Transforming Biomedicine

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Delivering personalized, patient-specific diagnostics, prognostics, and therapy via quantitative biological simulations of virtual tissues

The world’s aging and sedentary population requires radically new, affordable and effective approaches to treat chronic human diseases that target critical tissues and susceptible organs, such as the mammary glands, the cardiovascular system, eye, kidney and liver. Key causes of degeneration and disease in these tissues include, obesity, diabetes, sedentary lifestyles, exposure to toxins, and aging. “One-size-fits-all” treatment regimens for these diseases are insufficient, expensive and have a high failure rate. Particular sub-populations have widely different risk profiles and responses to treatments. The future lies in more efficient routes to new and personalized treatments that address degenerative disease, including approaches based on personalized and regenerative medicine that can also minimize the costly contact of aging and underdeveloped populations with health providers, and make it more affordable. To be effective, these new treatment approaches require detailed prediction of the complex interactions between customized therapies and the highly specific responses of individual patients’ tissues and organs. This IUB Grand Challenge Initiative addresses this compelling challenge, the resolution of which would significantly affect the people of Indiana and beyond, by delivering mechanistic-based computational tools that will enhance patient-specific diagnostics, prognostics, and therapy via quantitative biological simulations.
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Overview. The world’s aging and sedentary population requires radically new, affordable and effective approaches to treat chronic human diseases that target critical tissues and susceptible organs, such as the mammary glands, the cardiovascular system, eye, kidney and liver. Key causes of degeneration and disease in these tissues include, obesity, diabetes, sedentary lifestyles, exposure to toxins, and aging. “One-size-fits-all” treatment regimens for these diseases are insufficient, expensive and have a high failure rate. Particular sub-populations have widely different risk profiles and responses to treatments. The future lies in more efficient routes to new and personalized treatments that address degenerative disease, including approaches based on personalized and regenerative medicine that can also minimize the costly contact of aging and underdeveloped populations with health providers, and make it more affordable. To be effective, these new treatment approaches require detailed prediction of the complex interactions between customized therapies and the highly specific responses of individual patients’ tissues and organs. This IUB Grand Challenge Initiative addresses this compelling challenge, the resolution of which would significantly affect the people of Indiana and beyond, by delivering mechanistic-based computational tools that will enhance patient-specific diagnostics, prognostics, and therapy via quantitative biological simulations.

Goals. The defined, achievable goals that deliver tangible benefits to the people of Indiana on which the proposed Virtual Tissues Initiative will focus are the following:

1. To improve the quality of health care and health customs of the people of Indiana by transforming diagnostics, prognostics, and therapy into tailored-made and patient-specific practice, based on computational models and biological simulations.
2. To facilitate collaborations that leverage IUB’s extensive and diverse knowledge-base and know-how in virtual tissues computational modeling by forming public-private partnerships with Indiana’s Bio-pharma and Bio-tech industry in pursuit of common goals in patient-specific medicine.
3. To support Indiana’s pharmaceutical and medical devices communities and make Indiana a national leader in health care research.
4. To develop technologies that reduce use of experimental animals and help designing more efficient in vivo experiments and clinical trials.
5. To create new opportunities for novel clinical innovations, intellectual property, and the commercialization thereof.
6. To make IUB a world-class international center for computational precision medicine, that will build expertise and resources for the design and the development of computational models and biological simulations and their clinical implementation.
7. To educate and prepare a new generation of trained employees in computational personalized biomedicine, in collaboration with IUB’s new Intelligent System Engineering School.

Outline and Impact. Although intended to operate at the individual level, precision medicine still remains today mostly probabilistic in its methods and relies heavily on epidemiological data and statistics. As such, from a methodological perspective it resembles statistical inference: based as it is on population data – be it diagnostic, prognostic or therapeutic – it employs non-mechanistic top-down strategies that are common in pharmacology: to test a new drug on a population one performs a series of material interventions that allow one to generate statistical knowledge about the average response in that populations. Extrapolations are then made, based on these averages, in
order to tailor specific interventions for an individual patient. “Big data” in genomics, metabolomics, and proteomics thus guides clinical practice, isolating “risk factors” in subpopulations with the help of machine learning principles that are aimed at finding correlations in large data sets. Since this approach relies on epidemiological statistics, its impact on a unique patient is often ineffective and costly. A telling example is the recent discovery of the mutations in the BRCA1 and BRCA2 genes. Traditional Precision Medicine has resulted in screening patients for these “biomarkers” and calculating risk factors accordingly. Decisions about actions to take and treatments in follow up to a positive test are very individual ones and there is no one right answer. Options range from closer monitoring for breast or ovarian cancer to surgeries such as the high profile Jolie Pitt’s double mastectomy. This suboptimal situation results from the methodology inherent in traditional precision medicine. Since correlation is not causation, having the mutation does not necessarily mean cancer will develop, but, as epidemiological data indicate, it does increase risk: women with inherited mutations in BRCA1 or BRCA2 have up to an 85% lifetime risk of developing breast cancer and a 30-50% lifetime risk of developing ovarian cancer. That risk drops considerably, but not completely, following surgery. One is thus left with a very precise prediction for a population, and a very imprecise one for an individual patient.

**Addressing Goal 1**, the initiative proposed here aims to complement the traditional approach with a bottom-up, causal, mechanistic modeling platform that can inform a rational understanding of disease onset, progression and successful interventions. By building on biological mechanisms, these models can connect variations across patients with variations in outcomes, and achieve higher sensitivity and specificity in diagnostics, prognostics, and therapy while reducing material interventions in humans or animals. In this platform we still use epidemiological data, yet rather than guiding clinical practice, the data will serve as a foil against which the success of the computational model can be tested and its parameters can be refined, to obtain better predictions for the individual patient. In the BRCA case, for example, we would rely on specific biomarkers measured across individuals, and use the data to calibrate the model so that it would yield the individual tumor growth rate for each patient, notwithstanding population averages. Based on the model and the patient’s actual physiological biomarkers, those who would traditionally receive a recommendation for mastectomy based on their BRCA profile would now have access to a more nuanced understanding of treatment options and timeline.

This alternative approach has another advantage. The current failure rate for new chemical entities (NCEs) in clinical trials is high (>90%) suggesting the there is a fundamental flaw in how new therapeutics are developed. The most common cause of the failure of an NCE is lack of efficacy. Current drug development pipelines generally focus on a single local effect (such as binding to a particular receptor on a particular cell type). The single local effect approach does not take into account the interactions of the multiple cell types within a tissue or organ or the interaction between the body’s organ systems. There is a critical need for the development of technologies to facilitate drug development that takes into account the multiple tissues, organs and interactions in the body. Computational personalized biomedicine via biological simulations of virtual tissues addresses exactly this point. In particular, the mechanistic, computational, approach becomes crucial in cases where interactions, be it cell-cell, cell-ECM, or tissue-immune-system, are important, or when mechanical structure is important (i.e., cardio surgery, orthopedic implants, laser eye treatment, tumor safety margin calculation). In these cases molecular information by itself isn’t sufficient. We thus foresee an ongoing optimization process between our mechanistic model-based approach, and the more traditional big-data/deep-learning correlations-based approach, which will enhance problem solving by minimizing uncertainty and by reducing the space of possible solutions to many open problems in biomedicine and in the clinic.

The main building blocks of this computational platform are biological simulations with virtual tissues. Virtual tissues are a new class of multi-scale quantitative mechanistic models specifically designed to predict the complex interactions between subcellular biochemical
networks, cell-level behaviors, tissues and the body as a whole. Virtual tissues provide a novel trans-disciplinary approach to capturing and integrating expertise in organ systems, biology, clinical practice, big data, modeling and software development, and in IUB we shall harness it to create a new Institute for Virtual Tissues (IVT), which will develop new and more efficient patient-specific diagnostic tools, prognostic assessment protocols and therapies for chronic diseases, and build a unique platform that can be used to cost-effectively test biomedical hypotheses.

Successful development of human health-relevant virtual tissues requires close integration of clinicians and physician scientists, biologists, toxicologists, computer-scientists, bio-modelers, bio-imagers and bio-engineers. Indiana University already has world-leading expertise in many of these areas. With the added leverage of the Grand Challenges program, Indiana University will become the world leader in the development and application of virtual tissues, to be hosted in the IVT at IUB. **Addressing Goal 2,** the IVT will also work closely with sociologists and media experts who can facilitate the dissemination of the new computational techniques among health practitioners and their patients, and with legal experts who can help navigate possible regulatory aspects, IP and commercialization infrastructure to support their transition from the lab to the clinic, and facilitate collaboration with Indiana's bio-pharma and bio-tech industry partners. In particular, students and faculty of the IUB School of Law’s Center for Intellectual Property Research (CIPR) will contribute to the institute's work by generating significant research on novel IP law questions relating to precision medicine, and by supporting the institute’s IP needs through the CIPR’s Intellectual Property Clinic.

Indiana University currently has significant strength in several of the key technologies needed for virtual tissue modeling. These areas include computational biology, biological Big Data and informatics, large scale computing, and advanced bio-imaging. These areas can be (and have been) coupled to some of IUSM’s areas of medical expertise including a wide range of chronic diseases of the kidney, liver, retinopathies, cardiovascular diseases, neuromuscular diseases, diabetes, breast cancer and the toxicity of therapeutics and environmental pollutants. **Addressing Goals 3, 4, & 5,** the new institute will thus comprise 5 cores that are built around these existing strengths and will tightly couple with IUSM researchers to provide new approaches to diagnostics, prognostics and treatment of diseases (Fig. 1). The cores and the IUSM collaborations have already secured initial extramural and intramural funding and have strong potential to transform IUB’s IVT into the leading center in the world in computational personalized biomedicine.

The Initiative recognizes the need for legal and social understanding of the science it creates to ensure that its integration with industry translates into real and effective improvements in clinical practice. In this process there is a crucial role of technology transfer and engineering, as well as to media and outreach. An IU effort built around existing areas of IU research strength could bootstrap a new and potentially world-leading life-sciences cluster around devices, services and modeling, areas where Indiana already has significant strengths. Consequently, the success of the project would have direct payoff for the health and welfare of the citizens of Indiana.

The five cores that comprise the IVT combine mathematical modeling, advanced bio-imaging techniques, computer simulations, and *in vitro* and *in vivo* experiments. Each has already established collaboration with IUSM’s physician scientists. Building on these existing
collaborations, concentrated and amplified efforts in these five cores will have tremendous payoffs to IU, the state, and beyond.

1. **Breast Cancer.** The rate of invasive ductal tumor growth varies considerably among individuals, and yet most screening schedules for breast cancer are still determined according to an average predicted growth rate for a certain age group. This unfortunate situation leads either to over-diagnosis (detecting tumors that will never become lethal), or, worse, to poor prognosis (detecting tumors that already have metastasized). This core will focus on optimizing breast cancer diagnostics and prognostics with a biophysical model for tumor growth (Fig. 2). A pilot study, funded by IUB JCEB in patients recently-diagnosed with T1 breast cancer is currently ongoing at IUB, in collaboration with a local surgical oncologist and two IU Health radiologists. A CTSI GLUE proposal and NIH R21/R03 grants are currently in preparation for an extension of the study to the Indianapolis area, in collaboration with IU NORTH Hospital.

![Fig. 2. Modeling angiogenesis in 3D](image)

2. **Vascular repair.** Determining the basic rules that guide both self-organizing capillary vasculogenesis and homeostatic angiogenesis can serve as a model for understanding the growth and homeostasis of other tissues. The computer simulations we have developed for different combinations of cells, signaling pathways and feedback mechanisms (Fig. 3) will predict quantitative changes in vascular morphology, tissue oxygenation, ECM and growth factor levels, which we will test both in *vitro* and *in vivo*. Definition of the homeostatic drivers for emergence of vascular networks will allow specific planning of cell delivery protocols. Control of vasculogenesis also has relevance to tissue engineering, which still suffers from the difficulty of producing functional vascular networks to supply engineered tissues and organs. Ongoing collaboration with IUPUI’s Program in Regenerative Medicine will use virtual tissues to optimize cell types (including patient-derived primitive cells), concentrations, scaffolds, and vasculization dynamics in the treated tissues, either by cell therapy or tissue engineering, to prevent or reverse organ function deterioration and structural degeneration. Initial funding from the Simon Foundation ($750K) is pending.

3. **Eye.** Diabetic retinal vascular disease (Diabetic Retinopathy, or DR), a disease caused by diabetes that can lead to blindness, and which affects over a hundred million people worldwide, still lacks mechanistic understanding despite huge expenditures of funds on the biochemistry and physiology of diabetes. This situation limits the number and effectiveness of current treatment options. IU has a unique opportunity to form the most promising group of DR experts to date because it is home to three world-leading research teams, namely, IU School of Optometry, IU Biophysics, and IUPUI Department of Mathematical Sciences. The core will integrate mathematical models of blood flow and vascular remodeling in the eye with computer simulations (Fig. 4) so that IU School of Optometry can apply virtual tissue models of the retina to optimize patient-specific treatment schedules and surgical intervention for DR. Initial research in this core was funded by an IUCRG grant.
4. Liver. Pharmacological and toxicological processes occur across a wide range of spatial and temporal scales and include multiple organ systems. A Systems-Biology in silico toxicological model must include sub-models that cover the multiple scales and the multiple tissues relevant to human medicine and toxicology. The core will develop a liver-centered mechanism-based multi-scale in silico simulation framework for xenobiotic toxicity and metabolism that incorporates several biological scales. Initial simulations of toxic challenge to the liver will concentrate on Acetaminophen (APAP) toxicity. APAP is a widely used over-the-counter pain reliever and fever reducer. An acute overdose of APAP is a leading cause of liver failure in the western world. APAP overdose leads to centrilobular liver necrosis that can progress to liver failure and in some cases patient death. The in silico simulation will be calibrated using microscopic imaging in the liver of a living mouse, and mouse liver immune-histology, along with standard histology and serology in animal studies of APAP toxicity. The proposed in silico model (Fig. 5) is a first step in toxicity prediction simulation that ultimately will lead to improved techniques for a patient-specific prediction of toxicity of therapeutic agents. Currently supported by an NIH U01 grant ($2.2M).

5. Kidney. Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive accumulation of renal cysts, culminating in kidney failure. Treatments are dialysis or transplant only, with no FDA approved options to alter disease progression. A critical need exists for a means to prevent, delay or slow ADPKD. ADPKD results from a mutation in either Polycystin-1 (PC1) or Polycystin-2 (PC2). Decades of research revealed multiple affected signaling pathways, but have failed to identify a mechanism that links PKD mutations and the cell behavior changes that drive cyst formation, thus hampering efforts to develop effective treatments. Collaboration between IUB and IUSM has already used in vitro and in silico models (Fig. 6) to interrogate pathway perturbation effects on cyst formation. The purpose of this core is to combine experimental data on cytogenesis with computer simulation environment to simulate cystogenesis, thus generating testable mechanistic hypotheses for patient-specific treatments. Current funding comes from Falk Medical Research Trust ($400K).

Resources. Building on IUB’s existing strength in the 5 initial cores of the IVT, as well as on the support of the new Intelligent Systems Engineering department, the Law school, the Media school, and COAS, we shall require support for additional lines as follows in order to address goal 6 and make IVT the best in the world (Fig. 7):

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<tr>
<th>Multi-core</th>
<th>Core 2</th>
<th>Core 3</th>
<th>Core 4</th>
<th>Core 5</th>
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<td>Modeling</td>
<td>Eye</td>
<td>Bioengineering*</td>
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<td>Molecular level/signaling</td>
<td>Liver</td>
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<td>Pathway/Metabolic</td>
<td>Comp. Toxicology &amp; QSAR</td>
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<td>Bio-mechanical/ECM</td>
<td>Computer Science</td>
<td>Tissue engineering</td>
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<td>Heart, lungs &amp; vascular</td>
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* Housed at new ISE dep.
We shall also require administrative and IT support, and in particular support from IUB’s UITS Research Technologies for high performance scientific computing, in addition to lab support for the bio-engineers and bio-imaging, and support for 15 post docs (2 for each core, and 5 to the modeling section, total of 3 per year), and 25 PhD students (5 per year). Addressing goal 7, in the first year we shall apply for an NSF NRT Training grant (~$3M) so that students could train in the new department of IS Engineering at IUB SOIC and in the IVT, to become the next generation of virtual tissues scientists. The students and post docs will also regularly attend professional workshops for responsible research at the IUB Poynter Center, which facilitates interdisciplinary conversations and research projects on contemporary and future bioethical challenges.

Team.

Point of contact Associate Professor Amit Hagar, Chair of IUB HPSC. Team leaders who are responsible for shepherding and providing intellectual leadership for this Grand Challenge initiative are:

Core 1, Tumor Growth: Amit Hagar, PhD, IUB HPSC. Hagar has won the 2011 IUB Outstanding Junior Faculty Award and two NSF scholar awards. He is a Fulbright Scholar, and is currently leading an IRB approved study on recently diagnosed breast cancer patients, for which he has an invention disclosure with IURTC, and funding from IUB’s JCEB.

Core 2, Vasculature: Keith March, PhD/MD, IUSM. March is recognized internationally for vascular and adipose-derived stem cell therapies. March has >60 patents and >130 articles. One of his inventions has been used in more than 7,000,000 patients. He is Co-PI along with six centers in the NIH-sponsored Cardiovascular Cell Therapy Research Network. His group is conducting a first-in-US trial of autologous ASC for critical limb ischemia. These trials provide platforms to evaluate interaction of vascular progenitors and clinical/vascular phenotypes.

Core 3, Eye: Steve Burns, PhD, IUB Optometry. Burns has held academic positions in ophthalmology at the U. of Pittsburgh and Harvard U. Medical School. He was an associate scientist at the Eye Research Institute and a senior scientist. He also served as associate director of Schepens Eye Research Institute. His memberships include The Optical Society of America (where he has been a fellow since 1993) and the Association for Research in Vision and Ophthalmology. He has served on the Visual Science C Study Section, and is a past editor of the Journal of the Optical Society of America, and a winner of the Optical Society of America’s Tillyer Medal. He is also serving on the National Eye Institutes “External Scientific Oversight Committee” for the NEI’s Grand Challenges.

Core 4, Liver: James Klaunig, PhD, IUB SPH. Klaunig was the director of the State Department of Toxicology and the State Toxicologist of the State of Indiana, he won the Kenneth P. DuBois Award, Midwest Toxicologist of the Year, Midwest Society of Toxicology George Scott Toxicologist Award, and the Sagamore of the Wabash, (highest award for Service to the State from the Indiana Governor). He was a member of the Cancer Etiology Study Section, NCI/NIH, and his research has been supported by the NIH, USEPA, DOD, ACS, and non-federal sources.

Core 5, Kidney: Robert Bacallao, MD, IUSM. Dr. Bacallao’s honors include Tau Beta Pi membership and the Burroughs Welcome Trust Fellowship. His laboratory is working on a vascular-based approach to reverse or prevent acute kidney injury. The lab uses advanced light microscopy methods, pioneered at IU, and is part of an NIH funded O’Brien Center of Excellence. He is the founder of several companies with a patent in his name, and has received an IURTC RISC grant and an Indiana SBIR grant.
Other team members and their areas of expertise that reach across departments, schools, and campuses include:

**Physician Scientists**
- Fadi Haddad, Surgical oncologist, IUB Biology/Medical Science
- Merv Yoder, Vascular formation, IUSM
- Maria Grant, Diabetic micro-vascular complications, IUSM
- Thomas Gast, Diabetic retinopathy, IUB Optometry
- Sunil Tholpady, Plastic surgery, IUSM and IU Health

**Vascular Biologists**
- Nicanor Moldovan, IUSM
- Dmitry Traktuev, IUSM

**Regenerative Biologists**
- David Stocum, Limb regeneration, IUPUI Biology
- John Foley, Cellular reconstruction, IUB Biology/Medical Science
- Sachiko Koyama, Tissue modeling, IUB Biology/Medical Science

**Applied Regenerative Medicine**
- Terry Loghmani, Physical therapy, IUPUI SHRS

**Computer Scientists**
- Andrew Lumsdain, High Performance Scientific Computing, IUB Informatics
- Robert Henschel, Scientific Applications and Performance Tuning group, IUB UITS RT

**Chem/Bio-Informaticians**
- David Wild, Chem-informatics, IUB Informatics

**Bio-modelers**
- James Glazier IUB Physics
- James Sluka IUB Physics
- Julia Arceiro, IUPUI Applied Math

**Bio-imagers**
- Kenneth Dunn, Indiana Center for Biological Microscopy, IUPUI Medicine
- Sherry Clendenon, IUB Physics
- Sharlene Newman, Director of Imaging Research Facility, IUB PBS

**Law (Regulation and IP)**
- Mark Janis, patent law and policy, IUB Law & IUB IS Engineering
- Michael Mattioli, IP aspects of big data, IUB Law
- Norman Hedges, patent prosecution – Intellectual Property Clinic, IUB Law
- Yvonne Cripps, regulation in the life sciences, IUB Law

**Sociology**
- Jutta Schickore, Big science methodologies, Science & Public, IUB HPSC
- Brea Perry, Medical sociology, bio-sociology, quantitative methodology, IUB Sociology

**Media**
- Amy Gonzales, Social media, Human-computer interaction, IUB Media School
- Margaret Dolinsky, Virtual Environment Design, IUB School of Fine Arts,

**Sustainability.** While the 5 cores proposed here share the methodology and approach of computational system biology, the deliverables in each are different, and as such will attract different government agencies and different external sources and industry partners.

**Core 1** uses a model that can be applied to optimize patient scheduling, or in prognostics and evaluations of the efficacy of current therapy for breast cancer based on metabolic data, or to provide early warning of failed treatments. **Core 2** can help regenerative physicians to test basic hypotheses on endothelial cell growth. **Core 3** would provide prognostics for diabetics to determine the frequency of eye exams and to warn of impending damage and also calculate the optimal
ablation locations for individual patient. In core 4 the goal is to predict toxic effects from chemicals and drugs to warn of possible rare effects in specific populations. In core 5 the goal is to identify specific modes of action of the two known mutations that are causative and to predict the effects of possible drugs acting on the pathways disrupted by those mutations.

Through seminars, workshops, and individual consulting we shall work closely with the legal, social, media and business components of the project, as well as with the regulatory ones, and with the newly formed intelligent systems engineering school, aiming for efficient transitions from the lab to the clinic in each of the 5 cores. The IVT deliverables would be software products and their output based on specific in vitro as well as clinical data sets; and as such will be incorporated into existing diagnostic devices, or disseminated as working tools to drive specific treatment protocols in the clinic. Guidance from the IU Foundations will allow us to target potential private or commercial funding sources, and we shall work closely with IURTC to ensure that the IP from the IVT is optimized with respect to its value for IU. For each of the 5 cores, our goal in 5 years is to reach at least a prototype level with proof of concept, that could then be commercialized either through state-funded SBIRs, STTRs or other funding spin-out, or through partnerships with relevant types of health care industry drug discovery, diagnostics, and large pharma companies.

**Partners.** Since the 5 cores target different areas of disorder and deliverables, each team leader will be responsible for cultivating connections with external organizations and individuals necessary to the guidance, implementation, and funding of the research and its translation into practical benefits for the people of Indiana and elsewhere. Potential such entities beside the NSF, DOD, NCI and NIH with whom we are already collaborating, or who expressed their support in our initiative include: Ora Pescovitz (Senior VP for Medical US), Andrew Dahlem (VP for Research Labs Operations – a formal letter of support is available on demand) & Tom Jones, CSO tox & path at Eli Lilly and Company, Reza Rasoulpour (group leader) and Daland Juberg (global leader) Dow agro, Craig Rowlands (Senior Scientist) Dow, Susan Felter (Senior Scientist) Procter & Gamble, Pfizer, Roche, Cyfuse Biomedical, a leading company in the field of 3D tissue printing, the Olcott Center, SIRA, Cell Therapy Foundation, Indiana Center for Vascular Biology and Medicine, Indiana Diabetes Research Center, Roudebush VA Medical Center, Krannert Inst. of Cardiology, Simon Found., the Juvenile Diabetes Research Foundation, the Joslin Diabetes Center, Boston Micromachines, imaging collaborations with The Ohio State University and Northwestern, Naga Chalasani and Raj Yuppalanchi (IUSM), Falk Medical Research Trust, Matthias Reuss Stuttgart Center for Systems Biology, Roeland Merks, Biomodeling Analysis Group, CWI, Netherlands.

**Metrics.** We have chosen 5 select areas of disorder for the proof of concept in each core. Our intention, within the first 5-year span of the Grand Challenge, is achieve those proofs of concept so that we can attract the external competitive, philanthropic, corporate, or government funding necessary to sustain the work in these cores to successful completion. As can be seen from the IVT blueprint, each stage in the development of the deliverable in each core will be assessed by its contribution to the next stages, and immediate feedback between stages would allow us to calibrate the process on an ongoing basis. The success of each core will be measured by the ability to translate the respective models and their implementation from the lab to the clinic, and then by the ability to transform current practices in the medical and patient communities in the state, making Indiana a world leader in computational precision medicine. Deliverables may include 3D simulations, software, wearable diagnostic devices, decision-making algorithms, and new platforms for hypothesis testing with virtual tissues that would reduce material interventions in animals and in humans, and allow the more efficient design and implementation of clinical trials. To ensure impact on the real world, they will be disseminated first into IUSM and IU Health system with the help of each core’s physician scientists, and then into other states via partnership with Indiana institutions and global health care industries.