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An informatics research agenda to support precision medicine: seven key areas

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ABSTRACT

The recent announcement of the Precision Medicine Initiative by President Obama has brought precision medicine (PM) to the forefront for healthcare providers, researchers, regulators, innovators, and funders alike. In order for PM to be fully realized, we must move toward a Learning Healthcare System model that extends evidence-based practice to practice-based evidence by using data generated through clinical care to inform research (Figure 1).2 The leadership and members of the American Medical Informatics Association Genomics and Translational Bioinformatics Working Group have identified seven key areas that informatics research should explore to enable PM’s vision.

PATIENTS: PAST, PRESENT, AND FUTURE

Stakeholders in the biomedical enterprise include researchers, providers, payers, and patients. But nearly everyone has been or will be a patient at some point. Patients thus are, and must remain, at the heart of the biomedical enterprise.

Key Area One: Facilitate Electronic Consent and Specimen Tracking

In the era of PM, research studies produce more data than they can possibly use and, paradoxically, would benefit from more data than they can possibly generate. As genomic sequencing becomes increasingly available, using de-identified biospecimens for research becomes more nuanced.5 Research participants may be asked to give broad consent to the future use of their data and biospecimens, and to acknowledge the possible, though unlikely, prospect of sequence-based re-identification.4,5 To maximize data and biospecimen reuse while protecting study participants’ privacy and adhering to their wishes, it is essential to develop machine-readable consent forms that enable electronic queries.4 As large biorepositories linked to electronic health records (EHRs) become more common, informatics will enable researchers to identify cohorts – both intra- and interinstitutionally – that meet their study criteria and have given the requisite consent. Proper local management of specimens and derived samples enables accurate tracking of chain of custody, sample derivations, processing/handling, and quality control – all of which are key elements of rigorous and reproducible research.7 Structured and electronically available consent forms can empower study participants by allowing them to access, review, and modify their preferences. A number of large-scale initiatives, including Sage Bionetworks, the Genetic Alliance, and the Global Alliance for Genomic Health, are making progress in this area.

Areas of informatics that can facilitate study participant consent and sample tracking include the development of structured consent forms and the adoption of relevant ontologies,6,8 user interface design, and infrastructure to enable participant engagement after the point of enrollment. Developing an infrastructure to perform role-based distributed queries over cohorts and sample collections, such as those provided by OpenSpecimen, the Shared Health Research Information Network (SHRINE), and PopMedNet, will also be important.5–11

DATA TO KNOWLEDGE

The promise of PM can only be realized by aggregating (virtually or otherwise) and analyzing data from multiple sources. A recent report by the National Academy of Sciences calls for the development of an information commons (IC) that amasses medical, molecular, social, environmental, and health outcomes data for large numbers of individual patients.12 The IC would be continuously updated, enable data analyses, and serve as the foundation for a knowledge base (KB) (see Key Area Five). Creating an IC would require informatics expertise to develop data standards, ensure data security, standardize processing pipelines, and establish data provenance.

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A primary goal of PM is to uncover subphenotypes defined by the distinct molecular mechanisms that underlie variations in disease manifestations and outcomes. One step toward defining subphenotypes is to establish agreed-upon phenotype definitions for existing disease classifications, a surprisingly complex task. A number of different initiatives (e.g., the Electronic Medical Records and Genomics [eMERGE] Network and the National Institutes of Health [NIH] Collaboratory) are working to make phenotype definitions computationally tractable and reproducible between sites. Although some progress in subphenotyping has been made, new methods, including analyses of high-dimensional data, integration of different types of data (e.g., “omics,” imaging, clinical, environmental), and simulating disease behaviors across multiple biological scales in space and time, are needed to address a number of challenges.

Although molecular biomarkers can help elucidate underlying physiological mechanisms of disease, only a minority of currently known biomarkers are clinically actionable. Moreover, critical disease subtype distinctions may be impacted by nonmolecular factors, such as socioeconomic status. Many questions must be answered before a potentially actionable biomarker can become part of a clinical guideline and translated into practice. Information that is necessary for bridging this gap might include the functional characterization of genes and pathways related to the biomarker, the level of evidence, and data about economic feasibility. Clinical decision making regarding actionable biomarkers would be facilitated by a framework for presenting different levels of evidence regarding whether and how a molecular abnormality, genomic or otherwise, might represent a therapeutically relevant biomarker. Variant annotations with actionable clinical information will enable decision support systems to provide interpretable and actionable patient-specific reports.

Immediate areas for informatics research to focus on include computational phenotyping, biomarker discovery based on heterogeneous data sources, and frameworks for evaluating clinical actionability and utility.

Key Area Four: Implement and Enforce Protocols and Provenance

Scaling up PM requires complex processing and analytic steps applied to large, heterogeneous datasets. With so many “moving parts,” there are many opportunities for errors in the analysis, interpretation, or exchange of information. It is important that both final results and intermediate steps be well documented and fully reproducible. Protocols, and deviations from them, must also be documented. Software versions, analytical parameters, and reference database builds must all be captured as readily available metadata. Although spreadsheets and documents can be useful for informal data exploration, they do not constitute an adequate data management system.
Large projects often share data between groups and may last several years, during which time key personnel may change institutions. All data processing and analysis for final results should be automated and documented so that another researcher can reproduce the work without making assumptions about what was done. There are various tools that enable this approach, including Taverna, preconfigured virtual machines, and Sage Bionetworks’s Synapse Platform. Though new challenges will always require novel and innovative solutions, the adoption of standard operating procedures when appropriate will facilitate consistency and improve interoperability. In addition, policies must be enacted and enforced to ensure responsible, reproducible, and reusable science.

Processes and protocols for capturing and exchanging metadata and data provenance must be established, standardized, and widely adopted. Furthermore, this information must be considered to be as important as the primary data it describes, and funding agencies and publishers should insist that it be included with any dataset that is produced and released publicly.

**KNOWLEDGE TO ACTION**
Clinical decision making requires the consolidation of PM knowledge and the development of clinical decision support tools (CDS), which, together with individual patient data, will provide actionable information at the point of care.

**Key Area Five: Build a Precision Medicine Knowledge Base**
A comprehensive KB will contain information about disease subtypes, disease risk, diagnosis, therapy, and prognosis that emerges from the ongoing analysis of data in an IC. Such a KB must be flexible, scalable, and extensible. Current KBs (eg, on genomic variants) are isolated from one another and do not support federated querying. Informatics solutions are needed for data-sharing and building a consensus on clinical interpretations of disparate, multiscale data. This KB must be machine-readable, as well as human-readable. Knowledge management technologies must enable effective ontological modeling, knowledge provenance, and new methodologies for updating and maintaining the integrated KB. Novel computational reasoning approaches must be utilized to allow efficient federated queries to be run across billions of knowledge units, enabling causal inference and decision support.

New methods and processes must be developed to organize biomedical knowledge into integrated and interconnected KBs that will enable precision diagnostics and therapeutics based on the latest genomic discoveries and clinical evidence. Such KBs must provide federated queries and flexible computational analytics capabilities tailored for use by physicians and researchers.

**Key Area Six: Enhance EHRs to Promote Precision Medicine**
Commercial EHRs enable CDS for PM that is focused on information about a single gene variant. Informatics challenges for CDS include integrating next generation CDS with PM KBs to provide genome-based risk predictions, prognoses, and drug dosing at the point of care, as well as representing discrete genomic findings and interpretations in a machine-readable format (vs a free-text pathologist or geneticist report). Masys et al. proposed a framework for integrating genome-level data (stored external to the EHR) in which decision support systems are implemented through the EHR. EHRs will need to better aggregate and display patient information in order to allow users to view the heterogeneous data available for each patient, and EHRs will also need to structure and visually display the aggregated knowledge about each patient. Open interfaces that facilitate modular development of genomic CDS outside of monolithic EHR vendor systems, enabling unencumbered parallel innovation/evolution of each element, should be provided.

EHR systems must provide standards-based programming interfaces that enable the integration of external data and knowledge sources as well as the development of tools that support custom workflows, novel analytics, data visualization, and data aggregation. The informatics community must partner with EHR vendors to author use cases and develop interfaces, such that both parties benefit from the collaboration.

**Key Area Seven: Facilitate Consumer Engagement**
PM includes more than the medical care administered in a provider’s office. Most of the population spends far more time outside of the doctor’s office than in it. PM will require explicit acknowledgement of this fact as well as deeper consumer participation, which will involve making consumers aware of their own ongoing health status and engaging them in healthcare decision making. It will also involve collecting more information about a person’s environment and lifestyle choices between visits to the doctor – eg, activity level, nutrition information, exposure, and sleep patterns – and incorporating that information into targeted therapeutic and preventive treatments.

Consumer access to genetic testing will increase as provider-ordered and direct-to-consumer genetic tests become more comprehensive and less expensive. Along with the recent announcement from 23andMe that the company will once again offer health-related information and Ancestry’s launch of AncestryHealth comes the increased importance of ensuring that consumers understand basic genetic principles and the implications of genetic testing, of trust in the accuracy of genetic tests, and of understanding of how these results, together with family history, will influence treatment decisions.

User-friendly interfaces for the collection, visualization, and integration of consumer data with healthcare information will be key to realizing the potential value of nontraditional data sources. Standards for new consumer data types, as well as patient engagement around ethical, legal, and social issues, will also be important.

**CONCLUSIONS**
The emergence of PM as a priority in biomedical research and healthcare emphasizes the importance of informatics’ contributions to PM. This brief overview highlights essential research directions for both informatics researchers and funding organizations.

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**CONTRIBUTORS**
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