STRATEGIC PLAN FOR PRECISION MEDICINE 2017 - 2020

On December 5, 2016, the MU School of Medicine, Cerner Corporation, and the Tiger Institute for Health Innovation convened for a day-long retreat to explore collaborative opportunities in the area of Precision Medicine (PM); the retreat included colleagues from the MU College of Engineering, the MU College of Veterinary Medicine, and others from across the MU campus with an interest in this field.

NIH DEFINITION: According to the National Institutes of Health, "precision medicine" is defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

BACKGROUND: Given the breadth of the definition, precision medicine (PM) can be conceptualized as "big data" medicine that utilizes rapidly accumulating information systems as related to the genome, metabolome, microbiome, environment, biosensor technologies, and individual behaviors, among others. Accordingly, the field is too broad to be approached in a general way. Clarity of focus is important when building research capacity in the area of PM.

PRECISION MEDICINE AND THE FUTURE OF THE ELECTRONIC HEALTH RECORD (EHR):
The emerging field of PM is creating many opportunities for innovation as related to EHRs and health-related information systems.

- Although PM is more than just genomics, these data are particularly relevant for many spheres of medicine.
- Genomic data presents many challenges for the current generation of EHRs, including data storage, the data life cycle, data standards, complexity of order entry, and complexity of data interpretation.
- Future EHRs are likely to become "platforms" that will utilize new standards such as HL7 FHIR (Fast Health Interoperability Resources) and SMART (Substitutable Medical Applications and Reusable Technology); these platforms will enable third-party developers to more rapidly integrate next-generation applications into EHRs.
- Future Clinical Decision Support (CDS) strategies are likely to involve "hooks" that can provide context-sensitive information, alternative choices for providers, and access to more in-depth applications when indicated.
- Future "pedigree capture" capabilities will facilitate access to valuable multi-generational datasets.
- EHR systems that capture more in-depth phenotypic and clinical information will become increasingly important for the emergence of PM capabilities.

UNIQUE PRECISION MEDICINE OPPORTUNITIES AT MU:
A key challenge for MU is to identify areas within the field of PM where faculty can make unique scientific contributions that do not largely duplicate research being done at peer institutions. Strong research domains for an MU investment in PM manpower and infrastructure include the interdisciplinary areas of oncology, cardiovascular disease, autism spectrum disorders (ASD), and research opportunities that go "beyond NGS" (Next Generation Sequencing).

Oncology
Precision Medicine already has contributed important advances to the care of patients with cancer as follows:
(a) HER2-positive breast cancer, (b) EGFR-mutant lung tumors, (c) EML4-ALK ‘fusion genes present in lung tumors, (d) BRAF-mutant melanoma, and (e) RAS-mutant cancer. Additional considerations for PM in the field of oncology at MU are as follows:

- Circulating tumor cells (CTCs) represent a key PM opportunity, given the scientific leadership and expertise that exists across the MU campus.
- Disseminated tumor cells (DTCs) and circulating tumor DNA (ctDNA) also present unique research opportunities.
- CTC detection techniques afford scientifically-compelling collaborative opportunities with the College of Engineering.
- A cancer-related IRB-approved consent protocol is already in place.
- Biorepository capabilities need to be vastly expanded and access to CLIA sequencing capabilities established.
- Collaborative opportunities with MU research cores need to be strategically developed in the areas of genomics, proteomics, metabolomics, and informatics.

Cardiovascular Disease
Emerging research in the field of PM has clinical relevance in the area of cardiovascular disease. Specifically, high-throughput quantification of circulating metabolites has been found to improve prediction of subclinical atherosclerosis, and advances in pharmacogenomics have the potential to lead to improvements in drug utilization and dosing. PM research in cardiovascular disease also is helping to
avoid rare side effects/complications of therapy and helping to reduce non-beneficial treatments. Unique opportunities for PM in the area of cardiovascular disease at MU are as follows:

- Opportunities exist to enhance CDS systems within the EHR.
- Research strengths in the areas of obesity, nutrition, and physical activity provide compelling opportunities for PM programs.
- Strengths and opportunities exist in the area of onco-cardiology.
- Existing research in the area of anticoagulation creates collaborative opportunities for PM projects.
- Strengths in the areas of microcirculation and vascular biology exist at MU, and these enhance PM research opportunities.

**Autism Spectrum Disorders**

Autism Spectrum Disorders (ASDs) represent a complex syndrome involving impaired communication, social interactions, and repetitive behaviors, but the existing evidence does not support a monogenetic etiology. Additional considerations for PM in the field of ASDs at MU are as follows:

- A compelling area for investigation involves the linkage between biological mechanisms and behaviors.
- Identification of biologically discreet subgroups of ASDs appears to be an important research strategy, including strategies for distinguishing complex from essential autism.
- The Thompson Center for Autism and Neurodevelopmental Disorders has collected multiple large datasets, including genomic information, which can serve as a core research resource; rich phenotypic datasets also are available.
- "Big data" analytics, including pattern mining, and the study of potential associations between the microbiome and behavior provide compelling research opportunities in the area of ASDs.
- Pharmacogenomic approaches can be studied for the treatment of clinically-actionable genetic variants, including pre-emptive pharmacologic strategies.
- Other potentially fruitful research opportunities at MU include brain imaging, autoimmunity/anti-inflammatory markers, epigenetics, microbiome, examination of comorbid conditions, use of animal models, and integration of research into clinical practice.

**Beyond NGS (Next Generation Sequencing)**

PM has the potential to incorporate much more than genomic information. In particular, data from other -omics sources, the environment, biosensors, bioimaging, and patient-reported outcomes, among others, have the potential to be important components of the PM strategy at MU. Additional considerations that go "beyond NGS" are as follows:

- Given strong MU expertise and resources in the area of biomedical imaging, innovative approaches to image analysis and the development of predictive models provide promising opportunities for PM collaboration.
- Given the MU/Cerner relationship, strong capabilities exist to integrate devices that involve various types of biosensor data.
- Strong informatics capabilities exist that allow for the development of predictive algorithms for high-risk patients.
- Opportunities exist for research involving "at-risk" populations such as cancer survivors, heart failure patients, and vaccine failure at the population level (e.g., university students).
- Opportunities exist for research that would enhance natural language processing (NLP) capabilities.
- Development of "apps" for a range of health care situations could be pursued with expertise that exists at MU, Cerner, and College of Engineering.

**ACTION PLANS**

The PM Retreat yielded several desirable action plans as follows:

- Charter four interdisciplinary PM research teams (and leaders) in the areas of oncology, cardiovascular disease, ASDs, and "beyond NGS."
- Charge each team with the development of a research program in their respective PM area, including specific plans and timelines for extramural applications.
- When applicable, charge each team to identify cohorts for targeted data collection.
- When applicable, charge each team to develop IRB-approved consent procedures for data collection.
- When applicable, develop biospecimen collection standards, storage protocols, and informatics analytics workflows necessary to support each of the interdisciplinary PM teams.
- Fund meritorious (peer-reviewed) PM pilot projects that have the potential to launch research applications that would be competitive for federal funding.
- Charter a fifth team (and leader) in the area of CDS, including representatives from MU, Cerner, and the Tiger Institute for Health Innovation, with a charge to develop a proposal for a technology-related PM project that would be competitive for federal funding.
- Expand the technical manpower needed to enhance the biomedical informatics infrastructure at MU (i.e., ResearchWorks) that will be required for PM research and clinical programs, including biorepository expansion and related research infrastructure.

Implementation of these action plans, and their timing, will depend upon a number of factors, including the availability of funding and resources.