AHRQ Grant Final Progress Report

Title of Project: Electronic Health Record-linked Decision Support for Communicating Genomic Data

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  - Key contacts: Carla Sproge (Project Manager), Lisa Moore (Project Leader)
- The Center for Inherited Disease Research at Johns Hopkins University, Bioinformatics and IT team (led by Lee Watkins, Jr., M.A., Director of Bioinformatics & IT)
  - Key contacts: Sean Griffith (Project Manager), Kevin Durr (Project Leader)
- The Pharmacy & Therapeutics Committee at Johns Hopkins Hospital (Brent G. Petty, MD, Chair)
- The Epic Decision Support workgroup at Johns Hopkins Hospital (Amy Knight, MD, Chair)
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Organization: Johns Hopkins University

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Grant Number: R21 HS023390
Electronic Health Record-linked Decision Support for Communicating Genomic Data

Structured Abstract

Purpose: This project aimed to: (1) employ user-centered approaches to design a prototype clinical decision support (CDS) system; (2) formalize genomic knowledge for use by the CDS system; and (3) integrate finalized CDS with the EHR.

Scope: Currently, existing clinical guidelines for using genomic data are inadequate for physicians to make informed health decisions. To address the need to effectively communicate genomic data, this project created the genomic CDS (gCDS) engine.

Methods: First, we conducted focus groups with stakeholders involved in two personalized medicine (PM) programs. Results informed the design of prototype gCDS. Second, for one PM program, we formalized genomic knowledge for use by the gCDS engine. It parses VCF files from specialty genomics labs and associates actionable variants with genomic clinical guidance. Third, we built CDS within the EHR in a way that is capable of interacting with our gCDS engine via Web services.

Results: We defined design principles for developing multi-gene sequencing lab report apps. We also found that there are some limitations to our ability to formalize genomic knowledge in the context of whole genome sequencing data interpretation. Lastly, we created two new services to enable revising CDS content based upon changes to the clinical guidelines.
Electronic Health Record-linked Decision Support for Communicating Genomic Data

Purpose

This project aimed to: (1) employ user-centered approaches to design a prototype clinical decision support (CDS) system; (2) formalize genomic knowledge for use by the CDS system; and (3) integrate finalized CDS with the EHR.

Scope

Background and Context: Currently, existing clinical guidelines for using genomic data are inadequate for physicians to make informed health decisions. In addition, CDS capabilities of existing clinical systems are not robust for distilling large quantities of genomic data in a way that is tailored to physician needs. To address the need to effectively communicate genomic data, this project leveraged existing tools and services for managing knowledge to develop the genomic CDS (gCDS) engine and software application. The vision for our gCDS engine and software application is to streamline the work required by a range of stakeholders to use of genomic test results in healthcare decisions.

Participants/Key stakeholders:

- **Clinical oversight committees**, PI Overby is a member of the Pharmacogenomics Task Force at Johns Hopkins University (led by co-I Daniel Ford M.D., M.P.H., Director for Clinical and Translational Research and Professor of Medicine, Institute for Clinical and Translational Research at Johns Hopkins University)
- **Health IT professionals**, PI Overby has formed strategic partnerships to develop gCDS at Johns Hopkins University. These include: The Johns Hopkins Hospital Epic Research Innovation team (led by Diana Gumas, M.S., Senior Director of Clinical Research Information Systems and Services at Johns Hopkins); The Johns Hopkins Hospital Healthcare Data Architecture and Integration team (led by Alan Coltri, Chief Systems Architect); and The Center for Inherited Disease Research at Johns Hopkins University, Bioinformatics and IT team (led by Lee Watkins, Jr., M.A., Director of Bioinformatics & IT)
- **Healthcare providers**, our team recruited clinical stakeholders of two precision medicine programs as University of Maryland School of Medicine and conducted focus groups. Study participants included: a clinical pharmacist (1), a laboratory professional (1), physician fellows (13), nurse practitioners (2), and clinical research coordinators (3). We are also monitoring the potential impact of Johns Hopkins Hospital system-wide implementation of gCDS. Findings will help to make revisions that mitigate any unnecessary alert burden for healthcare providers.
- **Patients**, we are monitoring the potential impact of Johns Hopkins Hospital system-wide implementation of gCDS to provide up-to-date, individualized, and evidence-based care.

Methods

**Aim 1:** Employ user-centered approaches to design and develop a prototype clinical decision support system for effectively communicating genomic data. To specify design requirements for genomic CDS (gCDS), we conducted focus groups with stakeholders involved in two exemplar PM programs at University of Maryland. Results informed the design of prototype gCDS for effectively communicating genomic data to physicians.
**Aim 2: Formalize genomic knowledge from exemplar personalized medicine programs.** We translated a Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline relevant to one PM program at Johns Hopkins University into a form that a computer can interpret. Genomic knowledge from the CPIC guideline were translated into standardized concepts and mapped to EHR data elements. These efforts were pursued in partnership with The Center for Inherited Disease Research at Johns Hopkins University.

**Aim 3: Integrate the finalized clinical decision support system with the EHR.** We deployed the gCDS engine designed to parse a variant calling format (VCF) file from a specialty genomics lab and to associate actionable variants with formalized genomic knowledge. We also built CDS within the EHR in a way that will be capable of interacting with the gCDS engine via Web services. These efforts were pursued in partnership with The Center for Inherited Disease Research at Johns Hopkins University, The Johns Hopkins Hospital Epic Research Innovation team, and The Johns Hopkins Hospital Healthcare Data Architecture and Integration team.

**Results**

**Aim 1: Employ user-centered approaches to design and develop a prototype clinical decision support system for effectively communicating genomic data**

Our work has employed user-centered approaches to obtain input from a range of PM stakeholders in order to characterize opportunities for health IT to improve the delivery of precision medicine in healthcare practices.

First, we characterized the genetic testing processes of an existing precision medicine program implemented under a research protocol[1]. Findings from that work indicated a reliance on the clinical research team involved in that program, and insufficient support and resources to assist clinicians in treatment decisions with a genetic test lab report alone. There was also general agreement from stakeholders participating in that study that implementing CDS had potential to reduce reliance on the clinical research team in a move to using precision medicine applications in standard healthcare practices.

Second, our work identified design principles for software applications that deliver multi-gene sequencing panel (GS) reports to clinicians[2]. In summary, our findings illustrated a need to support customized notification approaches, user-specific information, and access to genetics specialists with GS reports. These design principles can be incorporated into software applications that aim to deliver GS-related decision support.

These findings set the stage for efforts to develop software that incorporates proposed design principles, leverages local health IT infrastructure, and responds to broader needs for institutions to respond to the rapidly evolving knowledge base of evidence based guidelines for precision medicine practice.

**Aim 2: Formalize genomic knowledge from exemplar personalized medicine programs.**

Through PI Overby’s participation on the Pharmacogenomics Task Force at Johns Hopkins University, we identified one PM program of institution-wide interest. That was to provide guidance to healthcare providers placing a thiopurine medication order (azathioprine, 6-mercaptopurine, or 6-thioguanine) for a patient with or without an *TPMT* observation result on file. Thus, we formalized genomic knowledge
consistent with a published CPIC clinical guideline. The purpose of formalizing genomic knowledge was to enable the core functionality of our gCDS engine to parse variant call format (VCF) files and to associate actionable variants with genomic clinical guidance. This process may serve as a generalizable approach to formalize knowledge for other CPIC clinical guidelines. The primary data sources we used are described in the Table below.

<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaviar Genomic Variant Database, db.systemsbiology.net/kaviar</td>
<td>Compilation of SNVs, indels, and complex variants observed in humans, designed to facilitate testing for the novelty and frequency of observed variants</td>
<td>To map rs number notation to chromosome number and chromosome position</td>
</tr>
<tr>
<td>PharmGKB, pharmgkb.org – TPMT Nomenclature Committee Haplotype Set (source: TPMT nomenclature committee)</td>
<td>Provides translation table that maps variants to haplotype information</td>
<td>Translation table to make haplotype calls</td>
</tr>
<tr>
<td>Clinical Pharmacogenetics Implementation Consortium (CPIC), cpicpgx.org – Guideline for Thiopurines and TPMT (source: CPIC)</td>
<td>Gene/drug clinical practice guidelines</td>
<td>To map genes to drugs to CPIC guideline</td>
</tr>
<tr>
<td>Personal Genome Project (PGP), personalgenomes.org</td>
<td>Public patient genomic data (patient condition, allergy, medication, immunization, procedure, and family data)</td>
<td>Patient data to test our data interpretation pipeline</td>
</tr>
</tbody>
</table>

Results from implementing gCDS engine data interpretation pipeline

An overview of the data interpretation pipeline for the gCDS engine are below:

1. The gCDS engine takes as input, a VCF file
   a. VCF files contain the variants for an individual (or multiple individuals) and are guaranteed to have a chromosome and position for each variant. These two pieces of information, along with the translation methods described in step #2, should theoretically allow for a determination of which haplotype an individual has for a given gene.

2. The gCDS engine makes haplotype calls
   a. Haplotype information is from PharmGKB: This file contains descriptions of each haplotype associated with the given gene and an identifier for each haplotype in the * notation form. Each haplotype, including the reference haplotype (*1) is described in terms of the variants (or lack thereof) that the haplotype consists in.
   b. Each possible variant is either described in terms of its rs number (dbSNP accession number) or is described in terms of HGVS notation. For some genes, the HGVS notation is in coding DNA reference sequence ("c.") and for others it is in genomic reference sequence ("g.").
   c. For those possible variants with RS numbers, kaviar (hg19 build) can be used to determine chromosome and positions. (NOTE: all data in the PharamGKB files uses HG19 (aka: GrCh37) for chromosome and position.)
   d. For those possible variants with "c." notation, you can use refgene from ucsc to look up the reference sequence in the first part of the HGVS notation. So, for example, if you had "NM_000367.2:c.124C>G" you would look up NM_000367 in the UCSC refgene file to
get that in HG19, NM_000367 starts at 18128544 on chromosome 6. Adding 124 to this
gives you the position for this variant in HG19 on chromosome 6.
e. For those possible variants with "g." notation, the HGVS encoding contains the
chromosome and position. So, for example, if you have
"NC_000022.11:g.42131420T>C" then the variant position is 42131420 on chromosome
11.
3. The gCDS engine gets clinical interpretations for use in gCDS applications
   a. Once that haplotype is determined, you should be able to associate it with any of several
clinical interpretations (e.g., CPIC guideline).

The primary outcome of this effort was establishing the data interpretation pipeline for our gCDS
engine. The gCDS engine has potential applications to other genes and clinical practice guidelines.
Given our interest in scaling this approach, we documented two main limitations that should be
considered in future work:

First, a lack of data in a VCF does not necessarily indicate that the individual is reference. We would
need to know that the region of interest was covered by the sequencing platform (this is likely for whole
exome and whole genome data). We would then be able to make a reasonable assumption that locations
that are not included are reference, and not simply missing.

Second, except in rare cases where the VCF format has been “adapted,” VCF files rarely contain
structural variants such as copy number variants. The consequence is that when haplotypes contain these
structural variants, a VCF does not provide enough information to accurately determine a haplotype.
This will become an important consideration in generalizing our approach to genes beyond TPMT such
as CYP2D6.

Results from translating CPIC guideline into standardized concepts and rules

For our next step, we formalized genomic knowledge by translating CPIC guidelines into standardized
concepts and rules. The goal for this effort was to enable the output of our gCDS engine to be
interpretable by a computer and to enable incorporation into CDS tools supported by Epic. A summary
of the standardized concepts and rules we defined for our thiopurine-TPMT PM case study are below:
**Rule 1:** IF patient has actionable gene diplotype THEN add the problem to the Problem List in Epic.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Diplopy (s)</th>
<th>Consequence</th>
<th>Phenotype Description</th>
<th>SNOMED or LOINC code</th>
<th>Ordered Drugs</th>
<th>Alert Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>Normal Activity</td>
<td>Normal metabolism/ Normal metabolizer</td>
<td>LOINC: LA25391-6</td>
<td>azathioprine, mercaptopurine, thioguanine</td>
<td>NA</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*2, *1/*3C, *1/*3B, *1/*3A</td>
<td>Reduced Activity</td>
<td>Impaired Metabolism/ Intermediate metabolizer</td>
<td>LOINC: LA10317-8</td>
<td>azathioprine, mercaptopurine, thioguanine</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Rule 2:** IF a pharmacogenomic condition is on problem list AND relevant medication ordered THEN fire Best Practice Alert in Epic

<table>
<thead>
<tr>
<th>SNOMED code</th>
<th>LOINC code</th>
<th>Ordered Drug</th>
<th>Dosing Recommendations (source: CPIC guidelines)</th>
<th>Alert Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>356744012</td>
<td>LA9657-3</td>
<td>azathioprine</td>
<td>Consider alternative agents. If using azathioprine, start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.</td>
<td>Best Practice Alert</td>
</tr>
<tr>
<td>356744012</td>
<td>LA9657-3</td>
<td>mercaptopurine</td>
<td>For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m2/d given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.</td>
<td>Best Practice Alert</td>
</tr>
<tr>
<td>SNOMED code</td>
<td>LOINC code</td>
<td>Ordered Drug</td>
<td>Dosing Recommendations (source: CPIC guidelines)</td>
<td>Alert Type</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>356744012</td>
<td>LA9657-3</td>
<td>thioguanine</td>
<td>Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing thioguanine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.</td>
<td>Best Practice Alert</td>
</tr>
<tr>
<td>356744012</td>
<td>LA10317-8</td>
<td>azathioprine</td>
<td>If disease treatment normally starts at the &quot;full dose&quot;, consider starting at 30-70% of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment.</td>
<td>NA</td>
</tr>
<tr>
<td>356744012</td>
<td>LA10317-8</td>
<td>mercaptopurine</td>
<td>Start with reduced doses (start at 30-70% of full dose: e.g., at 50 mg/m2/d or 0.75 mg/kg/d) and adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m2) than that tolerated in wild-type patients (75 mg/m2). In setting of myelosuppression and depending on other therapy, emphasis should be on reducing mercaptopurine over other agents.</td>
<td>NA</td>
</tr>
<tr>
<td>356744012</td>
<td>LA10317-8</td>
<td>thioguanine</td>
<td>Start with reduced doses (reduce by 30-50%) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thioguanine over other agents.</td>
<td>NA</td>
</tr>
<tr>
<td>356744012</td>
<td>LA10317-8</td>
<td>azathioprine</td>
<td>Start with normal starting dose (e.g., 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.</td>
<td>NA</td>
</tr>
<tr>
<td>356744012</td>
<td>LA25391-6</td>
<td>mercaptopurine</td>
<td>Start with normal starting dose (e.g., 75 mg/m2/d or 1.5 mg/kg/d) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.</td>
<td>NA</td>
</tr>
<tr>
<td>356744012</td>
<td>LA25391-6</td>
<td>thioguanine</td>
<td>Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.</td>
<td>NA</td>
</tr>
</tbody>
</table>
Results from mapping CPIC guideline standardized concepts to EHR data elements

- Laboratory tests

<table>
<thead>
<tr>
<th>Standardized concept</th>
<th>Description</th>
<th>Exists in Epic?</th>
<th>Alternative option used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOINC: LA25391-6</td>
<td>Normal metabolizer</td>
<td>No</td>
<td>Yes, selected the 5 most commonly ordered TPMT tests (includes both genotype &amp; enzyme activity tests)</td>
</tr>
<tr>
<td>LOINC: LA10317-8</td>
<td>Intermediate metabolizer</td>
<td>No</td>
<td>Yes, selected the 5 most commonly ordered TPMT tests</td>
</tr>
<tr>
<td>LOINC: LA9657-3</td>
<td>Poor metabolizer</td>
<td>No</td>
<td>Yes, selected the 5 most commonly ordered TPMT tests</td>
</tr>
</tbody>
</table>

- Medication orders

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Description</th>
<th>Exists in Epic?</th>
</tr>
</thead>
<tbody>
<tr>
<td>azathioprine</td>
<td>Azathioprine is used with other medications to prevent transplant rejection in people who received kidney transplants. It is also used to treat severe rheumatoid arthritis when other medications and treatments have not helped.</td>
<td>Yes, grouper code 2982 (groups medication preparations under one generic name)</td>
</tr>
<tr>
<td>mercaptopurine</td>
<td>Mercaptopurine is used alone or with other chemotherapy drugs to treat acute lymphocytic leukemia.</td>
<td>Yes, grouper code 3522</td>
</tr>
<tr>
<td>thioguanine</td>
<td>Thioguanine is used to treat acute myeloid leukemia.</td>
<td>Yes, grouper code 2985</td>
</tr>
</tbody>
</table>

- Disease or condition names

<table>
<thead>
<tr>
<th>Standardized concept</th>
<th>Description</th>
<th>Exists in Epic?</th>
<th>Alternative option used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNOMED: 356744012</td>
<td>Thiopterine methyltransferase deficiency</td>
<td>No</td>
<td>Yes, Internal code 721485 &quot;Intermediate thiopterine methyltransferase activity&quot;</td>
</tr>
</tbody>
</table>

The primary outcome of this effort was translating one clinical practice guideline into standardized concepts and rules in a way that has potential to generalize to other clinical practice guidelines.

The main limitation that we encountered was an inability to map standard concepts to codes used in Epic for many laboratory tests and condition names. This limitation highlights an opportunity to better enable communication between those developing gCDS content and those involved in the IT implementation of gCDS leveraging Epic tools and coding systems to ensure that internationally recognized standard concepts are supported by Epic.

**Aim 3: Integrate the finalized clinical decision support system with the EHR.**

Our last aim involved creating two new gCDS services to enable revising EHR-embedded CDS content based upon changes to CPIC guidelines. As a starting point, we considered two rules defined in Aim 2:

- **Rule 1:** IF patient has actionable gene diplotype THEN add the problem to the Problem List in Epic.
- **Rule 2:** IF a pharmacogenomic condition is on problem list AND relevant medication ordered THEN fire Best Practice Alert in Epic

Early on, we found that the majority of TPMT laboratory tests were not recorded as gene diplotypes and would be unable to trigger genotype-specific gCDS. Thus, we replaced Rule 2 with the following rules:
- **Rule 2a**: IF a thiopurine is ordered AND the patient does not have a historical TPMT result AND the patient does not have a TPMT test order THEN
  - Recommend removing thiopurine order and ordering a new TPMT test order,
  - Enable the user to remove thiopurine order,
  - Enable the user to order a TPMT genotype test,
  - Enable the user to click on a link to review dosing guidelines to consider patient TPMT genotype

- **Rule 2b**: IF a thiopurine is ordered AND the patient does not have a historical TPMT result AND the patient does have a TPMT test order THEN
  - Inform the clinician that a TPMT test has been ordered for the patient but that the results are not yet available to review,
  - Enable the user to remove thiopurine order,
  - Enable the user to click on a link to review dosing guidelines to consider patient TPMT genotype,

- **Rule 2c**: IF a thiopurine is ordered AND the patient does have a historical TPMT result THEN
  - Recommend reviewing TPMT test results,
  - Display TPMT test results,
  - Enable the user to click on a link to review dosing guidelines to consider patient TPMT genotype,
  - Enable the physician to remove or keep the thiopurine order.

**Preliminary results and future work to evaluate Web services**

We have completed an informal assessment with a simulated patient that has TPMT test results, and have demonstrated that our gCDS Web service to add a problem to a patient’s problem list is functional. The second Web service that will populate the content of BPAs in Epic is still under development. Our team intends to submit grant applications to fund future efforts building on the work we have completed to date. In the following Figure, we have illustrated on one of our BPAs, three sections that would be of initial focus to be populated via gCDS Web services:

1. Major recommendation
2. Link to test-specific dosing guidelines
3. Acknowledgement reasons
The primary outcome of this aim is our implementation of Rule 1 as a new Web service that interfaces with Epic (i.e., an “Add To Problem List” web service). We have also implemented Rule 2 in the background of our production EHR (i.e., three Best Practice Alerts).

Areas for future research
One promising area for future work is to demonstrate and assess the performance of an end-to-end system that includes the gCDS engine and Epic Web services that we have prototyped in this work. In addition, we would implement novel technology approaches to address the challenges to achieving the collaborative work required by institutional review committees, health IT professionals, and clinical leaders to approve of clinical guidance for the use of genomic test results in healthcare decisions. In future grant submissions, proposed efforts will contribute to the field of computer-supported cooperative work (CSCW). Methods from CSCW will guide our research into collaboration and improve our abilities to build and deploy the proposed gCDS system. Furthermore, we intend to assess the overall impact of gCDS on helping healthcare providers use genomic data to make informed health decisions and to direct treatments that are more comprehensive for patients and produce better health outcomes. To this end, we have formed and plan to grow recent strategic partnerships with The Pharmacy & Therapeutics Committee at Johns Hopkins Hospital (Brent G. Petty, MD, Chair), The Epic Decision Support workgroup at Johns Hopkins Hospital (Amy Knight, MD, Chair), and The Division of Clinical Pharmacology at Johns Hopkins University (Craig W. Hendrix, MD, Chair).
List of Publications and Products

Publications (* indicates co-first author)

Presentations

Other products
- Multi-gene sequencing laboratory report app prototype - GitHub webpage and repository: https://translational-informatics.github.io/gma/

Note: we intend to release code for the gCDS engine and share gCDS Web service documentation after publishing those efforts as a manuscript.

Acknowledgment of Project Advisory Committee Members: James J. Cimino (University of Alabama), Guilherme Del Fiol (University of Utah), Mark Hoffman (University of Missouri – Kansas City), Kensaku Kawamoto (University of Utah), Mark Kelemen (University of Maryland School of Medicine), Harold Alan Pincus (Columbia University), and Marc S. Williams (Geisinger Health System).