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Revised Discussion White Paper on Multi-Disciplinary Research Opportunities at Wayne State University: Advancing Precision Medicine through Imaging and Diagnostics into Clinical Settings

Overview: New Era and Promise of Precision Medicine as a Disruptive Innovation for Health Care

The advancement of imaging and molecular diagnostics technologies are ushering in a new era of precision medicine, which is heralded as a disruptive innovation for health care. As explained in *The Innovator's Prescription* – an award winning book written by Clay Christensen, a professor at the Harvard Business School and world renown for his theory of disruptive innovation, and two medical leaders, the late Dr. Jerome Grossman, the former CEO of the New England Medical Center, and Dr. Jason Hwang, formerly a practicing physician and Executive Director of Healthcare at Innosight Institute and now a health care entrepreneur:

"The technological enablers of disruption in health care are those that provide the ability to precisely diagnose by the cause of a patient's condition, rather than by physical symptoms. These technologies include molecular diagnostics, diagnostic imaging technologies and ubiquitous telecommunications .... Only when diseases are diagnosed precisely can therapy that is predictably effective for each patient be developed and standardized. We term this domain precision medicine."[1]

With precision medicine it is possible to advance more standardized "rules-based care" that can allow for a disruptive business model that can profitably deliver routine health solutions to patients in affordable and convenient way. The treatment of infectious diseases is viewed as an example of where precision medicine has been put to work. Through the use of diagnostics, it is now possible to precisely define many of the different types of infections causing common illnesses, such as tuberculosis, pneumonia, measles, strep throat and whooping cough. As a result, family physicians and nurses can now provide care for many of these infectious diseases, and patients with these diseases often can be treated without hospitalization. So due to being able to diagnose precisely and target treatments to the specific conditions, patients receive higher value through low cost, high quality, accessible care.

While groundbreaking, these advances in precision medicine using diagnostic imaging and molecular diagnostics have not had much impact in the delivery of health care to date because the precision medicine innovations have simply been grafted onto the existing business model of health care driven

[1] Christensen, Grossman and Hwang, The Innovator's Prescription: A Disruptive Solution for Health Care, McGraw Hill, 2009 – winner of the American College of Healthcare Executives 2010 Book of the Year and recipient of the 2011 Health Service Journal Circle Prize for Inspiring Innovation.

by a "fee-for-service" model embedded in hospitals and physician practices. However, with the passage of the Affordable Care Act and its focus on evidence-based practices and accountable care (with incentives to health providers tied to keeping costs down while meeting specific quality benchmarks), the opportunity to advance new health care delivery models translating precision medical services to higher value is upon us.

Meanwhile, the technology enabler of ubiquitous telecommunications also brings significant value in extending the reach of imaging and diagnostic technologies. It offers the ability to remotely monitor, capture and integrate a patient's data using diagnostics and then facilitate real-time medical decision support. Eric Topol, formerly head of Cleveland Clinic's Lerner Research Institute and now Chair of Innovative Medicine and Director of Scripps Translational Science Institute, calls this digital innovation. He provides examples of how the transformation of medicine through digital innovation is taking place today building upon increased ability to understand and diagnose of how an individual variations in genomics relates to diseases:

> "Imagine a genomic panel that indicated a high risk of diabetes mellitus in an individual who therefore now uses a sensor that adheres to the skin that continuously tracks blood glucose levels, promoting lifestyle changes or facilitating tailored pharmacologic approaches. Or imagine a woman with an increased risk of breast cancer who can monitor herself for breast cancer using a smart phone with the capability of acquiring and transmitting ultrasound images. Even today, remote wireless monitoring can be used to detect previously undiagnosed yet important heart rhythm disorders in individuals who carry DNA markers associated with increased risk for atrial fibrillation or ventricular tachyarrhythmia."[2]

Critical to advancing these new disruptive innovation models for deploying precision medicine is engineering. Engineering solutions are needed at the organizational/business process level to integrate precision medicine into health care delivery as well as at the level of more specific technological solutions using non-invasive imaging, molecular diagnostics and digital innovation. In an article for the National Academy of Engineering's quarterly journal, *The Bridge*, Jerome Grossman explains:

> "The dynamics of disruptive innovation in health care present general as well as specific challenges for engineers. On a general level, disruptive innovation will require combining the technologies, tools, and techniques of systems engineering with a deep understanding of business processes and organization in the health care and services industries. As health care markets open up to new business models, engineers can pursue fruitful research on tools, techniques, and engineered technologies to support the design, analysis, and governance of new delivery modes and networks. On a more specific level, engineers can develop, adapt, and help implement the technological enablers of continuing disruptive innovations in health care. These will include wireless integrated microsystems to support the remote delivery of high-

[2] Eric J. Topol, Transforming Medicine via Digital Innovation, Translational Medicine, January 27, 2010, Vol. 2 Issue 16, pages 2–3.

> value care (e.g., monitoring, diagnosis, and therapy); the development of decision support tools for professional providers, health care purchasers, and equally important, patients and their families; the application of bioengineering and systems engineering to accelerate the spread of personalized, precision medicine; and the application of systems engineering tools and techniques for managing and improving the performance of complex, interdependent processes and subsystems, guiding investment in ICT infrastructure, and managing policy, reimbursement, and regulatory systems to support the transformed health care system."[3]

So looking forward, precision medicine depends upon advances in imaging, molecular diagnostics and digital innovation, but these technology enablers are not sufficient. Along with new ways of reimbursing for health care services, a wide array of engineering solutions will be required to ensure their adoption.

[3] Jerome Grossman, "Disruptive Innovation in Health Care: Challenges for Engineering," The Bridge, National Academy of Engineering, Spring 2008, pages 10-16

Wayne State University's Research Opportunities and Current Position in Imaging, Diagnostics and Health Care Systems Engineering

Based on a detailed examination of Wayne State University's existing research competencies reflecting areas where there is a critical mass of faculty scholarly and funded research activities, Battelle found that the basic building blocks to advance precision medicine into clinical settings exists across the university. Namely, Battelle identified research competencies at Wayne State University in medical imaging, genomics and molecular diagnostics, digital innovations in medical-oriented informatics and nano/MEMs-based sensing technologies and systems engineering of health care delivery.

In medical imaging, Wayne State University has well-accomplished research centers in MRI and PET imaging activities, and recently added an accomplished research leader and pioneer in molecular-genetic in vivo imaging. These imaging activities involve faculty from across the Medical School, the Karmanos Cancer Center, the Biomedical Engineering Department, the Chemistry Department and the Pharmacy School.

- The PET imaging research center at Wayne State University is housed at the university's pediatric neurology research program in collaboration with Children's Hospital. Its main focus on pediatric neurology has helped distinguish this program effort, particular in diagnosing epilepsy in children using imaging and developing surgical treatments. The strength of the PET center involves advancing novel techniques and reagents. Today, the PET center is actively involved in the emerging field of developmental neurosciences using imaging to identify neural phenomena and linking with follow-up genomic analysis, including to identify specific biomarkers for different medical conditions. Still, the leaders of pediatric neurology see Wayne State as slipping in its PET imaging center by not keeping up in the quality of its instrumentation. The university lacks a combined PET-MR scanner, and is losing its competitiveness to other universities.

- Pre-clinical and clinical-translational research in diagnostic molecular imaging using PET imaging modality has recently been greatly enhanced by recruitment in Biomedical Engineering of one of the pioneers of molecular-genetic imaging, who has a strong track record in development and clinical translation of several novel radiolabeled PET imaging agents for diagnosis of different types of cancers, neurologic and cardiac diseases, and for individualization and monitoring of novel molecular-targeted therapies, gene therapies, stem cell therapies, and immune cell therapies. Several novel PET imaging agents are ready for Phase I clinical trials or are in the late pre-IND stages of development . Also, the BME group is the current leader in the rapidly advancing field of epigenetic imaging using PET (i.e., epigenetic regulation of CNS functions and plasticity in different diseases). However, this cutting edge translational research is currently significantly impeded by the lack of state-of the art high resolution PET/CT and PET/MRI instruments for imaging small animals, dedicated instruments for imaging large animals (i.e., pigs), and dedicated instruments for early stage clinical trials in human patients (Phase I and II).

- A small imaging core exists at Wayne State University, though it is more service-oriented in supporting research activities of different investigators that use fluorescence confocal microscopy and FACS as tools for their research. At Karmanos Cancer Institute, there is an NIH-supported Small Animal Imaging Facility (SAIF) located in the Elliman building. This facility is equipped with micro-PET, SPECT/CT and X-ray instruments for imaging rodents (mice and rats). However, the micro-PET instrument is extremely outdated, has low resolution and poor sensitivity, as it is the first PET instrument ever produced for small animal imaging, dating more than 15 years back (there is no tech support or spare parts for this model anymore). Therefore, a modern PET/CT or PET/MRI hybrid instrument with high resolution and sensitivity is very critical for all R&D programs in PET at WSU. Furthermore, for a successful translational program in PET, FDA prefers the late pre-clinical (pre-IND) imaging studies to be conducted in large animals, which requires a dedicated large animal PET/CT imaging instrument that can be installed within the available space in this Small Animal Imaging Facility (SAIF).

- The Magnetic Resonance (MR) Research Facility has been a highly productive research group housed in the Medical School's Radiology Department, with over $50 million in grant funds since 2000. It has supported the imaging needs of a wide number of faculty at Wayne State University, while advancing its own leadership in MR research. It is particularly known for advancing the imaging of the vasculature of the brain to address research questions in traumatic brain injury, stroke and tumors, including advancing the techniques and novel contrast agents involving susceptibility weighted imaging. It is also advancing the use of nanoparticles in cell imaging. Similar to the PET Imaging Center, the MR Research Facility is concerned about its aging infrastructure and need for more advanced instrumentation to support neuroscience and cardiovascular research. At the same time, the MR Research Facility recognizes the growing interdependence of different imaging modalities and sees an opportunity to advance a more integrated and collaborative infrastructure through a focused university-wide Center for Advanced Imaging Research. This lack of coordination and missing generation of PET-MR and NMR Hyperpolarizer instruments, especially micro systems focused on animal models, is a concern expressed by all imaging research leaders interviewed.

- Also advancing medical imaging at Wayne State is a number of faculty in the Chemistry Department and School of Pharmacy involved in the development of new chemical contrasts.

- Furthermore, there are two Ultrasound instrumentation development groups at WSU: one, in the department of Biomedical Engineering (College of Engineering); and another, in Oncology (School of Medicine/Karmanos Cancer Institute). Noteworthy, one of the ultrasound imaging instruments developed at WSU has been recently awarded a 510K approval by the FDA and is now in clinical trials for detection of breast carcinomas. BME researchers are developing novel hybrid imaging modalities, including Photo-Acoustic Imaging and Optical Coherent Tomography – Ultrasound instruments.

In genomics and clinical genetic analysis to advance molecular diagnostics, there are notable research centers and programs found at Wayne State. One is the Center for Molecular Medicine and Genetics housed in the Medical School. It is an interdisciplinary research effort built around advancing molecular genetics, and comprising basic researchers, physician-scientists, computational scientists, and genetic counselors. It has an active research program focused on mitochondrial-related medical conditions, including mitochondrial DNA mutations associated with diseases such as ischemic stroke and modulation of mitrochondrial function to prevent ischemia/reperfusion injury in both the heart and brain. Its extensive bioinformatics core – including resources for microarray data analysis, DNA/RNA sequence analysis, protein sequence analysis and modeling and SNP-related analysis -- is used by many researchers, particularly in neurosciences, cancer research and basic developmental biology. It also offers a broad educational program, including an PhD and MD/PhD program in molecular biology and genetics, a masters program in genetic counseling and a residency program in medical genetics. The other is the Applied Genomics Technology Center which is part of the Department of Ob/Gyn at the School of Medicine and closely aligned with Perinatology Research Branch and the Karmanos Cancer Institute. It serves as a service center for genomic analysis, offering a wide suite of advanced, multi-platform instrumentation and services, including for gene expression, genotyping, next generation sequencing, DNA methylation, and help in the design of research experiments and bioinformatics analysis. The Karmanos Cancer Center also has an active molecular imaging research program involving over 30 faculty drawn from across the Medical School, College of Arts and Sciences and College of Engineering. It has two scientific themes: 1) synthesis and development of new methods to image tumor pathways and drug pharmacodynamics and 2) imaging diagnostics for risk assessment, detection, radiation targeting and response to therapy.

Aiding the genomics and clinical genetic analysis at Wayne State are active biospecimen banks. This includes the Michigan neonatal biobank in operation for roughly 30 years with demographic data and biospecimen collections underway at the School of Medicine, mostly notably at the Karmanos Cancer Institute. The biospecimen bank at the Karmanos Cancer Institute offers a full service core for biobanking and correlative sciences that supports preclinical studies, translational research and pharmacodynamic endpoint studies for clinical trials .

Wayne State is also active in the digital innovation side needed to advance precision medicine. There are several faculty at the Department of Electrical and Computer Engineering advancing technologies for medical diagnostics and sensing technologies using nano/MEMS technology. This includes work involving lab-on-a-chip technologies for portable diagnostics, raman chemical analysis chip to distinguish normal cells from cancerous ones, advancements in micro-fluidic devices using nano-sensors to detect and analyze breast cancer, and advancing novel types of biological assays for single cells using microdroplets. Also at the Department of Electrical and Computer Engineering are faculty working on wireless and sensor network communications systems, though not involving medical monitoring devices.

In the Department of Computer Sciences, there a number of faculty advancing bioinformatics and medical informatics. This includes research into machine learning for genome-wide inferences, novel methods for analysis of gene signaling pathways, medical image analysis, medical data management systems, and predictive models using data analytics of clinical information. Funding for these computer science efforts comes from NSF, NIH, National Library of Medicine and health providers, such as Henry Ford and Karmanos.

Finally, the Department of Industrial and Systems Engineering has been actively involved in re-engineering health care delivery for a wide range of health organizations, including Henry Ford, Veterans Administration and Blue Cross/Blue Shield. Projects have involved improving patient flow, development medical evaluation and decision analytic systems, near real-time decision support systems, make/buy evaluation and validation, workload balancing for patient-centered medical homes, improved claims processing, and supply/demand alignment tools.

Advancing precision medicine can also align Wayne State University with growth industries in the Tri-County Detroit Region (Wayne, Oakland and Macomb counties). One leading industry driver of note is hospitals and medical centers, which employs nearly 97,000 workers in the in the Tri-County Detroit Region and stands out as a significant industry specialization for the Tri-County Detroit Region with a 47% higher concentration than for the U.S. Most importantly, hospitals and medical centers have been a consistent job generator for the region growing by 12.6% from 2001-2012, including during the recent recession years.

Another regional industry connection for precision medicine is to the emerging biomedical industry in the Tri-County Detroit Region. It is one of the region's growing technology industry sectors and now employs over 5,000 workers across nearly 300 business establishments. The Tri-County Detroit Region has outpaced the national growth of biomedical industry over the economic recovery period of 2009 to 2012, though it is still a relatively low concentrated industry in the region – so is more of an emerging industry.

Insights from Benchmarking

Precision medicine is at a very early stage of development, though it is moving ahead quickly. Among disease areas, precision medicine approaches are most promising today in the application of genomics to cancer research, which is having a major impact on advancing novel therapeutics involving companion molecular diagnostics. For example, the drug imatinib (Gleevec) was designed to inhibit an altered enzyme produced by a fused version of two genes found in chronic myelogenous leukemia. Another example is the breast cancer drug trastuzumab (Herceptin), which works only for women whose tumors have a particular genetic profile called HER-2 positive. Studies have also found lung cancer patients whose tumors are positive for EGFR mutations respond to the drugs gefitinib (Iressa) and erlotinib (Tarceva) which target this mutation.

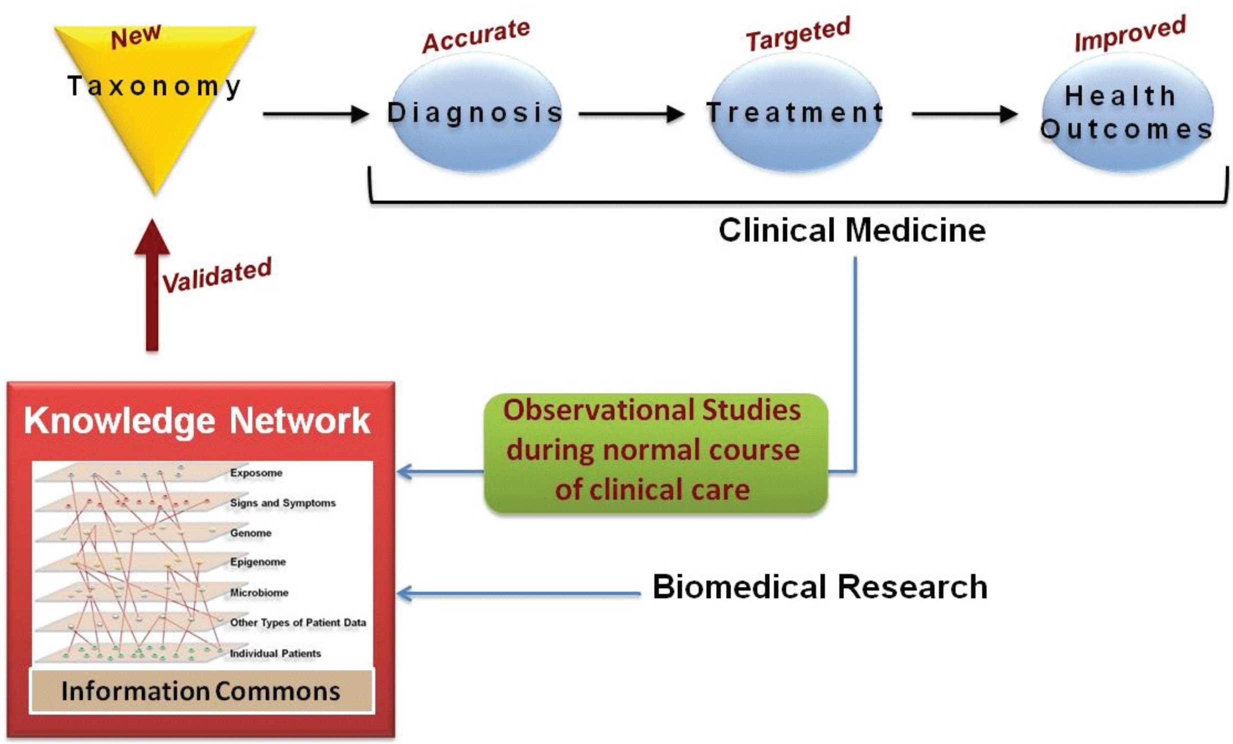
Federal Initiatives Moving Precision Medicine Forward

The National Institutes of Health has been helping to spur development through some targeted initiatives. One long-standing effort is the Electronic Medical Records and Genomics (eMERGE) Network, a national consortium organized by NHGRI, to combine DNA biorepositories with electronic medical record (EMR) systems for large-scale, high-throughput genetic research with the ultimate goal of returning genomic testing results to patients in a clinical care setting. In eMERGE Phase I (September 2007 - July 2011), each institution participating in the consortium led specific studies of the relationship between genetic variation and at least two common human traits using the technique of genome-wide association analysis of patients involved in particular diseases. The Phase II effort (August 2011 - July 2015) has transitioned eMERGE to bring forward a sharper focus on precision medicine issues by exploring the best avenues to incorporate genetic variants into EMR for use in clinical care such as improvement of genetic risk assessment, prevention, diagnosis, treatment, and/or accessibility of genomic medicine.

NIH through The Cancer Genome Atlas (TCGA) is working to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies. TCGA's efforts are focused on generating comprehensive, multi-dimensional maps of the key genomic changes in major types and subtypes of cancer. This catalog will serve as a powerful resource for a new generation of research aimed at developing better strategies for diagnosing, treating and preventing each type of cancer. It is a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), and involves a network of more than two dozen non-NIH research institutions providing genome characterization, sequencing and data analysis services.

More recently, NIH issued a funding opportunity to create Research Centers for Pharmacogenomics in Precision Medicine. A limited number of large-scale multidisciplinary centers is envisioned to be built around a tightly-focused theme at the forefront of understanding drug actions. The experimental approaches should go beyond pharmacogenomics, to include for example, examination of gene expression and regulation patterns, assessment of post-genomic modifications, other small-molecule "signatures" that contribute to the prediction of drug actions both therapeutic and adverse, and/or systems and pathway analysis. Each center should have a clinical interaction, either as a patient-oriented core or through an established relationship with clinical studies or trials conducted elsewhere. There should be bi-directional exchange between the research and clinical components, with a mix of experimental methods yielding complementary datasets that collectively enhance the foundational understanding and prediction of drug actions.

NIH has also spurred increased discussions on approaches needed to move precision medicine ahead, including requesting the National Research Council to examine explore the feasibility and need, and develop a potential framework for advancing precision medicine involving the creation of a "new taxonomy" of human diseases based on molecular biology.[4] It concluded that this goal could best be met by rooting future improvements in disease classification through new data repositories and a knowledge network for integrating basic biological knowledge with medical histories and health outcomes of individual patients. Building this infrastructure of data repositories and a knowledge network to interpret the data is viewed as a grand challenge that, if met, would both modernize the ways in which biomedical research is conducted and, over time, lead to dramatically improved patient care through more precision medicine approaches. Below is a graphic advanced by the National Research Council committee showing the infrastructure required.



[4] Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease, National Research Council, 2011

The vision captured in the recommended infrastructure of data repositories and knowledge network is that genomic and other health data needs to flow in two directions. One direction is from population data to direct more precise care to an individual patient and the other is from collecting patient data to inform the broader scientific community on links between genetics, health, the environment and response to therapies. Enabling that to happen will require both the ability to guarantee that this information will be properly de-identified so it can be safely and privately shared, and to gain the trust of the public to share this data.[5]

In digital innovation for healthcare, there are increasing sources of federal funding. One example is the NSF program offered in partnership with NIH in Smart and Connected Health. The purpose of this program is to develop next generation health care solutions and encourage existing and new research communities to focus on breakthrough ideas in a variety of areas of value to health, such as sensor technology, networking, information and machine learning technology, decision support systems, modeling of behavioral and cognitive processes, as well as system and process modeling. Effective solutions must satisfy a multitude of constraints arising from clinical/medical needs, social interactions, cognitive limitations, barriers to behavioral change, heterogeneity of data, semantic mismatch and limitations of current cyberphysical systems. Such solutions demand multidisciplinary teams ready to address technical, behavioral and clinical issues ranging from fundamental science to clinical practice. It is anticipated to invest $15 to $20 million a year and fund 15 to 25 awards per year.

[5] Lisa Cisneros, UCSF Steps Forward to Lead Advances in Precision Medicine, UCSF News, June 19, 2013

First Movers in Precision Medicine

At this time, we are beginning to see the first movers in precision medicine at a university-wide or medical school-wide approach rather than stand-alone research center or an effort with a Cancer Center. For instance, UCSF in 2013 convened a precision medicine summit involving NIH Director Frances Collins. Coming out of that summit, UCSF under the leadership of its Chancellor has put forward a multi-prong platform for precision medicine including a Global Alliance with nearly 70 other health care , research and advocacy organizations; launching a public awareness campaign; established a new UCSF Center for Digital Health Innovation as well as new programs in bioinformatics and health care data analytics; and has engaged with the FDA to address issues raised at the summit such as maintaining patient privacy. In January of 2014, UCSF announced a collaboration with Quest Diagnostics to accelerate precision medicine through advanced diagnostics, with an initial focus on autism and brain tumors. The collaboration combines UCSF's research efforts with the national testing database of Quest to bring together the data on molecular, clinical, population and other research to inform new precision medicine approaches. Quest Diagnostics would independently develop and validate any lab-developed tests for clinical use that emerge from the collaboration's research.

Another university tackling how to advance precision medicine is the University of Pennsylvania. It announced in 2013 the creation of a new position of Vice Dean/Vice President for Precision Medicine and recruited a cancer genetics expert and pioneer in the development of targeted therapies, with industry experience, to create a national model for the delivery of precise, personalized medicine to patients across cancer, heart and vascular, neurosciences and other disease areas. The focus of Penn's efforts are to create a more coordinated infrastructure across its separate efforts in EMR, biospecimens, genomic analysis and diagnostics development.

Similarly, there is a more focused effort emerging in the area of health systems engineering and digital innovation taking place. The area of health systems engineering is an emerging one, with a limited number of universities with formal programs. Three well-established research programs that have participated in an NSF-funded I/UCRC for Health Organization Transformation are Northeastern University, Penn State and Georgia Tech. Examining these programs shows the diversity of this emerging field:

- Georgia Tech's Healthcare Systems Institute has evolved over the past 40 years and today is a multi-institutional and interdisciplinary initiative in collaboration with Emory University through the joint Georgia Tech-Emory Department of Biomedical Engineering. It brings together faculty from public health, medicine, industrial engineering, biomedical engineering and computer sciences. The technical emphasis of its research efforts include: disease modeling, treatment, management and control; health delivery systems modeling and analysis; and information and decision support technologies development for novel delivery of healthcare services. Its research work spans topics involving pediatric care, sustainable aging, chronic care and disease management, telehealth, integrative patient-centered systems, and reimbursement and payment systems. The focus It offers both a Masters and PhD program in Health Systems with more than 600 graduates to date.

- Penn State Center for Integrated Healthcare Delivery Systems is housed administratively in the College of Engineering, and strategically in the Penn State NIH-funded Clinical and Translational Sciences Institute. The CTSI at Penn State has a strategic focus on improving healthcare, particularly to keep patients in the community, through the use of transformational information technologies – so the Center for Integrated Healthcare Delivery Systems is a strong fit. Its focus on healthcare delivery has emphasized patient-centered interventions, technology and informatics and operational efficiency and improvement analytics spanning topics such as care coordination for chronic kidney disease, physician decision making for obesity counseling, prediction of early onset Parkinson's disease and mobile health interventions for teen risk behaviors. It has focused on having active engagement with industry members, including Siemen's and Verizon, who are both gold members supporting its research and workshops. The Center does not offer a separate degree program but supports graduate students and post-doctoral "scholars" from the schools of medicine, nursing, engineering, information sciences and technology and health and human development. These students work with faculty advisors on research themes aligned to the Center's scope. The scholars become active participants in the Center and present their projects at the annual workshop.

- Northeastern University's Healthcare Systems Engineering (HSyE) program is a university-level institute whose history now spans 30 years. It focuses more narrowly on applying systems engineering techniques to healthcare than either Georgia Tech or Penn State. It has successfully blended pursuing federally funded research centers to advance its activities together with coop education and summer internship programs. It is highly focused on translation. In addition to being a site for the NSF-funded I/UCRC for Health Organization Transformation, HSyE was awarded in 2012 a $8 million 3-year grant from the Center for Medicare and Medicaid Innovation (CMMI) to conduct a National Demonstration Project of the value that systems engineering methods used in other complex industries can have to reduce healthcare costs, improve quality and safety, reduce waits and delays, and improve clinical outcomes and overall population health. The CMMI grant funds the first phase of a large scale 10-year project to establish a national network of healthcare systems engineering regional extension centers across the U.S. The goal within this first phase is to demonstrate the potential impact and viability of extending this initiative on a national scale. HSyE is also part of a New England consortium of universities that is partnering on the New England Veteran's Affairs engineering resource center to advance industrial engineering solutions to VA hospitals and medical centers in the region. There is no separate degree program for HSyE, but specialized courses at the graduate and undergraduate level. There are plans for an undergraduate minor in healthcare industrial engineering minor as part of an industrial engineering major.

In the area of digital innovation for health care, encompassing bioinformatics and medical informatics, there is a growing set of university research centers. Examples of more integrative multi-disciplinary team awards from the NSF Smart and Connected Health Program include:

- Data e-platform leveraged for patient empowerment and population health improvement at the University of California-San Diego.
- Large scale probabilistic phenotyping applied to patient record summarization at Columbia University
- Biosensing and computational modeling applied to smart diagnosis and monitoring of heart conditions at Johns Hopkins University
- Novel techniques for patient-centric disease management using automatically infrerred behavioral biomarkers and sensor-supported contextual self-report at Cornell University
- Learning and sensory-based modeling for adaptive web-empowerment trauma treatment at University of Colorado at Colorado Springs
- Physiological studies of brain signals using a wireless neuro-sensing-diagnostic system at Ohio State University

Initial Discussion Questions and Issues for Wayne State University on Advancing Precision Medicine through Imaging and Diagnostics into Clinical Settings

What Areas of Research Is Wayne State University Positioned to Advanced in Precision Medicine

From Battelle's interviews with faculty leaders at Wayne State University, a broad array of research opportunities can be advanced for precision medicine through imaging and diagnostics into clinical settings:

- Research to improve or develop advanced diagnostic imaging technologies – including MR. PET and CT and their combination – as well as the interpretation and analysis systems of these images.
- Advancing nano-based microfluidics-technology that offers high content information on specific diseases and its progression.
- Utilizing in vivo molecular-genetic and epigenetic imaging to provide spatial and temporal information on biochemical, genetic and epigenetic changes that occur in cells and tissues during disease processes. Advanced molecular imaging will enable more precise diagnosis and differential diagnosis of variants of diseases for selection of personalized precision therapies/interventions, providing the means for monitoring early responses and allow for triage to more effective therapies to improve the outcome. Key advances are needed in the development of new probes and imaging agents, along with emerging new imaging technologies.
- Advancing new molecular diagnostic tests, leveraging availability of biobanks (including the Michigan neonatal biobank) and core genomic facilities at Wayne State University.
- Developing the combined approaches in disease identification across population groups by combining phenotype imaging with genomics.
- Establishing the bioinformatics capabilities to analyze and to interpret the large and complex data sets from across imaging and molecular diagnostics.
- Fostering interoperability among healthcare software applications and the design of clinical information systems.
- Adoption and integration of biomedical innovations into healthcare delivery
- Apply operations research and management principles to assist with healthcare related logistics
- Using decision analysis methods to advance health decision and risk analysis

More generally, there may be an opportunity to bring forward precision medicine through imaging and diagnostics into clinical settings across existing research activities underway at Wayne State University. This could be a critical added value for existing research activities to stay competitive and grow.

For instance, a recent research center grant award to Wayne State University for the Center for Urban Responses to Environmental Stressors (CURES) highlight many elements that lend itself to advancing precision medicine in the domain of addressing environmental-related illnesses. The hypothesis of the CURES Center is that diseases that compromise the quality of life in an industrialized urban environment, such as Detroit, occur as a consequence of dynamic interactions among an individual's genetic and epigenetic make-up, nutritional status, and environmental stressors, which include chronic low-level toxicant exposures as well as psycho-social and physical stressors, that re-program key cellular regulatory networks to favor pathogenesis. Among the research activities of CURES is applying integrated, state-of-the-art genomic, epigenomic, proteomic, and bioinformatic strategies to environmental health science research that is expected to help identify biomarkers for these environmental-related diseases. Through its Community Outreach and Engagement Core, CURES also provides for bi-directional exchange between the urban community at risk for environmental illness and Center members.

Going forward, advancing the precision medicine capabilities at Wayne State University could add substantial value to the impact of CURES. As new biomarkers are identified, Wayne State University could advance them into new diagnostic tools to identify those in the urban population at risk. For those identified as susceptible to environmental illnesses, home monitoring systems could be developed to stay abreast of how that at-risk patient is doing and through health systems engineering business processes could be developed to advance new protocols to head off major flare-ups of illnesses that would require costly hospitalization.

What Faculty Enhancements are Required at Wayne State University?

Battelle's initial examination suggests the following possibilities:

- Recruit a national leader in digital innovation for health care to help create a larger program bringing together wireless communications, sensing, informatics and systems engineering capabilities found at Wayne State University
- Strengthen epidemiology and biostatistics with key recruits – this is also an enhancement area for the Urban Health Disparities multidisciplinary area.
- Recruit more faculty in evidence-based medicine, including for School of Nursing and School of Pharmacy – again an enhancement area for Urban Health Disparities as well
- Recruit 2-3 promising new graduates and rising junior faculty in molecular-genetic imaging and biomedical imaging instrumentation engineering

What (if any) Facility Enhancements are Required, Including Specialized Cores and Equipment?

Battelle's initial examination suggests the following possibilities:

- Upgrade the imaging capabilities and focus on improved coordination – consider bringing imaging centers at Wayne State University together under a broader Center to further research into multiple and combined modalities (i.e., PET/MRI, hyperpolarizer for MRI, small and large animal imaging high resolution PET/CT systems)

- Seek to strengthen CLIA-certified clinical genetics lab capabilities found at Wayne State University to go beyond providing clinical tests to be an active in clinical test development and commercialization of innovative genomics research into new molecular diagnostics

- Create test beds for digital innovation in healthcare

What Educational Program Enhancements at Wayne State Should be Pursued?

Through the Center for Molecular Medicine and Genetics, Wayne State University already offers important programs connected to precision medicine including: a PhD and MD/PhD program in molecular biology and genetics, a masters program in genetic counseling and a residency program in medical genetics. Additional educational programs to be considered would include:

- Undergraduate minors and Graduate level Masters and PhDs in Health Systems Engineering.
- Health Informatics Masters that combines bioinformatics and medical informatics. Focus on data analytics, large database management and data mining.

What Specific Connecting Activities to Engage Community:

Battelle's initial examination suggests the following possibilities:

- Establish university-wide research collaboration center in health systems engineering and informatics for precision medicine that partners with regional health systems.

- As recommended by the National Research Council study on precision medicine, a key element of the new collaboration center with health care systems would be to pilot observational studies in the health-care setting to assess the feasibility of integrating molecular parameters with medical histories and health outcomes in the ordinary course of clinical care. These studies would address the practical and ethical challenges involved in creating, linking, and making broadly accessible the datasets. As this process evolves, there should be ongoing assessment of the extent to which these new informational resources actually contribute to improved health outcomes and to more cost-effective delivery of health care.

- Seek out partnerships with established molecular diagnostic and diagnostic imaging companies to advance the translation of new diagnostic tools and tests.