown of Vanderbilt who leads the VA group developing models, standards-based decision support, and open source sandbox environments and would likely be interested in hosting genomics use cases. Betsy Humphreys also reported that VA provided funding to NLM for expansion of terminology standards in areas related to the VA. Betsy could assist in setting up a discussion with Steve Brown who was involved in this effort [***action***]. Josh Peterson stated that there is interest in bringing PGx to the Nashville VA through the IGNITE project. Casey volunteered University of Maryland for the sandbox effort as it is doing PGx work with VA through the Pharmacogenomics Research Network (PGRN). Ken Kawamoto will make introductions to the Cognitive Medical Systems team building the sandbox for the VA next generation system to identify potential overlap [***action***]. The PGRN Translational Pharmacogenomics Project has eight different sites that are all implementing their own PGx rules. It would be helpful to engage them to help in identifying use cases.

A primary challenge for working with vendor systems is licensing that precludes systems from being tested in a sandbox. This might interfere with testing transportability unless everyone is using the same vended EHR system in the sandbox. Groups with liberal software licensing policies will be easier to collaborate with.

Ken Kawamoto, Josh Peterson, Casey Overby, Betsy Humphreys, and Ken Wiley (NHGRI/NIH) will form an initial working group to identify, develop, and test 3-5 PGx CDS rules or use cases to be represented in the ONC CDS repository. Ken Kawamoto will facilitate a demonstration of the sandbox environment to help interested people understand the system [***action***].

This project should also consider workflow and user interactions to explore the socio-technologic aspects that could influence GCDS implementation. After developing and testing cases in the sandbox, a GMVII group can create formative usability assessment projects to evaluate user perspectives.

Open CDS knowledge Library

Blackford suggested that the GCDS sandbox group apply CDSC knowledge repository infrastructure to build an open library as part of the sandbox architecture. VA has commissioned a team that is working on a prototype public library, but it would not be for nationwide use. However, VA is exploring nationwide capabilities with AHRQ, which funds and directs the United States Health Information Knowledgebase (USHIK), a publicly accessible repository of healthcare-related metadata, specifications, and standards. The group agreed that it would be prudent to establish an incremental research agenda to achieve a nationwide public library for GCDS knowledge.

Jamie Skipper, Dan Masys, Teri Manolio, Ken Wiley, Jim Cimino (Clinical Center/NIH), Jim Ostell, and Betsy Humphreys will investigate opportunities to build a repository for GCDS use cases [***action***]. Jamie can connect this group with AHRQ representatives who are filling some ONC positions [***action***]. GMVII attendees can lead a group to evaluate what the architecture would be more making socio-technical progress on more than one level and getting natural sponsors for the public good that results. In creating a public library of this type, this group can evaluate the implications of GINA. However, the group agreed that it should not promote genetic exceptionalism.

End-to-end project
Josh Peterson, Josh Denny, and Dan Roden of Vanderbilt PREDICT project, Sandy Aronson (Partners), Paul Dexter (Indiana) and Mark Hoffman (St. Jude's) will start outlining an agenda for an end-to-end project [***action***]. Sandy will share this with the IOM group that is beginning to identify challenges for end-to-end project implementation [***action***]. There would also be an opportunity to partner with ACMG Medical Director David Flannery to represent the ACMG Newborn Screening list ACTion (ACT) Sheets in GCDS using infobutton standards.

Business case on return on investment
The business case fits into the sandbox and use cases initiative. When Marc and Brian collect use cases from existing groups, one of the criteria would be to include an assessment of impact on cost of care and on the cost of implementation. Abacavir might not be used for this because the reduction potential for this drug is limited due to the small affected population. A potential source for this use case could be a partnership scenario with pharmaceutical companies or other investors to support research that leverages GCDS data. Aleksander Milosavljevic (Baylor) will help in developing a use case on the research perspective in generating additional income streams [***action***].

It would be possible to team up with the Common Fund-supported Health Economics program that can offer a number of genetics use cases. They might be interested in working with us on a technology-based use case. The Health Economics program is trying to set up a large stakeholder meeting in February 2015. Josh Peterson will introduce a willing GMVII attendee to his Health Economics program contacts to see if this representative can speak for the investment technology side at this conference [***action***]. Jamie would like to be involved in any follow-up discussions on a business case.

The business case can also be applied to the end-to-end project because it has been shown that improving quality of care generally results in return on investment. Healthcare systems will be interested in financial return on investment, but clinicians will likely not be as concerned about costs.

Public health vs. public's health role: screening vs. care, portability, and interoperability
The group agreed that post-market surveillance should be added to the scope of this initiative and patient-facing activities would be a separate activity. Aleks will develop a use case around how genetic information can be integrated in GCDS in a way that allows genomic scientists to mine these data and feed it back into knowledge systems, potentially using BD2K as an example [***action***]. A research-focused use case could demonstrate using GCDS to search for predictors of adverse outcomes or lack of efficiency of relatively new drugs. FDA could be involved in this effort. Ken Kawamoto raised the point that this sandbox would not support actual patient data, but GMVII attendees can create mechanisms to perform predictive analytics to port to contributors' systems.

Exploration of the role of the patient/caregiver for genomic CDS
This group will assess the impact of patient-facing decision support methods and patient ownership of data. The National Patient-Centered Clinical Research Network (PCORNet), the NIH Health Care Systems Research Network Collaboratory, and others are working together to study rare diseases in large pools of patients. Marc will connect GMVII attendees willing to participate in a patient-facing CDS project to these organizations to see if their activities might overlap with our ideas on patient-centered data [***action***]. Marc will lead a use case in looking at user input from families at Geisinger [***action***].

Sustainability of the GCDS group

The group discussed reconvening GMVII attendees to form a steering committee with potential working groups in the future. To find partners in supporting the GMVII group's activities, GMVII attendees who know of any NIH institutes conducting CDS will propose these to Teri [***action***]. Dan Masys thought that the new leadership of the NCI Center for Biomedical Informatics and Information Technology (CBIIT) might be interested in working with the GMVII group. Dan Masys and Ken Kawamoto will facilitate conversations through their connections at CBIIT [***action***]. If a GMVII group can develop a compelling, patient-centered project, PCORI/PCORNet might be interested in supporting this group. Marc will speak with PCORI contacts about working with the NHGRI Genomic Medicine Working Group [***action***]. AHRQ is considering restoring funding for next generation health IT research. Ken Kawamoto will link GMVII representatives with John White of AHRQ to discuss collaboration [***action***].

J.D. Nolan (Cerner) offered to support a future meeting of the GMVII group at Cerner. Marc, Blackford, and J.D. will discuss coordinating this event [***action***]. JD would have his colleagues participate in an observational role.

Preliminary action items and next steps

Marc and Blackford will continue communications with this group following the meeting using the GMVII distribution list. Those who have interest in participating in working groups formed around the GMVII priorities and initiatives will contact assigned leads or Marc/Blackford.

GMVII publications and engagement within the scientific community

1. Incoming AMIA Chair Jessie Tenenbaum and current Chair Bob Freimuth agreed to sponsor this group's proposal for a late-breaking session related to the outcomes of GMVII.
2. Josh Denny and Marc will investigate the possibility of speaking at outcomes of the upcoming late-breaking AMIA session organized by Neil Sarkar.
3. Josh Peterson will introduce a willing GMVII attendee to his Health Economics program contacts to see if this representative can speak for the investment technology side at a February 2015 stakeholder meeting.

GCDS use cases and sandbox

1. Ken will circulate information on the CDC ACIP recommendations.
2. Brian Shirts and Marc will gauge interest from the eMERGE-CSER decision support group in collecting GCDS use cases.
3. Betsy and Ken Kawamoto will assist in setting up a discussion with Steve Brown to assess feasibility of using the VA sandbox to test use cases.
4. Ken Kawamoto will make introductions to the Cognitive Medical Systems team building the sandbox for the VA next generation system.
5. Ken Kawamoto will facilitate a demonstration of the sandbox environment to help interested people understand the system.

Open CDS knowledge library

1. Jamie can connect the GMVII open library group with AHRQ representatives who are filling some ONC positions.

End-to-end project

1. Josh Peterson, Josh Denny, and Dan Roden of Vanderbilt PREDICT project, Sandy, Paul Dexter, and Mark Hoffman will begin outlining an agenda for an end-to-end project.
2. Sandy will share this group's plans with the IOM group that is beginning to identify challenges for end-to-end project implementation.

Business case on return on investment

1. Aleks will develop a use case on the research perspective in generating additional income streams.

Public health vs. public's health role: screening vs. care, portability, and interoperability

1. Aleks will develop a use case around how genetic information can be integrated in GCDS in a way that allows genomic scientists to mine this data and feed it back into knowledge systems, potentially using BD2K as an example.

Exploration of the role of the patient/caregiver for genomic CDS

1. Marc will connect GMVII attendees willing to participate in a patient-facing CDS project to PCORNet to see if their activities might overlap with our ideas on patient-centered data.
2. Marc will lead a use case in looking at user input from families at Geisinger.

Sustainability of the GCDS group

1. To assist in finding partners in supporting the GMVII group's activities, GMVII attendees who know of any NIH institutes conducting CDS will let Teri know.
2. Dan Masys and Ken Kawamoto will facilitate conversations through their connections at CBIIT to see if they would be interested in supporting GMVII activities.
3. Marc will speak with PCORI contacts about working with the NHGRI Genomic Medicine Working Group.
4. Ken Kawamoto will link GMVII representatives with John White of AHRQ to discuss collaboration.
5. Marc, Blackford, and J.D. will discuss coordinating this group's next event at Cerner.