GRAND CHALLENGE PROPOSAL

Precision Health Initiative

Summary

Indiana University School of Medicine and its partner IU schools, along with external corporate participants, propose a bold plan within their **Precision Health Initiative (PHI)** grand challenge. The goal of the PHI grand challenge is to position IU among the leading universities in *understanding and optimizing the prevention, onset, treatment, progression and health outcomes of human diseases through a more precise definition of the genetic, developmental, behavioral and environmental factors that contribute to an individual's health.* We will achieve this by building new research programs; generating novel discovery platforms; creating new and expanded degree, certificate, and professional medical education programs; and, most importantly, bringing transformative, patient-centered, precision medicine therapies and prevention into our clinical services. This initiative is designed to fully realize the vision of the Bicentennial Plan articulated by President McRobbie to improve the education, health, economy and quality of life of the people in Indiana. We have benefited greatly from the comments provided by the reviewers of the pre-proposal, and we believe the present full PHI proposal is a comprehensive approach to addressing this grand challenge.

Coordinated by a robust administrative structure, PHI will establish three major scientific pillars and two cross-cutting themes, operating as five integrated virtual clusters across IU. These clusters include Genomic Medicine; Cell, Gene and Immune Therapy; Chemical Biology and Biotherapeutics; Data and Informatics Sciences; and Psychosocial, Behavioral and Ethics. Additionally, each of the five PHI clusters will develop many new educational and degree programs to create the future workforce necessary for transforming health care across Indiana and beyond. The initiative will also create a comprehensively-characterized Precision Health Participant Cohort of subjects who will provide a rich resource for longitudinal data collection, population based outcome studies, and many future biomarker and disease mechanism discoveries. We believe that PHI will make IU a leader in this exciting area of health sciences, and have a transformative effect not only on IU, but also on the health, well-being and economy of Indiana.

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I. The Grand Challenge

Responding to the Indiana University Bicentennial Grand Challenge request which calls for bold initiatives addressing "major and large-scale problems facing humanity that can only be addressed by multidisciplinary teams of the best researchers", the Indiana University School of Medicine (IUSM) has identified **"Precision Health"** as its grand challenge. 'Precision health' and 'Person-centered' approaches will be the next paradigm shift for health care delivery and are likely to become the dominant forces in the training of the next generation of graduates from the health sciences schools. The principles of person centered precision health is defined here as "*the science of understanding and optimizing the prevention, onset, treatment, progression and health outcomes of human diseases through a more precise definition of the genetic, developmental, behavioral and environmental factors that contribute to an individual's health*". Thus, precision health spans the full range of health promotion, disease prevention, as well as individualized treatment and recovery strategies (see **Fig. 1**).

Biomedical research is poised to revolutionize our approach to patient care by introducing new genomic, biological and behavioral knowledge to provide personalized and precise medical care. High-throughput technologies for molecular characterization of an individual's own genetic makeup are becoming more readily available and affordable. In the area of oncology, we are already at a point in time where personalized molecular medicine is *required* for certain select diseases and molecular subtypes. Examples of these include anti-HER2 (Herceptin receptor 2) targeted therapy for HER2-positive breast cancer, epidermal growth factor (EGFR)-targeted therapy for EGFR-mutant lung tumors, and the mutation-selective kinase inhibitors for murine sarcoma viral oncogene homologue B1 (BRAF)-mutant melanoma [1-4]. This type of biomarker-based approach will soon become the standard of care for most patients with cancers—indeed, industry data suggests that from 2000 to 2015, genetics-based cancer drug sales have grown from 9% to nearly 50% of the market share [5]. President Obama singled out precision medicine as a key future direction (State of the Union address, 15 Jan, 2015). It is expected to be a major area of investment for the National Institutes of Health (NIH) as noted by Director Francis Collins [6]. The NIH and Patient Centered Outcomes Research Institute (PCORI) have partnered to form the One Million Americans Initiative [7], and other federal funders are preparing to invest as well. Similarly, genetically modified cell therapies have begun to revolutionize the treatment of cancer and other conditions [8-10]. We at IUSM have submitted an ambitious proposal to the NIH to create a Midwest Precision Medicine Consortium (PMC) of 7 academic major institutions, recruiting over 150,000

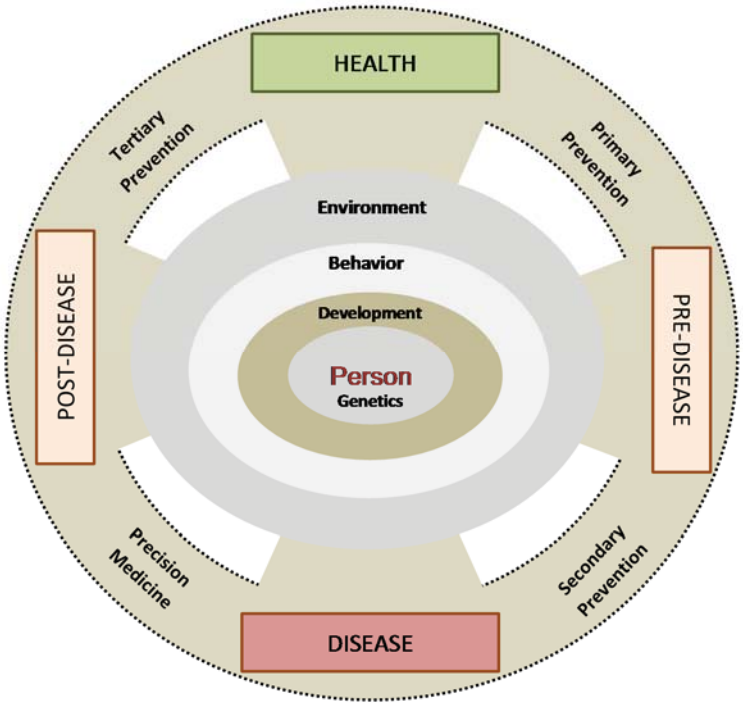


Figure 1. Conceptual Model of Person Centered Precision Health
In this model, each individual is treated as a unique case shaped by their particular genetic makeup, early developmental influences and psychosocial and environmental factors. These factors will be considered throughout the full cycle of health promotion, primary and secondary prevention of disease, individually tailored therapeutics for emergent disease, and personalized recovery/tertiary prevention programs designed to reestablish a healthier life style.

subjects into precision medicine studies across 8 states in the Midwest (see Appendix). The PHI grand challenge will provide the necessary research programs that can leverage such resources and position IU to be one of the national leaders in this area.

Precision health approaches have begun to make significant impact in health care and outcomes across a wide range of medical conditions, but nowhere is this impact felt as dramatically as in the area of cancer treatments. The following case illustrates the real life impact of precision medicine right here in Indiana:

An Illustrative Case of Precision Medicine: Mr. Smith is a 62 year old man who presented to IUSM with metastatic anaplastic thyroid cancer, an aggressive tumor with a median survival of 3 months, at a stage of advanced disease in the neck and metastases to the lung. The disease was progressing rapidly despite chemotherapy with doxorubicin/cisplatin and subsequent paclitaxel. He was not expected survive beyond a few weeks. When precision genomics tests were conducted, his tumor was found to have a BRAF V600E mutation. He was treated off-label with the BRAF inhibitor vemurafenib with partial response. He was also found to have PDL1 positivity in both the tumor and in the tumor infiltrating lymphocytes. Based on this immune positivity, he was treated off-label with the immune checkpoint inhibitor, nivolumab. With this combination, he experienced complete radiographic remission (no disease visible). He has now remained disease free for almost a year, and is still being followed at IUSM precision medicine clinic.

II. Goals of the Precision Health Initiative

As indicated above, IUSM and its partner IU schools, along with several external corporate participants, are proposing a bold plan within their **Precision Health Initiative (PHI)** grand challenge. The aim of the PHI grand challenge is to position IU among the leading universities in this field by building new research programs, generating novel discovery platforms, creating new and expanded degree, certificate, and professional education programs, and, most importantly, bringing transformative, patient-centered, precision medicine therapies and prevention into our clinical services. The following are the specific goals of the PHI and the areas they address:

1. Establish outstanding precision health research programs and transform Indiana University through strategic hires that will significantly enhance the volume, quality, impact, and reputation of research at IU in this area (Research Initiatives).
2. Improve in tangible ways the quality of advanced health care provided to the people of Indiana and beyond by expanding existing and building new precision health clinical services (Clinical Programs).
3. Make critical investments to build the infrastructure needed for precision health research, including eventually a planned precision health research building at IUSM (Infrastructure)
4. Create new and expanded professional degree, certificate, and continuing education programs; engage the public, especially the next generation of learners and citizens, into precision health concepts (Education).
5. Facilitate industry collaboration to pursue our common goal of generating new discoveries for commercialization in the context of precision health, and thus improve the economic vitality of Indiana (Commercialization).

Achieving these goals will require substantial recruitment of new investigators and building new infrastructure across the state, a scale of transformation that will only be possible through a “grand challenge” mechanism. We believe that the PHI programs and clusters detailed below will make IU a leader in one of the most exciting areas of health care discovery and innovation, and will have a transformative effect not only on IU, but also on the health, well-being and economy of Indiana.

III. Response to Pre-proposal Reviews

We greatly appreciate the input from the reviewers, which we believe has enabled us to design a much stronger, cohesive and responsive application for the Grand Challenge (GC). Reviewers recognized significant merit of the application, and stated "that this proposal is instrumental to the long-term success of IUSM and critical to enabling IUSM to remain among the top 25 NIH-funded medical schools". "Precision medicine is a key initiative if Indiana residents are to have state-of-the-art therapies". "The team has experience and demonstrated success in working together on multi-investigator grants and programs like CTSI…and is talented and accomplished". "The program has a high likelihood of long-term external funding through NIH and industry partners like Roche and Lilly". Overall, this application was judged to "have enormous potential". However, there were several areas noted for improvement and we address each major concern.

1) Strengthening the 'human aspect of this line of investigation' – that is, the patients, as well as the legal, ethical and philosophical implications of precision medicine. This perspective has greatly focused our new application in many ways. The most substantial aspect is that we have added one major cross-cutting cluster and a comprehensive approach to collecting precision health cohort designed to address this concern: the Psychosocial and Ethics Core and the Midwest Precision Medicine Initiative Consortium – Indiana Cohort Enhancement Study (MPC-IC). Each core serves to incorporate a broader conceptual vision, engaging the social sciences and ethics fields, in the implementation of the Precision Health Initiative. Within the MPC-IC, the Social Symbiome offers a unifying mechanism of action. Health, disease and risk behaviors are conceptualized as a bio-psycho-social process managed by social networks in the community and in treatment systems. Network ties serve as the mechanism linking influences within and across societal levels.

2) Increasing the "prevention" component of precision medicine. In recognition of the crucial importance of this topic, we have re-designed the application into the "Precision Health Initiative" (PHI). At all levels, we have considered the potential impact of identification of risk, and the importance of the social and behavioral determinants of health. In this manner, the prevention of disease and the promotion of health remain at the forefront of the mission of the PHI.

3) Identifying and collaborating with outstanding national and international leaders in precision medicine. We have elected to engage a group of internationally regarded external advisors in support of the PHI. Furthermore, we fully anticipate that the targeted recruitments will focus on national and international leaders. Moreover, in an organic sense, the expected extramural funding resulting from these collaborative efforts will involve national and international efforts.

4) Enhancing the expertise in computing through increased collaboration with SoIC at IUB (to add expertise in areas such as cloud computing, database design, text analysis). We have embraced a more comprehensive and inclusive approach to this essential element and have expanded the network of participation. Our precision health informatics team spans two campuses and incorporates the faculty from the Center for Computational Biology and Bioinformatics (CCBB; IUSM), Center for Biomedical Informatics (CBMI; Regenstrief), School of Informatics and Computing in Bloomington (SOIC-B), and School of Informatics and Computing in Indianapolis (SOIC-I) to include advanced phenotyping, clinical decision support, functional annotation of mutations, and systems biology and pharmacology. An important converging construct involves the integrated health record/omics data mining and literature based discovery. Selecting the significant genomic and clinical predictors is the key step to translate them to their clinical utilities, or validate them in biological experiments.

5) Adding public health/health education components, involving formal (K-12) and informal science education so as to best disseminate results to practitioners and the general public. In addition to the formal educational programs outlined, the institution of the Psychosocial and Ethics Core, as well as the MPC-IC, directly addresses this concern of educating the public.

6) Demonstrate what makes IU uniquely suited for this effort, given how strong the competition from others will be "whether it can be done in time to beat others who are also working in this area – and there are lots of others interested in this – is less clear." The Precision Health Initiative brings a broad and ambitious goal into clear focus with a highly unique capability to engage many departments, centers, schools, and disciplines in the effort. IU is uniquely positioned for this initiative, given the statewide network of healthcare, and the integration with corporate partners from the region, and focusing on targeted research areas and implementing precision health clinical interventions across a statewide health system (something no one has accomplished in the country), IU has the opportunity to quickly leapfrog others to be among the leaders in this area.

7) Identify metrics that adequately measure outcomes and the metrics are more "goals and timelines" rather than real outcomes assessment. The improved application directly addresses metrics regarding health, wellness, education, and research outcomes.

8) Describe plans for faculty hiring with more specificity. Each pillar program and cross-cutting theme has comprehensively enumerated the number of recruits (significantly smaller than the original letter of intent) and the specific area of expertise requisite for the success of the program. We believe these details more accurately reflect the critical focus areas for successful completion.

The PHI Programs, Management, Personnel, and Resources

IV. Integrated Components of PHI

The PHI will establish three major scientific pillars and two themes, structured as virtual clusters (see **Fig 2** below). These include: 1) Genomic Medicine Cluster, with a focus on integrating PHI principles into routine health care practices and creating a learning health care system for precision medicine and research ; 2) Cell and Immune Therapy Cluster, which will bring emerging genetically modified cell, gene and immune therapy approaches to treat previously untreatable disorders; and 3) Center for Chemical Biology and Biotherapeutics (C2B2), dedicated to translating newly discovered genetic pathways of disease states into chemical biology targets and generating tool and drug-like molecules to engage such targets. These three pillars will be supported and complimented by two cross-cutting themes: 1) Data and Informatics Sciences Cluster (DISC), dedicated to creating an integrated program to coordinate the bioinformatics, clinical informatics and high end computational services necessary to support this grand initiative; and 2) Behavioral, Psychosocial and Ethics Core that will enrich the initiative through behavioral, environmental and humanistic approaches to health promotion. Additionally, each of the five PHI clusters will

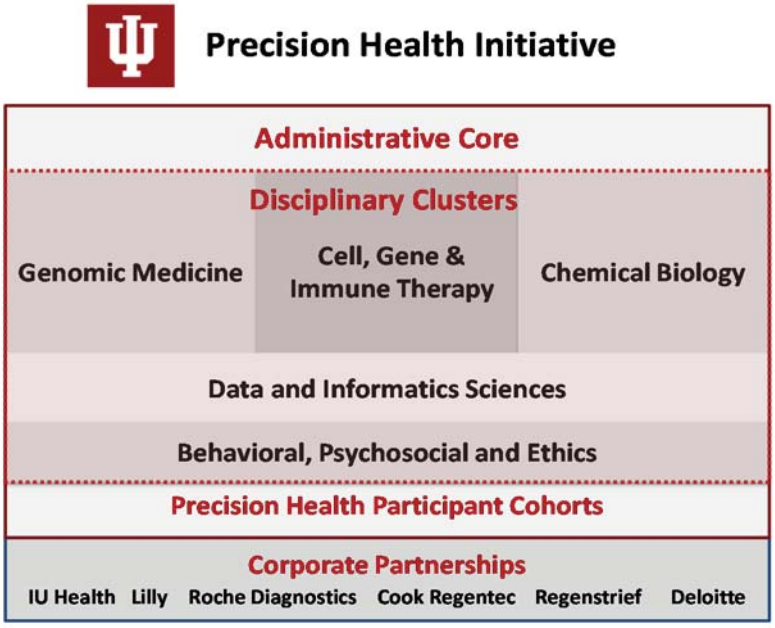


Figure 2. Components of the Precision Medicine Initiative. PHI will establish three major scientific pillars and two cross-cutting themes, operating as five integrated virtual clusters across IU. It will also create comprehensive cohorts and develop corporate partnerships to enhance each cluster. An administrative core manages the coordination and timely execution of the initiative.

develop many new educational and degree programs to create the future workforce necessary for transforming health across Indiana and beyond. The initiative will also create a comprehensively-characterized Precision Health Participant Cohort of subjects who will provide rich resource for longitudinal data collection, population based outcome studies and biomarker discoveries. A robust administrative core will coordinate the activities of the different clusters (**Fig. 2**). Finally, we have developed partnerships with five different corporate entities from Indiana and elsewhere to ensure seamless translation of the output of these research clusters into patient care or product development. Each of these components of the PHI is detailed below in this proposal.

V. Administrative Core

The PHI will have a well-positioned, empowered leadership team across and an administrative structure that has been highly effective in serving the mission of IU in similar initiatives such as the Lilly Endowment funded Physician scientists Initiative (PSI) or the IU Health funded Strategic Research Initiative (SRI). The overall management of PHI will be under the direction of Anantha Shekhar, MD, PhD, who will be assisted by an **administration team** and a **Steering Committee** consisting of the leaders from the five PHI Clusters and Rick Van Kooten, PhD, the Vice Provost for Research at IU Bloomington. Dr. Shekhar who reports directly to Jay Hess, MD, PhD, MHPA, the vice president for University Clinical Affairs and dean of IUSM, who in turn is a direct report to Michael A. McRobbie, PhD, the president of Indiana University.

A. Administration Team:

Anantha Shekhar, M.D., Ph.D. Dr. Shekhar is the August M. Watanabe Professor of Medical Research and Executive Associate Dean for Research Affairs at IUSM. He is also the founding director of the Indiana CTSI, and as such will have the responsibility for the overall function and success of PHI.

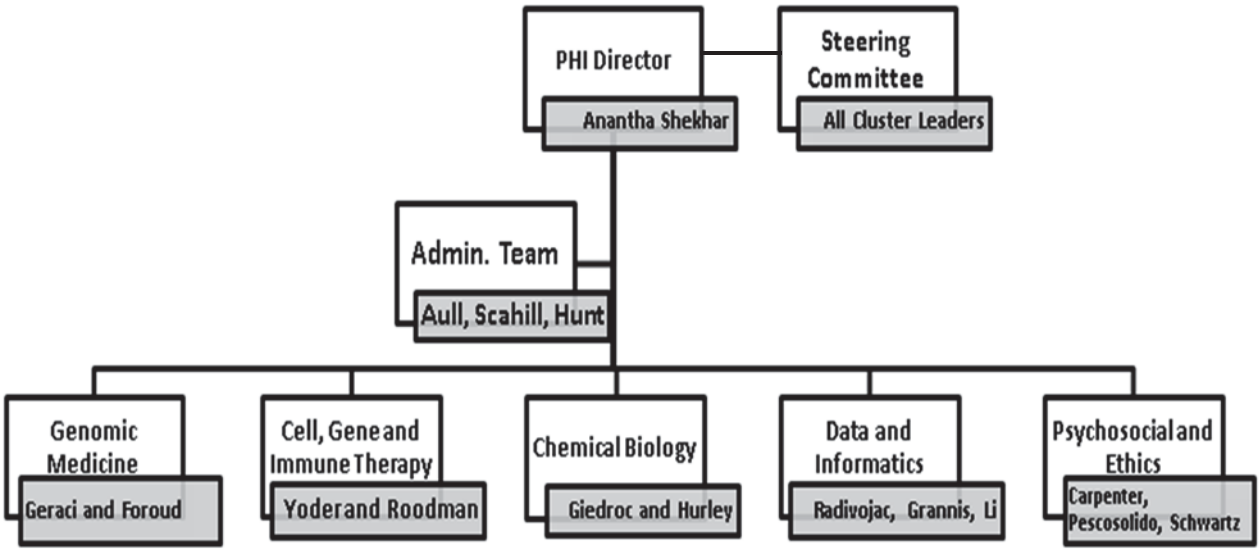


Figure 3. The organizational chart and the leadership teams of PHI. The proposed leaders of the thematic areas will coordinate the campus activities of the cluster and begin implementing the foundational activities until a PHI-funded expert is recruited. The administrative team will manage the operations of the initiative.

Robert Aull, MA, Director of Research Affairs Office, will assist in managing budgets, grant accounts, program and pilot award accounts and will have general responsibility for all accounting and fiscal matters with partner institutions.

Samantha Scahill, Administrative Manager, will be responsible for the operations of the director's office, human resources functions of the PHI initiative, and planning PHI events and communications.
Joe Hunt, MS, Evaluation and Metrics Specialist will oversee all the evaluation and progress metrics operations of the Indiana CTSI and is nationally recognized expert in logic models and results based accountability methods. He will be assisting the administrative team to ensure we collect accurate data and manage the initiative to deliver the expected results and make the right impact. Administrative Team Meeting: The above group and a subset of cluster leaders will meet at IUSM biweekly for a 90 min administrative team meeting to discuss any operational issues of PHI, current recruitment activities of the cohort program, progress being made in the clusters, as well as strategic directions and tactical steps for operational success.

B. Steering Committee (SC).
The Implementation and strategic directions of the PHI will be enabled by a Steering Committee whose members include all the senior leaders representing the different components of the PHI proposal. The SC chaired by Dr. Shekhar will meet monthly for 90 min. in person at IUSM with leaders from the other campuses joining live by videobridge. Monthly operational updates will be provided by the administrative team. Agenda items are solicited from all members and prepared ahead for the meeting by Ms. Scahill. The SC will review the overall progress of the PHI, plans for future recruitments and investments, and approve any major programmatic or funding initiatives. Funds will be approved by the SC similar to the 'council' model followed by NIH institutes. The meeting minutes will be recorded for each meeting.

C. Internal Advisory Board (IAB).
The IAB will be comprised of senior administrative officers of the universities, deans or their designees from the participating schools at IU and PU, executives of major hospital systems and institutes, and other key leaders from the participant organizations. The IAB will be chaired by Dr. Hess and will have the membership shown in **Table 1** below. The PHI director and SC will meet with the IAB at least once every six months, and Dr. Shekhar will consult with Dr. Hess regularly.

Table 1. Members of the IAB and their affiliations

Name	Title	Institutional Affiliation
Dr. Jay Hess, Chair	VP and Dean	Indiana University School of Medicine
Dr. Lauren Robel	Provost	Indiana University
Dr. Nasser Paydar (or designee)	Chancellor	IUPUI
Dr. Fred Cate	Vice President for Research	Indiana University
Dr. Jonathan Gottlieb	Chief Medical Officer	IU Health
Dr. Robin Newhouse	Professor and Dean	Indiana University School of Nursing
Dr. Brad Wheeler	CIO and Interim Dean	Indiana University School of Informatics
Dr. Paul Halverson	Professor and Dean	Fairbanks School of Public Health

D. External Advisory Board (EAB)

The PHI will also have a distinguished **External Advisory Board (EAB)** comprised of outstanding leaders from our community partner institutions (see **Table 2**); and five scientific advisors who are leaders in the field of precision medicine approaches at other academic institutions. The PHI administration and SC will meet with the EAB at least once a year.

Table 2. Members of the EAB and their affiliations		
Name	**Title**	**Institutional Affiliation**
Dr. Andrew Dahlem (Chair)	COO of Lilly Research Laboratories	Eli Lilly and Company
Dennis Murphy	President (and CEO starting May, 2016)	IU Health
Jack Phillips	CEO	Roche Diagnostics
Dr. Lisa Harris	CEO	Eskenazi Health
Rob Lyles	CEO, Cook Regentec, Inc.	Cook Industries
External Scientific Advisors (N=8)	Genomic medicine: Christopher O'Donnell, MD (NIH) and Charis Eng, MD, PhD (Cleveland Clinic) Cell-, Gene- and Immuno-Therapies: Carl June, MD (U Penn) and Madhav Dhodapkar, MD (Yale) Chemical Biology & Targeted Therapeutics: Jeffrey Kelly, PhD (Scripps) and Jeff Aubé, PhD, (UNC) Biomedical Informatics & Cyberinfrastructure: Michael Becich, MD, PhD (U Pittsburgh) and Atul Butte, MD, PhD (UCSF)	

E. Accountability for Structure, Function and Budget

Dr. Shekhar, as the program director, is ultimately accountable for managing the structure, function, and budget of the PHI. To assist him in these responsibilities, several processes are incorporated into the initiative. A succession plan will be in place in case Dr. Shekhar was to step down from his role as the PHI director. A new designee will be identified by Dean Hess. In the interim, the EC will continue to function as a team. For the entire PHI, we will set quarterly goals and defined timelines for achievement of measurable objectives. Similarly, every program within the PHI will have an implementation plan and measurable milestones and metrics. These objective timelines and measurable outcomes are tracked on a continuous basis by the Tracking and Evaluation process led by Joe Hunt. This tracking function is followed by the administration team on a monthly basis and shared with each of the responsible program directors. Working in conjunction with the T&E, the leadership of each program assesses the progress, recruitment, and financial status of the program for which they are responsible. Should any issue arise, the matter will be brought to the SC for consideration. Annually, the PHI will report a summary of the year's events to the university leadership, IAB, and to the EAB. The performance of the PHI and all programs are assessed on an annual basis. This review occurs in the form of a written evaluation prepared by the T&E program with ongoing feedback provided by the director.

F. Evaluation and management of failure to reach appropriate milestones

The performance of each PHI-funded activity is formally assessed on a quarterly basis with well-defined milestones. This continuous evaluation process identifies any failure to reach appropriate milestones, such as program delays, low productivity, or other performance problems. Once identified, the problem is discussed with the SC and corrective response is developed.

V. Genomic Medicine

Overview

Precision Medicine is an innovative approach that tailors medical management to the individual characteristics of each patient. This novel approach affords medical professionals the resources they need to attenuate risk of developing specific illnesses and to target the specific treatments for all illnesses to ultimately keep people healthier. In his 2015 State of the Union Address, President Obama introduced precision medicine as a national initiative. The mission of the White House

Precision Medicine Initiative is: *To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments*.

Long-term Goal
To implement a center of excellence in genomic medicine focused on cancer, neurogenetics, neurodevelopment and cardiovascular health in which research advances, clinical care and education are seamlessly woven together and continuously inform each other to improve patient health outcomes across Indiana in selected clinical areas.

Achievable Goals within the Grand Challenge
- Establish innovative genomic medicine research programs through recruitment and facility enhancement.
    - Recruit physician scientists and scientific leaders in the targeted areas who can build upon existing IUSM strengths and build collaborative teams to expand and initiative new research programs.
- Build research infrastructure to support genomic research
    - Build new gene editing and sequencing cores that will support translational research allowing researchers to rapidly focus on the functional effect of newly identified genes/variants that affect the risk for disease.
- Expand precision health care initiatives in the targeted areas
    - Enhance existing efforts in precision medicine to include larger numbers of patients and expand current research efforts.
    - Implement uniform collection of family history information to inform subsequent efforts to implement genomic medicine in health care decision making.
    - Recruit precision genetic counselors to provide counseling to patients participating in the growing genomic medicine implementation.
- Provide increased educational opportunities for students, health care providers and the community in Indiana and beyond.
    - Transform the exceptional genetic counseling program in Indiana to train a new breed of precision genomics counselors (PGCs) to meet the health care needs.
    - Develop innovative online certificate and CME programs designed for health care providers that utilize modules to focus on genetics/genomics, genomic medicine, ethics, as well as implementation in critical areas of health care.

A. Research Programs and Faculty Recruitment
Overview: A major element of the implementation of the Grand Challenge is the recruitment of new faculty that will lead initiatives to expand research programs on campus and will be pivotal to the success of Genomic Medicine. Following careful review of crucial areas that could lead this new initiative, we have identified critical recruits that will be targeted as the priorities for this initiative. Recruitment packages for each are proposed to encompass faculty salary, start-up packages, and junior faculty recruitment. In each case, we propose the recruitment of a physician scientist who can lead new research efforts and also guide plans to expand the scope of genomic medicine in the clinical setting. Through the Grand Challenge we request funds for only a portion of the recruitment package. We propose to leverage existing institutional funds, including available endowed chairs, the Strategic Research Initiative (SRI) and the Physician Scientist Initiative (PSI), to further augment the recruitment package.

Targeted Recruitment Areas:
1. **Cancer genomics:** To catalyze research opportunities on campus, we propose the recruitment of a senior cancer researcher in the area of genomics. This physician scientist must have an NIH-funded research program and have the ability to lead efforts to expand

the use of genetics and genomics in the clinical setting. The recruitment is not focused on a particular type of cancer, but rather the investigator must have the demonstrated ability to lead and innovate through team science. A focus for the IUSM is to increase the number of NIH-funded program project grants and specialized programs of research excellence (SPORE) with a focus on cancer.

2. **Pharmacogenomics:** Indiana University School of Medicine is the home of the Indiana Institute of Personalized Medicine (IIPM). The goals of the IIPM are based in precision medicine. The IIPM has led efforts to implement pharmacogenomic testing as part of standard care when prescribing particular medications. Ongoing NIH support (INgenious) is focused on testing whether instituting pharmacogenetics testing can reduce health care costs and improve clinical outcomes. The IIPM was founded by Dr. David Flockhart who passed away in 2015. One of the goals of the Grand Challenge will be to recruit a new leader for the IIPM. This individual must be a physician scientist with current NIH research funding. One of the primary goals of this individual will be to expand opportunities to implement innovative ways to inform physicians of relevant pharmacogenetic testing and to also expand research opportunities across campus.
3. **Neurodevelopment:** Substantial efforts are underway to understand the etiology of neurodevelopmental delays, including most notably autism and autism spectrum disorders. There is extensive genetic heterogeneity underlying the potential causes contributing to these disorders. The IUSM is investing substantial resources to develop a comprehensive neurodevelopment clinic that can broadly assess patients to develop a precision diagnosis and a treatment plan. A significant component in this effort is expanding research and clinical efforts in this area. As part of the Grand Challenge, a senior faculty will be recruited with an established, funded research program in one of the key areas. This individual could be recruited into Pediatric Neurology or Psychiatry and would have a genomics focus in their research. Their close collaboration with the Stark Neuroscience Institute would provide enhanced opportunities for collaboration. This individual would lead efforts to establish new collaborative research and clinical efforts.

We will focus first on recruiting faculty leaders in the above three areas. After we meet that milestone successfully, we will explore the opportunities to expand PHI to build the following two programs: 1) **Adult neurogenetics:** The field of neurology has benefited from the ability to utilize modern high throughput genomic approaches to delineate the cause of disease. As a result, adult neurogenetic clinics have been able to rapidly implement precision diagnosis using genetic testing. Currently at the IUSM, research in the area of neurogenetics has been largely focused on neurodegenerative disorders, particularly Alzheimer disease, Parkinson disease, or motor neuron disorders such as amyotrophic lateral sclerosis. The Grand Challenge will recruit a senior researcher with extensive external funding to build new research programs in the area of adult neurogenetics. The links to the Stark Neuroscience Institute will facilitate basic science collaboration. This individual will also be responsible for leading efforts to implement a broader range of neurogenetic clinics through Indiana University School of Medicine. 2) **Adult cardiovascular genetics:** A key area in precision medicine is adult cardiology, where genetics has already identified a number of genes that are important in cardiomyopathy as well as sudden cardiac death. In both instances, identifying individuals at risk and instituting genetic testing are critical and must be performed rapidly. There are substantial opportunities for Indiana University Health to develop destination services in these areas which would be key to efforts in genomic medicine. Substantial research is ongoing in both areas, since the genetics of cardiomyopathy and sudden cardiac death and/or long QT syndrome are still not fully understood. We propose one senior faculty recruitment with established research funding in the area of adult cardiovascular genetics who can lead new research efforts in these areas and also institute new clinical opportunities.

B. Research Infrastructure

Overview: A key element of the Grand Challenge is rapid translation between basic discovery and clinical application. Infrastructures for two critical cores that bridge the three primary areas of the Grand Challenge are proposed. The first is an entirely new core that will provide gene editing using CRISPR/Cas9. This is an approach that has revolutionized genome editing and recombination methods in eukaryotic cells. It has enabled remarkably rapid and cost-effective strategies for generating both genetically manipulated animals and cells with precise genetic alterations that will prove essential in efforts focused on personalized medicine and research. The Gene Editing Core will enable the precise genetic manipulation of newly identified variants for comprehensive functional analysis in either cellular or animal-based systems. The second is a completely redesigned sequencing core that will provide competitively priced sequencing for large and small projects and will have seamless collaboration with the Bioinformatics Core. The Bioinformatics Core has already developed very mature pipelines for most major next generation sequencing applications. The pipeline source code has been optimized for the IU supercomputer systems. As a result, the new sequencing core will provide significantly faster turnaround time, uniform processing of the sequencing data, and the capacity to provide high-quality downstream analysis support. This will ensure a broad group of researchers can utilize sequencing in their research.

Approach:

1. **Gene Editing Core:** Discovery of the CRISPR (***c***lustered ***r***egularly ***i***nterspaced ***s***hort ***p***alindromic ***r***epeats)/Cas9 bacterial acquired immune system has prompted a revolution in approaches to genome editing. The CRISPR/Cas9 system has been shown to work in vast array of cells and animals. In addition, given the efficiency of CRISPR/Cas9, multiple genes/DNA sequences can now be targeted in a single experiment, thus enabling studies examining genetic epistasis/interaction and genetic pathways that was previously extremely laborious and difficult. Recent technological advances also enable cell-type specific genetic alterations via CRISPR/Cas9 and have dramatically reduced potential off-target mutations. Thus, the CRISPR/Cas9 system represents an efficient and programmable DNA cleaving apparatus that has all but supplanted traditional homologous recombination approaches to genetic engineering in both animals and cells. While this technology is extremely powerful and versatile, it is constantly evolving and improvements are made almost on a monthly basis. Gaining full advantage of CRISPR/Cas9 requires dedicated support personnel who keep abreast of these technologies and can assist investigators in design and implementation of the technology to rapidly and efficiently generate novel cell and animal models. The goal of the Gene Editing Core is to streamline the efficiency of creating cell lines and animal models with specific gene edits for scientists at Indiana University. The core will provide consultation services for investigators who wish to perform their own manipulations and will design and perform the gene edits for an investigator. The Gene Editing Core will create and verify various gene edited cells and animals.
2. **Sequencing Core:** The newly redesigned Sequencing Core will support all standard next generation sequencing experiments and will also develop or implement new protocols using cutting-edge molecular assays such as CLASH assay for miRNA-target identification, and CRISPR/cas9 genome-wide screening. The core will pair with investigators at the IUSM in technology development such as high-throughput reporter assays (Dr. Todd Skaar) or high throughput validation-based insertional mutagenesis screening (Dr. Tao Lu). The core will also partner with other CTSI cores to develop new services such as a single-cell RNA-seq protocol and analysis pipelines (with the Flow Cytometry Core and the Bioinformatics Core). In all activities, the sequencing core will develop and be guided by standard operating procedures which can be included in extramural grant applications. One of the most critical decisions for the redesign of this sequencing core is the platform on which to build the technology. While there are multiple providers of next generation sequencing platforms, Illumina has become the proven industry-leader in terms of data quality and accuracy, with

competitive price. More importantly, it is also compatible with the largest selection of biological assays and informatics analysis tools. A recent IUSM survey suggests that having access to the most advanced Illumina platforms is strongly desired by the IUSM investigators and is one of the reasons that they are not utilizing the current core.

C. Implementing PHI into Routine Clinical Practice

Overview: Indiana University has already begun to establish cutting-edge clinical implementation of precision medicine and the Grand Challenge affords the opportunity to unify efforts in order to improve the health of the people of Indiana. The Indiana University Health Cancer Precision Genomics Program was established in 2013 as an innovative approach to providing personalized care for patients with refractory cancers by molecularly characterizing individual tumors to identify important drivers of tumor growth. This program has been very successful and has established an important foundation upon which to grow precision medicine more broadly within the IU Health Precision Genomics Program. We have treated about 500 patients with cancer in this precision genomics program and Figure 3 below shows the significant disease Progression Free Survival (PFS) for these patients compared to standard therapy treated patients in our clinics. The PFS, which is an established measure of comparative efficacy of cancer treatment regimen, is the ratio determined by dividing the PFS of the new therapy (genomically guided) by the PFS for the patient during their most recent regimen on which the patient had experienced progression.

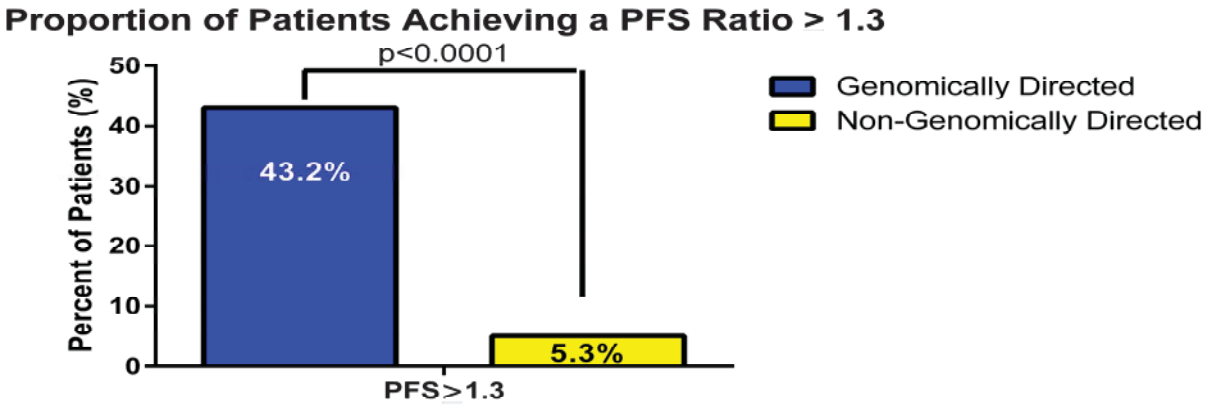


Figure 3. **Progression free survival (PFS) analysis of cancer patient population**. Comparing the percentage of patients who achieved a PFS ratio equal to or greater than 1.3, 43.2% (19 of 44) of patients in genomically directed therapy achieved a PFS ratio of 1.3 compared to only 5.3% (3 of 57) who received non-genomically directed therapy (p<0.0001). Schneider et al., 2016 (in press)

The Indiana Institute of Personalized Medicine (IIPM) was recently awarded the INGENIOUS (INdiana GENomics Implementation: an Opportunity for the UnderServed) grant from the NIH. This investigation will answer critical questions about the utility of pharmacogenetics testing in clinical practice by testing the hypothesis that a CLIA certified genotyping targeted at 24 widely used drugs is associated with significant reductions in hospital and outpatient economic costs incurred over 1 year. Furthermore, the analysis will test whether pharmacogenetic testing is associated with significant improvements in clinical outcomes over 1 year. These two endeavors (Cancer Precision Genomics and INGENIOUS) form the foundation for the expansion of Precision Medicine to primary care practices. Expansion through the implementation of Precision Health Clinics represents a significant opportunity to improve health outcomes for all individuals.

Approach: As Indiana's most comprehensive academic health center and one of the busiest hospital systems in the United States, Indiana University Health, in partnership with the IUSM, is uniquely positioned to provide cutting edge precision medicine. In the grand Challenge, we propose to initiate the first phase of growth of the Precision Genomics Program in the adult primary care arena. While there are many important areas of growth for this program, establishing a

primary care program will provide a multitude of interdisciplinary opportunities, which will be important for future growth and expansion and to ultimately be a leader in changing the way healthcare is provided for all individuals. Furthermore, to provide the best possible healthcare for all Hoosiers and optimize the process of embedding high throughput genomics into the healthcare system, we must learn as much as possible from this unique program and deliberately link such innovative clinical and research programs.

Specific Areas of implementation:

1. **Cancer Precision Medicine:** Led by Drs. Bryan Schneider and Milan Radovich, this program has successfully expanded to Ball Memorial Hospital (Muncie, IN) with plans to expand to both Arnett (Lafayette, IN) and Bloomington over the next two years. These expansions represent real world implementation of cutting edge personalization to the rural clinical setting. To date over 500 patients have been seen in our clinics, with a Biobank in place that curates tumor tissue, blood, plasma, and clinical follow-up for much planned and future translational work. More recently, we have begun to routinely offer a more comprehensive evaluation of the tumor and the germline; this includes tumor whole genome, whole exome, transcriptome, and proteomics using mass spectrometry as well as the whole genome of the germline. Between our main campus (Indianapolis) and our expansion sites, we expect to have detailed and comprehensive genomic data available on over 300 patients in the next year alone with matching clinical follow-up available for researchers across Indiana University. Additionally, this program has served as a “feeder” to the early phase program with 71% of the patients having an actionable target and 69% of those patients having a clinical trial option offered based on their genome.
2. **Precision Health in Primary Care Clinics:** Led by Drs. Jamie Renbarger and Todd Skaar, the proposed Precision Health in Primary Care Program will develop new therapeutic approaches to improve health outcomes and overall wellness for all individuals. This program will enroll primary care patients with at least one ongoing illness to the program using a stair step approach (i.e. increasing enrollment each year as the program progresses). This Center presents a unique opportunity for the IU to support a critical mission aimed at linking an innovative clinical program with focused groundbreaking research, crucial for the ultimate success of the program. This deliberate partnership will drive the future success of precision medicine for all Indiana residents and will serve as an example for future programs throughout the U.S.
3. **Precision Health in Cardiovascular and Renal Diseases:** This team is led by Drs. Brian Decker and Michael Eadon. The clinical pharmacogenomics implementation consortium has recommended the use of pharmacogenomic data to guide dosing for dozens of medications. As a result, pharmacogenomic data is increasingly translated into clinical programs across the United States. At IUH, we have one of the largest Nephrology Divisions in the US. We are home to over 750 dialysis patients and have the largest home dialysis program in the country. Over 200 kidney transplants are performed per year; the 18th most in the United States. Our home and transplant programs are already using telehealth. Our transplant program is providing unique desensitization protocols to prevent acute rejection. Our Division is home to one of nine O’Brien Centers of Excellence, with an emphasis in intravital imaging. Both Drs. Decker and Eadon have joint appointments in clinical pharmacology and unique expertise in pharmacogenomics. The vision for the future is to 1) use genomics and pharmacogenomics to improve control of hypertension and to target therapy to prevent progression of kidney disease, 2) leverage our expertise in 3D imaging in conjunction with transcriptomics and proteomics to transform the approach to renal pathology diagnosis. These cutting edge techniques allow cell-specific signatures within the kidney to aid in diagnosis and facilitate targeted precision medicine.

Integrate family history into clinics

Overview: Collecting information about an individual's family and their health conditions is a critical component of health care; however, this is inconsistently assessed due to the time needed to collect this information during a short appointment with a clinician. In addition, even when this information is collected it is not uniformly documented within an individual's medical chart. Having an individual's personal and family medical history can assist in identifying diseases for which an individual is at risk and can also direct appropriate genetic testing.

Implementation: As part of the Grand Challenge, we will purchase software compatible with the Indiana University Health electronic medical record system, which will enable the patient to easily provide their family pedigree (tree) along with relevant history of disease. This will be stored then uniformly in the patient's electronic medical record, making it easily accessible. This approach will form the backbone of new efforts to provide better patient care by easily identifying those individuals appropriate for genetic counseling due to a family history of disease. This approach will be initially implemented in the IU Simon Cancer Center and will be available to all patients seen there. This will then be expanded to other clinics and will be paired with our expanded number of genetic counselors to allow us to effectively provide genetic counseling to targeted individuals. Pedigree and family history information will also be used to more effectively and uniformly identify appropriate genetic testing for individuals assessed in precision diagnosis clinics such as those that will be expanded in adult neurology and cardiology.

Precision genomics counselors (PGCs) to staff new precision medicine clinics

Overview: The Grand Challenge will recruit new faculty in several key areas (cancer, neurology, cardiology and pharmacogenomics) selected because of the ability and potential to perform precision medicine or precision diagnosis using genetic testing. To complement the expansion of precision medicine clinically, the number of precision genomics counselors (PGCs) employed at the IUSM must also be augmented. These PGCs will be a new breed of care facilitators who will be content experts in their focused area and will add to the multidisciplinary team approach of precision medicine clinics by providing clinical support to identify appropriate genomic testing and communicate test results. These certified PGCs will also develop innovative programs, including the expansion of telemedicine capabilities to provide counseling to those unable to come to the academic health campus.

Implementation: We propose as part of the Grand Challenge to hire 6 PGCs. These counselors will support patient care in the following precision medicine clinical areas that have already been detailed above: Cancer Precision Medicine clinics (2 counselors); Precision Health in Primary Care Clinics (2 counselors); Precision Health in Cardiovascular and Renal Diseases (2 counselors). New software will be purchased as part of the Grand Challenge that will enable patients to easily report on family history electronically. The PGCs will lead efforts to provide counseling to individuals with family histories suggestive of a need for further genomic testing.

D. Education Programs

1. **Transform traditional genetic counseling training into a PGC training program**

   Overview: Today, there are just 4,000 certified genetic counselors in the United States; one genetic counselor for every 80,000 Americans. Despite the presence of a genetic counseling training program at the IUSM, the state of Indiana does not currently have enough traditional genetic counselors to fill all open positions. With the emergence of genomic medicine, the demand for genetic counselors in healthcare and research setting will far outstrip the number of available professionals. For example, fewer than 300 genetic counselors will graduate this spring, far too few to fill the estimated 650 job openings around the country. Traditional genetic counselling programs must also substantially transform their training curriculum to meet the needs of interpreting and communicating the much broader, genomics-based diagnostic tests and therapeutics choices that patients and families need to make in their care. We must therefore transform our training program to train precision genomics counselors (PGCs). To

meet the implementation of genomics in health care both nationally and in the state of Indiana, the number of PGCs being trained must be substantially increased. Given the strong national reputation of the 25-year old genetic counseling program at the IUSM, the Grand Challenge will support the expansion and transformation of the IU program from eight genetic counseling students/year to 15 PGC students/year.
Approach: The infrastructure of the recently re-accredited Genetic Counseling program is extremely robust and scalable to allow for an increase in the number of trainees. Several factors are essential in order to expand the size of the program. These include a larger number of clinics in which the students can perform clinical rotations, expanded support staff for the program, and student stipends to maintain a highly competitive and diverse student population. We propose an innovative approach for the retention of genetic counseling students in the state of Indiana. As part of the Grand Challenge, we will support tuition costs (in-state fees only) for all students along with a $5,000 stipend for each of the two years of the program. We will then in turn require that students commit to stay in the state of Indiana for a minimum of two years if appropriate genetic counseling position are available. In this way, we can grow our own pool of genetic counselors within the state through the expansion of our program.

2. **Certificate Programs**
Overview: There is significant demand among healthcare providers for more information about genetics, genomics and precision medicine. Currently, there are few online opportunities for individuals who wish to expand their knowledge in these areas in order to improve their ability to understand and interpret genetic testing which is becoming available. As part of the Grand Challenge, we propose to create online modules that can educate care providers with this information along with a certificate demonstrating their participation and successful completion of the program. In addition, participants would also be able to receive continuing medical education/continuing education (CME/CE) credit. We would model our program after one of the few opportunities currently available (https://www.coursera.org/course/genomicmedicine).
Approach: Our certificate/CME/CE program would be designed for a range of healthcare providers including physicians, physician assistants, nurse practitioners, genetic counselors, etc. The scope of the program would include a review of basic genetics, new genomic technologies, available genetic testing applied to a range of disorders, biomarkers, etc. To develop this content, we will hire a dedicated faculty member, with an emphasis on education, whose focus will be to develop and present the online course content. The course content could also be provided in person as part of CME/CE offerings in the state of Indiana. We will work closely with the health sciences schools at IU to ensure that materials meet all CME/CE requirements.

VII. Cell, Gene, and Immune Therapies

Long-term Goal

To establish a world class cell, gene, and immune therapy research program that will permit the design and implementation of novel cellular, genetic, and immunotherapeutic interventions for patients, which are based upon a detailed understanding of the individual patient's genotype and phenotype, that will improve patient health outcomes across Indiana in selected clinical areas.

Achievable Goals within the Grand Challenge

- Establish an exceptional human immunology research and therapy program at IUSM through recruitment and facility enhancement that will form the foundation for expansion of cell, gene, and immunotherapy development
    - Building a Cell Good Manufacturing Practice (cGMP) facility to accommodate translation of results of cell, gene, and immunotherapy research to human subjects in selected clinical areas

  - Recruit expert cell transplantation clinician scientists to facilitate translation of innovative cell, gene, and immune therapies into human subjects
- Provide increased educational opportunities and access to the cell, gene, and immune therapies program for physicians, patients and students in Indiana and beyond.
- Create cohorts of cell, gene, and immune therapy patients towards building comprehensive precision health cohorts. This will include acquisition of individual patient health care and risk factors, psychosocial determinant profile, along with genomics, metabolomics, and proteomics data that can be studied (in subsequent funding periods) to identify predictive markers for subjects who most favorably responded to such therapies and to examine the impact of the treatment on the patient's endogenous "omics" homeostasis.

A. Research Programs

Overview: In keeping with the identified strategic research priorities of the Indiana University School of Medicine and with the strengths of other components of this proposal, the Cell, Gene, and Immune Therapies program will focus our research on 1) two cancers, multiple myeloma and triple negative breast cancer, that afflict significant numbers of patients in Indiana and throughout the nation and that remain largely incurable for the majority of patients. We will also focus research on 2) novel immune therapies for Alzheimer's disease (AD); the most common form of dementia that is increasing at an alarming rate to exceed 100 million adult subjects worldwide by 2050. Finally, we will also focus research on 3) rare genetic diseases generally identified in pediatric patients that have an impact throughout the ever increasing lifespan of the subjects; many who are palliated by treatments but who lack curative therapies.

1. **Cancer:** We have chosen multiple myeloma and triple negative breast cancer as our focus research areas in cancer, because we have large numbers of these patients available and ongoing personalized medicine approaches are planned or underway for these two malignancies. These include a clinical trial led by Dr. Bryan Schneider that examines the efficacy of genomically directed therapy for patients with triple negative breast cancer and our very active clinical trials program for multiple myeloma. For example, the multiple myeloma program sees more than 200 myeloma patients per year with more than 1800 patient visits.

   Although there have been dramatic improvements in the survival of patients with breast cancer, with an increase in over 99% for the five year survival rates of patients with localized disease and more than 85% for regional advanced disease, the five-year survival rate for patients with metastatic disease remain at only 26%[11]. In particular triple negative breast cancer continues to have a very poor prognosis and its rate of occurrence is increased in African-Americans. Triple negative breast cancer represents 15 to 20% of all newly diagnosed breast cancer patients, but has an extremely high risk of recurrence, resulting in the lowest disease-free and overall survival rates compared to all subtypes of breast cancer. Gene expression profiling has been performed on 3000 patients with triple negative breast cancer and multiple subtypes have been identified within this classification[12]. These results show that there is tumor heterogeneity among patients with triple negative breast cancer, suggesting that a much more personalized approach for these patients must be undertaken to successfully treat and potentially cure these patients. Targeted therapies that inhibit signaling pathways and DNA repair enzymes such as PARP 1, have recently been developed and are in clinical trial for treatment of patients with breast cancer[13]. Most recently our improved understanding of the tumor promoting effects of interactions between breast cancer cells and cells in the tumor microenvironment has led to the development of the immune checkpoint inhibitors that allow T-cell activation against tumor cells[14]. Thus, developing new therapies that target host immune responses that promote breast cancer cell growth and preservation of breast cancer stem cells is an important emerging area of investigation, and will be an initial focus of our studies in the human immunotherapy therapy program. These studies will take advantage of the cohort of breast cancer patients at IUSM and the availability of the Komen normal breast tissue bank established at IUSM.

Similarly, although great advances have been made in the treatment of multiple myeloma patients, myeloma remains incurable for the vast majority of patients. Immunotherapies are an important area of research for treating myeloma patients. Ongoing studies are examining immune checkpoint blockade alone or in combination with modern therapies for myeloma, dendritic cell vaccines, antibodies targeting myeloma cells (eg. an anti-CD38 antibody was recently approved by the FDA for treating patients with relapsed/refractory myeloma), as well as, treatments targeting elements in the tumor microenvironment that promote the growth of myeloma cells and their resistance to chemotherapy as new therapies for myeloma patients. Most recently chimeric antigen receptor (CAR) T cells have been used successfully treat a patient with refractory myeloma. CAR T cells are generated by transfecting autologous T cells from the patient with a lentiviral vector that encodes a single variable chain fragment of a monoclonal antibody directed against a surface antigen (specific to the tumor cells of the patient) coupled with an intracellular signaling domain that allows activation of T cells to attack the patients tumor cells in a major histocompatibility independent manner. The engineered T cells are expanded in a cGMP facility and infused into the patient. CAR T cell therapy has been successfully used to treat patients with refractory acute lymphoblastic leukemia and results in a high response rate and persistence of the response. Recently, anti-CD 19 CAR T cells were used to successfully treat a highly refractory patient with myeloma[15]. These exciting results produced by our consultant and collaborator, Dr. Carl June and his colleagues, will be pursued at Indiana University in collaboration with Dr. June. These studies will be our initial cell-based immunotherapy studies for refractory myeloma patients and can be initiated within the first two years of our grand challenge grant. This is possible because the infrastructure needed to administer the cells is already in place and we are establishing a collaboration with Dr. June to generate the CAR T cells at his institution. This will allow us to bring a cutting-edge therapy to patients with myeloma in Indiana. This will occur as we develop our human immunology program at IUSM that will be established with funds provided by the grand challenge grant. Since our current cGMP stem cell lab is not adequate to handle larger numbers of patients than are already served through the stem cell transplant service, we will build a cGMP facility that will permit a more wide spread application of the CAR T cell therapy to eligible patients and allow other clinical trials of cell-based immunotherapies and cutting edge cell-based regenerative medicine protocols for patients in Indiana and beyond.

2. **Alzheimer's and neurodegenerative diseases**: Focusing on novel immunotherapies to treat AD is appropriate given the increasing prevalence of this disease, the presence of the Indiana Alzheimer's Research Center and the Alzheimer's biobank at IUSM, and the focus on genomic approaches combined with brain imaging to identify genetic alterations associated with plaque deposits in individuals diagnosed with AD or at risk for developing AD[16]. In addition, one of our commercial partners, Eli Lilly and Company, is interested in developing immunotherapies to AD and has developed one product that has shown promise in delaying progression of AD in patients.

   AD is a neurodegenerative disorder that is the most common cause of dementia[17]. To date, about 35 million people worldwide are affected and the prevalence is rising because of an increased life expectancy in our aging society. Alarmingly, this number is expected to triple by 2050. AD is primarily characterized by accumulation of two proteins in the brain; amyloid-β (Aβ) in amyloid plaques in the extracellular space of the brain and tau in neurofibrillary tangles inside neurons. Aggregation of Aβ and tau seems to lead to neurotoxicity. Aβ and tau begin to buildup 15-20 years before the clinical onset of AD dementia. Increasing evidence suggests that preventing or decreasing the amount of aggregated forms of both Aβ and tau in the brain can serve as potential disease-modifying treatments for AD. To date, no cure or therapeutic intervention is available for AD that can slow disease progression.

Recent evidence in animal models of AD has suggested that delivery of monoclonal antibodies targeting Aβ and tau or use of inhibitors of T cell immune checkpoints (such as the PD-1 pathway) results in enhanced clearance of Aβ and tau and can lead to improved brain function. For example, PD-1 blockade evokes a systemic IFN-γ–dependent immune response that enables the mobilization of monocyte-derived macrophages into the brain. This PD-1 blockade treatment reduced the cerebral Aβ plaque load in two mouse models of AD in advanced stages of the disease[18]. Repeated treatment sessions were required for maintaining a long-lasting beneficial effect on disease pathology. Given that immune checkpoint blockade releases self-reactive T cells from immune tolerance mechanisms, these findings support a neuroprotective role for CNS-specific cell-mediated immunity. Notably, immune checkpoint blockade is not meant to target a single disease-causing etiologic factor in AD; rather, this approach is meant to augment the overall ability of the immune system to clear brain pathology. Of interest, anti–PD-1 and anti–PD-ligand antibodies were shown to be relatively safe and well tolerated in human subjects with cancer for which this therapy improved outcomes. These and other papers identify immune checkpoint blockade as a novel therapeutic strategy for AD and, potentially, for other neurodegenerative diseases.

Another potential mechanism to target AD involves development of vaccines against Aβ and tau[19]. This approach is supported by the presence of natural immunity against AD. Indeed, the positive results in the treatment of early AD obtained with the monoclonal antibody (mAb) aducanumab (Biogen), a replica of a protective antibody found in mentally competent elderly individuals that recognizes Aβ oligomers, confirms the existence of natural protective immunity. Evidence to support this approach has been strengthened by the results of administering solanezumab (Eli Lilly and Company) in human clinical trials; this humanized mAb that binds monomeric Aβ, has been reported to slow AD progression. While antibody or passive immunotherapy can be an effective treatment for AD, supply and cost could limit its availability to the public; hence vaccination may be a practical way to prevent or delay the onset of this disease. Development of a preventive AD vaccine is a practical alternative that still needs to be clinically tested.

3. **Childhood genetic diseases**: Our focus on developing cell, gene, and immune therapies for rare genetic illnesses that present at birth or in early childhood is warranted given the common referral of these complex patients to our medical center. Most of the children are diagnosed by a health care team involving pediatricians and medical geneticists with sophisticated testing performed by the Department of Medical and Molecular Genetics. These patients are often cared for by the Medical Genetics and Developmental Pediatrics clinics throughout their childhood with contributions made by other pediatric medical subspecialists as needed. As the lifespan of these children has increased through improvements in medical care, we are now seeing transitional clinics where the young adult patients are transitioned to medical internists and other specialists for their care as adult patients.

   Advances in the use of gene therapy where a correct copy of a specific gene is delivered via some form of viral vector into selected tissues, organs, or stem cell populations has shown great promise in numerous animal models of human disease and now in some human clinical trials. As an example, members of our pediatric faculty are leading a human clinical trial in which the normal variant of the mutant gene causing Fanconi anemia (a congenital disorder that causes bone marrow failure with predisposition to cancer development) in children will be delivered into mobilized bone marrow stem cells from the patient and after a short-term culture, will be reinfused into the patient. Studies performed by these faculty members has shown improved hematopoietic stem cell function after expression of the normal gene in these cells containing the mutant gene in animal models of the human disease and the animals do not develop bone marrow failure. This is but one example of the power of gene therapy as a tool to provide curative therapy to patients with monogenetic disorders. Improvements in genetic

diagnostics and prediction of functional consequences of the mutated proteins in cells, may help provide new gene therapy approaches that could be applied to overcome the mutant protein deficiencies that are altering cell functions in the patients.

Psychosocial issues related to gene, cell, and immune-based therapy: Development of novel gene, cell and immune therapies at IUSM offers patients in Indiana and beyond potentially curative treatment options for diseases that are currently incurable. However, the implementation and acceptance of these therapeutic approaches face significant psychosocial challenges that must be addressed. For example, these highly technical and complicated procedures must be explained to patients in a manner that takes into account an individual's physical, mental and spiritual well-being[20], if patients are to agree to undergo these therapies. Thus, new approaches must be developed to enhance the ability of patients to make informed decisions and that take into account the religious views and socioeconomic status of the patient if these new immunological therapies are to achieve their potential. Socioeconomic issues are important because these technologies are expensive. Thus, ethical and financial issues will also need to be addressed, if these therapies are going to be available to all patients in Indiana. Finally, training current and future physicians to effectively communicate the risks and benefits of these treatments to individual patients must include an understanding of the psychological, religious and ethical issues that can arise. Therefore, as part of the core curriculum for medical students on the Personalized Health Initiative, behavioral, educational and social science initiatives will be developed to facilitate successful implementation and dissemination of these novel therapies to patients in Indiana, as well as provide current and future physicians with the necessary skills to discuss these complex treatments with patients.

B. Recruitments of Research Faculty Leaders

Several key recruitments are required to accomplish the goals proposed for this program:

1. **Director of Human Immunology and Cell Immunotherapies.** Given the recent widespread interest in immunotherapy approaches to cancer, investigators with expertise in this area are highly competitive to recruit. We seek to recruit a physician scientist with basic and/or translational research interests in human immunology to direct this program. The Director will recruit up to 4 research faculty members; faculty members with expertise in human B, T, and dendritic cell development, novel vaccines, chimeric human antibody generation, novel methods for activating human immune subsets to promote enhanced target cell killing are areas of greatest interest and a technical director for the Human Immunology Phenotyping Core who can use the cellular time of flight mass spectrometer (CyTof) and state of the art flow cytometers and cell sorters in the Simon Cancer Center Shared Cell and Molecular Analysis Facility to identify and quantitate human immune cell subsets.
2. **Director of the cell GMP facility**. The Director will help build and manage the cell GMP facility. They will recruit technical personnel to handle cell processing, study coordination, quality assurance, regulatory affairs, patient recruitment, and data management; positions critical for effective facility use/approval.
3. **Director of the Viral Vector Core**. This NIH supported facility has been active in producing lentiviral vectors for human gene therapy for numerous human clinical trials throughout the country. The Director will manage the existing facility and recruit an additional scientist to continue to make advances in the ability to use novel viral vectors to target specific stem and progenitor cells in specific tissues and translate advances in gene therapy in animal models of human disease to pediatric and adult patients.
4. **Stem Cell Transplantation**. We seek a clinician scientist who performs hematopoietic stem cell transplantation and has an active translational or basic research program on stem cell biology. Experience in viral vector transduction of the hematopoietic stem cells for gene therapy, such as, for our planned clinical trial in patients with Fanconi anemia is preferred.

5. **Cell Transplantation**. We seek an expert in transplanting diverse immune cell types, such as, activated T cells and CAR T cells or dendritic cells and clinical management of patients undergoing these innovative cell transplants. Experience in the unique modes of cell infusion and specialized clinical support for selected disorders, such as, the cytokine storm induced by CAR T cells upon infusion, is preferred.

C. Research Infrastructure

Construction of a Cell GMP facility: Development of Cellular Immunotherapy approaches will build on the existing strengths of IUSM capable of construction of lentiviral vectors in the Indiana University Vector Production Facility that was established in 1995 by Ken Cornetta, and designated by NIH as the NIH/NCRR National Gene Vector Biorepository for the NCRR (www.ngvbcc.org) and the lentiviral production site for the NIH/NHLBI Gene Therapy Resources Program (www.gtrp.org). It has certified over 30 products for Phase I/II human clinical trials. Recruitment of an outstanding leader and an additional investigator for the further development and management of this Viral Vector facility is absolutely required.

Construction of a new Cell GMP facility is required. This facility will require a minimum of 3 ISO 7 clean room suites supported by dedicated space for cell and product cold storage, quality control testing, data management and storage, and quality assurance activities. The facility will also require office and conference room space for the personnel managing and performing the cell production. The facility (Director and support technical staff) and investigators in the Human Immunology and Cell Immunotherapy program (Director and 4 faculty investigators) and Viral Vector facility (Director and scientist) would permit and facilitate engagement in human clinical trials of cancer immunotherapies, stem cell gene therapy, and stem cell transplantation in patients with malignancies or genetic diseases for whom regenerative approaches are already under investigation or under consideration at IUSM.

D. Education Programs

To provide increased educational opportunities and access to the cell, gene, and immune therapies program for physicians, patients and students in Indiana, we propose a number of educational opportunities:

1. Develop a Precision Health Initiative that becomes part of the core curriculum of all first year medical students (MS) in all campuses. We envision this curriculum to be taught by faculty members participating in each of the pillars of the present Precision Medicine Grand Challenge. This course would serve as an introduction to all the MS to fundamental principles of precision medicine and applications to case studies focusing on the primary thematic areas of Neuroscience, Cancer, and Cell, Gene, and Immune therapies. The MS could develop tools for presenting these concepts to be used to educate high school students (below) and as continuing medical education courses for practicing physicians; physicians throughout the entire state can be reached by the MS from the various IUSM regional campuses and the main Indianapolis campus. In many cases, the MS could use these opportunities for conducting research projects to find the best modes for educating these diverse audiences. MS students may also reach out to nursing, dental, and other allied health professional students to present these topics to diverse audiences (high school students, nurses, and practicing physicians and to conduct educational research projects. Costs for preparing the educational materials and teaching the core curriculum are included in the budget.
2. Expand the Molecular Medicine in Action (MMIA) program successfully hosted for 17 years by the Wells Center for Pediatric Research in which 1 high school student from every county in Indiana is selected by a committee of Indiana High School science teachers to attend a 2 day seminar in Indianapolis. This is a hands-on program for high school sophomore, junior and senior students to experience the methods scientists use in unlocking and deciphering the molecular,

cellular and genetic basis of diseases and processes such as cancer, diabetes, and use of stem cells for cell therapy. We would provide these students instruction and case studies in our Precision Health Initiative and reach out to every high school represented by MMIA students to allow visitation by medical students, scientists, and educators to reach out to all high school students.

3. Provide summer research programs for high school and college students to conduct research in cell, gene, and immune therapies. A highly successful high school program in cancer research and several research programs for college and medical students are held each year at IUSM and could be expanded to the Bloomington campus.
4. The program in Human Immunology and Cell Immunotherapies could collaborate with basic science departments to write several training grants in Cancer Immunotherapy and/or Human Immunology.
5. We anticipate developing certificate conferring programs to educate and qualify high school graduates for training in various technical positions in the various expertise required for cell GMP facility management that includes cell processing, study coordination, quality assurance, regulatory affairs, and data management.
6. Development of Master's degree completion for nurses who desire training as clinical research coordinators for cell based therapies is anticipated in coordination with the School of Nursing.
7. We anticipate developing continuing medical education (CME) activities for practicing physicians that would provide CME credit to become familiar with advances in cancer immunotherapies, stem cell gene therapy, regenerative medicine via use of cell, gene, and immunotherapies, and the use of 'omics' technologies to conduct precision analytics on patient's suffering from illnesses amenable to cell, gene, and immune therapies.

VIII. Chemical Biology and Biotherapeutics

Overview: The challenge for Genomic Medicine, and genomics in general, is providing direct linkage between gene expression data (transcriptomics, epigenomics; ***Fig. 5***) and function or activity of proteins encoded by those genes. There is rarely a simple correlation between gene expression and protein activity since regulation of protein synthesis, degradation (turnover), and myriad post-translational modifications (PTMs) all impact the biological activity of a specific protein, thereby impacting all subsequent signaling processes or metabolic transformations that occur downstream. Consequently, *quantitative profiling* (chemical 'omics; ***Fig. 5***) of the cellular proteome as to expression levels and PTMs, and investigating how this profile changes in a specific disease state over time, or with a particular drug treatment, become key measurements for our ability to correlate perturbations in cellular function with changes in protein function. Furthermore, changes in protein function will nearly always be manifest in perturbations in metabolite levels, glycan profiles or lipid profiles. This cluster of the PHI will facilitate the acquisition of what are fundamentally orthogonal 'omics (profiling) data sets from patient cohorts, to be integrated and robustly analyzed by new informatics tools in service of the Genomic Medicine and Cell, Gene, and Immune Therapies clusters. These findings facilitate hypothesis-driven research into the cellular processes that are impacted by aberrations in gene expression or protein function to discover and validate new pathways or molecular targets that impact allele-specific disease states.

Goal: We propose to build an inter-campus Center for Chemical Biology and Biotherapeutics (C2B2) that integrates the precision medicine clinical cohort and basic chemical sciences to drive discovery of fundamental mechanisms that underlie patient-specific disease states. The appointment of 11 new tenure-line faculty (5 at IUSM; 6 at IUB), including the C2B2 Director, and the acquisition of state-of-the-art instrumentation and infrastructure are proposed to support two broad areas of chemical biology investigation: *1)* targeted discovery and development of novel small molecule therapeutics (ligands) that can be used to probe the impact of specific macromolecules to biological outcomes, as leads for future development[21] (***Fig. 5***; Ligand

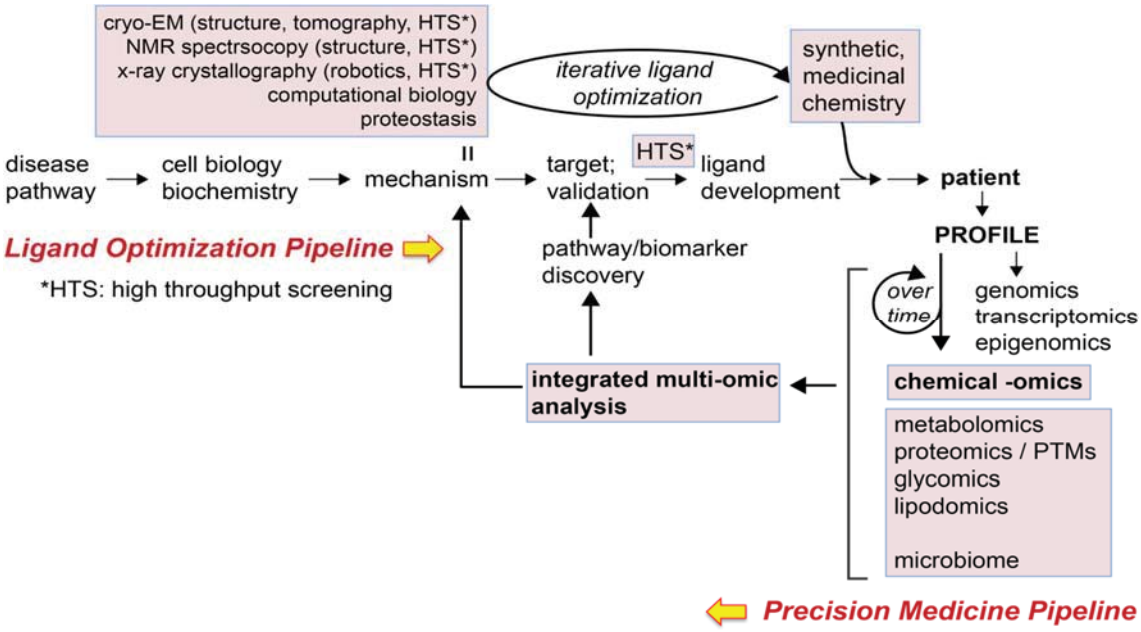


Fig. 5. **An integrated view of pathway, biomarker and therapeutics discovery organized under the C2B2 umbrella.** The more translational, ligand optimization pipeline will dominate IUSM activities, while the discovery science-based precision medicine pipeline (chemical –omics) activities will dominate IUB efforts. However, there are intentional synergies that further enhance vertical integration of the C2B2 within Indiana University.

Optimization Pipeline) and *2)* high throughput, untargeted molecular science to identify disease-relevant changes in protein expression and function sue to PTMs[22], and biochemical pathway flux[23], resulting in downstream changes in the metabolome[24], glycome[25], lipodome[26] and/or microbiome[27] (***Fig. 5***; Precision Medicine Pipeline). These new data acquisition capabilities and faculty expertise will be leveraged by enhanced, integrated multi-omics analysis capabilities[28] and faculty expertise to be added in Informatics and Computer Science on both campuses, as part of the Informatics cross-cutting activities of the Precision Health Initiative (PHI), with the goal to identify new molecular targets or pathways associated with a specific disease state.

These C2B2 efforts will be coordinated by the Indianapolis and Bloomington campuses by broad integration of translational applications (IUSM) and discovery science (IUB) on these campuses (***Fig. 5***), in a way that leverages existing local programmatic strengths and infrastructure, directed toward a common objective: *Development of human disease allele-specific ligands for use as molecular therapeutics and diagnostic agents.* A C2B2 Director will be recruited in year 1 and will oversee efforts on both campuses, while acting as a liaison between research groups within the Chemical Biology cluster, and the other PHI clusters, Genomic Medicine and Cell, Gene and Immune Therapies. Faculty hires and infrastructure proposed for each campus are complementary and designed to provide broad PHI programmatic support for themes in cancer biology and neurological dysfunction. Faculty hires can be grouped into five broad areas: *1) medicinal chemistry and small molecule discovery (IUSM, IUB); 2) membrane protein structural biology, cryo-electron microscopy, and computational biology (IUSM, IUB); 3) pathway and systems biology (IUB, IUSM); 4) neuroscience proteostasis (IUSM); 5) bioinformatics and genomics (IUB).*

1. Planned Faculty Recruitments

A. IU School of Medicine

C2B2 Director, medicinal chemist #1: This recruit is targeted as C2B2 Director and a chaired Full Professor. Two calendar months of salary are cost-shared with the IUB component of this Pillar. Strong chemistry training in discovery and development of novel molecules is essential, with application to probing pathways that underlie stem cell function and pathways for differentiation.

Biological areas of interest would be open to either the Cancer or Neuroscience Program areas, with thematic linkages to either the Genomic Medicine or the Cell, Gene and Immune Therapies Pillar, depending on expertise. Cross-cutting interactions with the *Informatics* group in pathway analyses and biological outcomes is envisioned.

Biology-focused medicinal chemist #2: This candidate's research area will focus on ligand optimization for the Cancer Thematic Program of IUSM. Specific expertise in structural methods, in particular high resolution cryo-electron microscopy (cryo-EM), for evaluation of drug/target interactions and ligand development[29] is desired, with target expertise relevant to the solid tumor or liquid tumor foci undergoing evaluation in the *Genomic Medicine Pillar* anticipated. Emphasis will be placed on an investigator focused on developing chemical tools to disrupt macromolecular machines[30] or assemblies of functional relevance to cancer. This hire leverages instrumentation and a proposed faculty hire at IUB.

Neuroscience proteostasis: This hire will be expert in the analysis and investigation of protein homeostasis, processes ranging from translational regulation to post-translational quality control and protein degradation. Areas of emphasis could also include autophagy and cellular senescence, and alterations in protein lifetime facilitated by small molecule intervention[31]. Linkage to, and leveraging of, strengths in Alzheimer's and Parkinson's Disease research is anticipated[32]. Genomic Medicine (Pillar 1), Informatics (cross-cutting theme) and stem-cell biology (Pillar 2*)* all interface well with this recruit.

In addition, we will recruit faculty to one of the following two areas after the above recruitments.

Pathway biochemist: Expertise in signaling pathway analysis is targeted with this appointment. Integration with the Genomic Medicine, Cell, Gene and Immune Therapies and the Informatics programs is anticipated. Hypothesis-driven research on pathway regulation will follow from analyses of genomics and targeted proteomics and post-translational modifications, *e.g*., phosphorylation and acetylation[33]. This recruit will complement the discovery-based untargeted approaches (***Fig. 5***) of the IUB C2B2 site for validation of genomic signatures on samples submitted by the Genomic Medicine Pillar, and will focus on mapping the regulation of clinically important pathways that drive phenotypic outcomes.

Chemo-proteomics: Expertise in the application of proteomic techniques to identify and validate cellular targets of chemical interventions is anticipated. In particular, this investigator will interface with the *Genomic Medicine Pillar* by utilizing cellular resources of the CRISPR/CAS9 core. High-throughput screening of compounds against such cell resources, followed by analysis of the targets whose activity is modified as a direct or indirect result of genomic modifications is anticipated.

B. IU Bloomington

Three faculty appointments are associated with the discovery science-oriented aspects of the Precision Medicine Pipeline, while three are more closely associated with the Ligand Optimization Pipeline of this pillar (**Fig. 5**).

Bioanalytical mass spectrometry/metabolomics (Chemistry): This candidate will possess expertise in metabolomics and ion mobility mass spectrometry[34], with leading-edge knowledge of glycomics, proteomics, and liquid/gas-phase separations. This investigator will provide programmatic expertise in disease models and chemical (onco)-'omics[35] to the PHI community, by interfacing with the Genomic Medicine and Cell, Gene, and Iummune Therapies clusters to obtain tissue samples. This individual will also interact closely with computer scientists (Informatics cross-cutting theme) to develop new algorithmic tools to analyze and integrate multi 'omics data to identify molecular signatures of a disease phenotype[24]. The hire will serve as the primary IUB liaison to the IUSM-based C2B2 Director and the IUB Laboratory for Biological Mass Spectrometry (LBMS) Director.

Single particle cryo-electron microscopy (Molecular and Cellular Biochemistry; MCB): This individual will be expert in the molecular basis of genome maintenance, deficiencies in which lead to both cancer predisposition and neurodegenerative disease. This hire will leverage existing

instrumentation (cryo-EM plus DE64 direct electron detector[36] to explore virtual drug screening in cancer biology[29], anti-virals[37], and immune therapy development against new targets for which structural information cannot be obtained by X-ray crystallography or NMR spectroscopy. This recruit is highly synergistic with IUSM recruit #2 who will use high-resolution single-particle cryo-EM analyses of chemical probes optimized to disrupt the function of macromolecular complexes. Interactions with Genomic Medicine and Cell, Gene and Immune Therapies Pillars are anticipated.
Chemical immunology and systems biology (Chemistry): This investigator will possess a strong immunology orientation, with expertise in the development of chemical biology approaches to investigate chemical communication between cells and/or between human immune cells and the microbiota[38], the latter of which impacts colorectal and stomach cancers. This candidate will undertake small molecule discovery and assessment of immune therapies during clinical treatment interventions. Strong interactions with Cell, Gene and Immune Therapies Pillar and the Informatics cross-cutting core are anticipated. This hire complements the metabolomics hire, and will make use of the same instrumentation in the LBMS.
Bioinformatics and genomics (Biology, Informatics): This investigator will focus on transcriptomic, proteomic and metabolomic analyses from human disease systems, with emphasis on cancer or neuroscience thematic program areas. Clear synergies with other hires at IUB and the IUSM in multi 'omics are anticipated. Application of evolutionary and natural selection models to cancer biology and understanding of cellular re-programming during oncogenesis and drug resistance in the context of molecular evolution are two areas of high interest. Clear synergies with *Genomic Medicine Pillar* and the *Informatics cross-cutting area* are expected.
Computational biology (Chemistry, Computer Science): Expertise in protein structural biology, molecular modeling and docking[39], and molecular dynamics, with a working knowledge of membrane protein simulation strategies desirable. This hire enhances the virtual drug screening expertise of the PHI group, and integrates well with informatics-originating projects focused on the molecular mechanisms of disease. *Genomic Medicine Pillar* and the *Informatics cross-cutting* areas are expected.
Membrane protein structural biology (MCB or Chemistry): This hire will possess expertise in solution-state[40] and/or solid-state biomolecular NMR spectroscopy[41], with the goal to develop programs in therapeutics discovery against membrane protein targets relevant to human neurological disease, *e.g.,* ion transport and signal transduction as well as neurological pathologies associated with protein misfolding, *e.g.,* Parkinson's[42] and Alzheimer's diseases (*Genomic Medicine Pillar*). This appointment is highly synergistic with recent hires at IUB in membrane protein proteostasis[43] and crystallography, and a proposed IUSM pillar hire in neuroscience proteostasis.

2. Thematic Coordination

The faculty and staff hiring priorities detailed for C2B2 are motivated to support and quickly exploit genomics and cell-based discoveries made in PHI Pillars 1 and 2. In particular, we will establish broad molecular-level and systems biology expertise in personnel and state-of-the-art instrumentation, most of which leverages prior support from external federal or foundation-based granting mechanisms. An overriding objective is to unambiguously link changes in protein expression and post-translational modification status to clinical phenotypes in patient cohorts selected for study. Implicit in this approach is that these perturbations in the proteome derive from functional perturbations and downstream changes in metabolite levels and flux (soluble or lipid-based). Consequently, we propose to significantly expand expertise in proteomics, metabolomics, lipidomics, and glycomics to create a cutting-edge Center capable of leveraging any potentially clinically-relevant finding from Pillars 1 and 2 toward patient cohort-specific ligand optimization and diagnostics/therapeutics discovery (***Fig. 5***).

Hiring priorities in IUB largely focus on the expansion of capabilities in broad discovery science to probe the changes in the complement of cellular components, as well as to support the informatics

analyses that come from the unbiased (untargeted) approaches implicit in the initial profiling studies. At the IUSM, the hires will follow on from those approaches to drive hypothesis-driven exploration of the 'omics findings and develop chemical tool-based approaches to interrogate the functions of macromolecular targets identified in the 'omics approaches (***Fig. 6***). The proposed purchase of the Maybridge Ro3 2500 and ChemBridge 60,000 Diversity Libraries, as well as potential access to Lilly compound libraries, followed by iterative ligand optimization of initial target hits, will facilitate this process (**Fig. 6**).

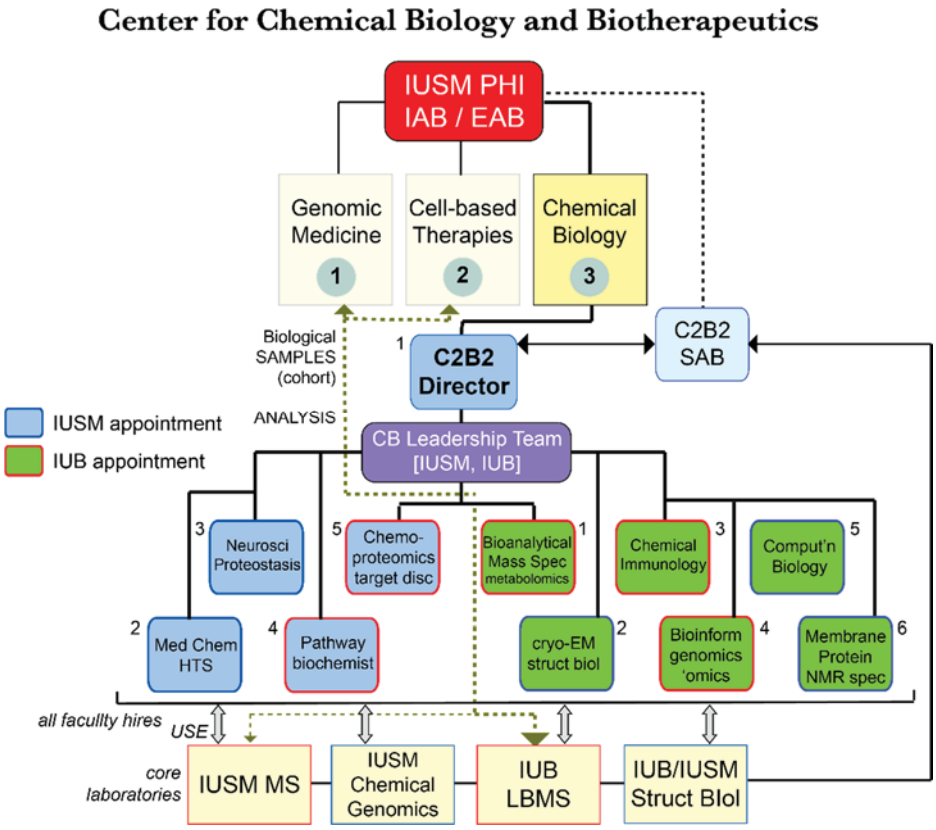


Fig. 6. **Proposed organization of the inter-campus Center for Chemical Biology and Biotherapeutics (C2B2).** The C2B2 Director will be administratively housed at IUSM in Indianapolis, who in consultation with the Chemical Biology (CB) Leadership Team comprised of Profs. Hurley and Giedroc, selected IUSM and IUB tenure-line and core directors (4 total), and an industrial partner (Jay McGill, Lilly), will oversee the development and day-to-day operation of the C2B2. IAB, EAB, SAB, internal, external and scientific advisory boards; LBMS, Laboratory for Biological Mass Spectrometry; MS, mass spectrometry. The numbers beside the tenure-line appointment descriptions are designated 1-6 as they appear in the text. 11 new faculty are proposed for appointment over the 5-year project period (5 IUSM; 6 IUB). *Blue outlined faculty boxes*, Ligand Optimization Pipeline components; *Red outlined faculty boxes*, Precision Medicine Pipeline components (see ***Fig. 5***). *Green dotted arrow*, indicative of iterative cycles of tissue sample data acquisition and analysis that connect the CB core laboratories to PHI Pillars 1 and 2 and ultimately, the patient cohort.

We note that both campuses propose to aggressively target hires in membrane protein structural biology and cryo-electron microscopy (cryo-EM). These are significant deficiencies in the overall research portfolio of Indiana University, given that a majority of existing therapeutics are known to target membrane proteins[44], while cryo-EM as a high resolution structural tool is literally transforming biomedical science[29]. New molecular insights into understanding mechanisms of cell proliferation and discovery of signaling pathways for cellular differentiation and neuronal dysfunction as programmatic areas of interest in PHI Pillars 1 and 2 become accessible with these appointments, while leveraging the impressive existing strengths in X-ray crystallography and NMR spectroscopy on both campuses. We anticipate that the success of both proposed IUSM and IUB cryo-EM hires and resulting synergies will catalyze a transformation of the cryo-EM capabilities within the OVPR-supported Electron Microscopy Center at IUB through extramural granting mechanisms near the end of the five-year project period. The C2B2 director – a year 1 hire – will oversee all research core laboratories associated with C2B2 at IUSM, and will coordinate research programs and establish thematic priorities in support of the broad goals of this Precision Health Initiative (***Fig. 6***). The

inter-campus financial support of the C2B2 director provides strong evidence of a commitment of both campuses to successfully further these goals.

3. Educational Elements

We envision our pillar education and training activities on at least three levels: *1)* post-M.D. clinical training for current medical practitioners (continuing education) in collaboration with the *Genomic Medicine Pillar*; *2)* medical student training; and 3) graduate student training, as described below.

a. Continuing education for practicing physicians: The C2B2 proposes to develop training modules to include representative case studies of informed consent conversations that describe the importance of patient-derived biological samples to be analyzed by genomics, proteomics and metabolomics technologies. These materials will emphasize the privacy and ethical aspects of personal medical data, its uses and provisions. The basics of the science underlying the analyses and the conceptual framework for precision health and treatment design and optimization will be discussed. Patient populations who are recruited into a specific cohort will also be educated on these important issues.

b. Medical student education: The C2B2 will provide enhanced opportunities to MS1-MS4 students to participate in translational and basic science-oriented research programs related to the Precision Health Initiative. This links to a key goal for the School of Medicine and the LCME, which is to expand summer research opportunities and senior elective programs so as to increase the percentage of our medical student trainee population that is exposed to biomedical research. Mentored PHI-related research activities at both IUSM and IUB will be made available. Educational objectives will be coordinated with the post-degree programs outlined above to improve the ability of our graduating medical students to communicate to their patients the underlying elements and potential promise of precision medicine-based treatment regimens to substantially alter clinical outcomes.

c. Graduate student education: The C2B2 will become the administrative home of one or several graduate student training programs designed to resonate with specific NIH-sponsored Biomedical Workforce Training (T32) programs, to be developed in way that leverages current CTSI-supported educational and training activities. We propose that graduate students in C2B2-associated laboratories (***Fig. 6***), along with others committed to Chemical Biology Pillar-related chemistry and School of Informatics and Computing projects in multi-‘omics and mutational analysis projects, be organized as a student cohort, characterized by a common pedagogical institutional experience within a traditional Ph.D. granting degree program. This will be leveraged as institutional commitment to develop a new graduate training program in Quantitative Oncology or Computational Biology of Precision Medicine that complements an existing NIH-supported Training Program in Quantitative and Chemical Biology (QCB) at IUB (T32 Chemical-Biology Interface program). This student cohort can be extended to postdoctoral scientists in PHI-oriented laboratories so as to build critical mass quickly. Alternatively, the existing QCB training program could be recast to include students at both IUB and IUSM, with full integration of the Molecular Therapeutics Program and all associated ligand optimization and precision medicine pipeline activities on both campuses (see ***Fig. 5***), including the Lilly academic-industrial collaborative already in place at IUSM. These training options will be fully vetted by the C2B2 and PHI IAB.

IX. Data and Informatics Sciences

Overview

The age of precision health (PH) has arrived. We can now sequence a person's genome, repeatedly interrogate his/her proteomic profiles, access medical record data, and monitor his/her physical and social activities using biometric technologies, smartphones, or wearable devices. This allows us to tailor health and healthcare decisions with increasing precision to individual patients, and to significantly improve the quality of life for millions of people. In addition to direct biomedical interventions, precision health faces challenges storing, analyzing, and securing large amounts of

heterogeneous data and is therefore also an **informatics challenge**. This section addresses three primary informatics challenges in the PH initiative:

- Scaling computing infrastructure to meet the needs for millions of patients. The new computing infrastructure will enable communication among patients, physicians, and the health care system; it will address the research needs for various disease and therapy conditions, as well as meet the analytics, storage, and security needs for integrated health and molecular data.
- Development of knowledge-discovery methodologies, collaborative research projects, and novel informatics tools for understanding: molecular mechanisms of disease, drug target and drug selection, omics data analysis and interpretation, clinical phenotyping of patients, and clinical decision systems.
- Training the next generation of experts through the biomedical informatics educational program. Next-generation informaticians will be broadly trained in a collaborative research-heavy environment that addresses the needs in both precision health research and clinical practice.

Our precision health informatics team spans two campuses and incorporates the faculty from the Center for Computational Biology and Bioinformatics (CCBB; IUSM), Center for Biomedical Informatics (CBMI; Regenstrief), School of Informatics and Computing in Bloomington (SOIC-B), and School of Informatics and Computing in Indianapolis (SOIC-I).

Long-term Goals

To establish and maintain cutting-edge precision health research and patient care, the informatics team will work closely with researchers across the entire range of the PH grand challenge. The main goals of the informatics team consist of initiating and supporting new research projects, developing new computing tools and methods for rapid deployment in clinical practice, hiring world-class faculty at Indiana University, and establishing educational initiatives that will not only support the initiative but also ensure broader impact in the State of Indiana and beyond. More specifically, the informatics team will:

- **Lead and support knowledge discovery and innovative clinical informatics implementations in precision health.** A rigorous, collaborative, and focused basic and translational informatics research program will support rapid discovery and innovation. This initiative will build upon bioinformatics, biomedical informatics, health informatics, and other computing fields to accelerate advances in genomic medicine, cell and gene therapy, and chemical biology and therapeutics.
- **Support knowledge integration and informatics workflows and data analytics.** Reaping the benefits of precision medicine research requires deployment in daily clinical care. We will work with our clinical partners to integrate high-quality PH evidence and knowledge into the clinical workflow, and create a feedback loop from clinical practice back to the basic and translational research.
- **Develop and support bio- and medical-informatics Ph.D. program.** A dual-track biomedical informatics graduate program (both bio- and biomedical informatics) will help create much-needed manpower for PH, both at IU and in the State of Indiana. The program will prepare graduates to become research faculty in translational and clinical research informatics, and biomedical data science; lead clinical informaticians and data scientists in health research and healthcare organizations, and lead bioinformaticians and data analysts in the biotech and pharmaceutical industry.

A. Proposed research and its impact

1. **Use Case Projects:** The link between informatics and the other pillars of the Precision Health Grand Challenge shall be initiated by the following projects (six use cases)
   a. **Cancer Precision Medicine Cohort** contains about 500 patients, and its patient number is growing. Currently, these cancer patients have genetic data on about 400 genes. These data need to be integrated with clinical data from medical record systems.

b. **Indianapolis Ibadan Dementia Study** contains 1178 African American individuals with genome-wide SNP array data. These genomics data will be further integrated with clinical data from medical record systems.

c. **Indiana Biobank** contains about 24000 blood samples. We have budgeted to sequence more than 2000 individuals in this proposal and are planning to further consent many of these individuals to acquire lifestyle data through wearable devices. These genomics and lifestyle data will be subsequently integrated with clinical data from medical record systems.

d. **Pharmacogenomics Randomized Trial** compares the adverse drug events and their associated hospital cost between 2000 patients receiving genetics-guided therapies and another 2000 patients who are not. Their genetics data will be integrated with clinical data from medical record systems.

e. **Precision Health Cohort:** The IU Network Science Institute led by Dr. Pescosolido will recruit a cohort of 4000 individuals to evaluate the influence of geographic, socioeconomic and physiological factors related to morbidity, utilization, and outcomes of the PH initiative. This cohort will provide unique data necessary for understanding psychosocial factors in PH.

f. **Cancer Tumor Samples** are available from 8 metastatic cancer tumor types and 12 primary tumor samples. This sample set will significantly grow with the accumulation of precision medicine cancer samples. Genome, transcriptome, and epigenome profiles are available for these tumor samples. Additional metabolomics and proteomics will be conducted in the Chemical Biology Pillar.

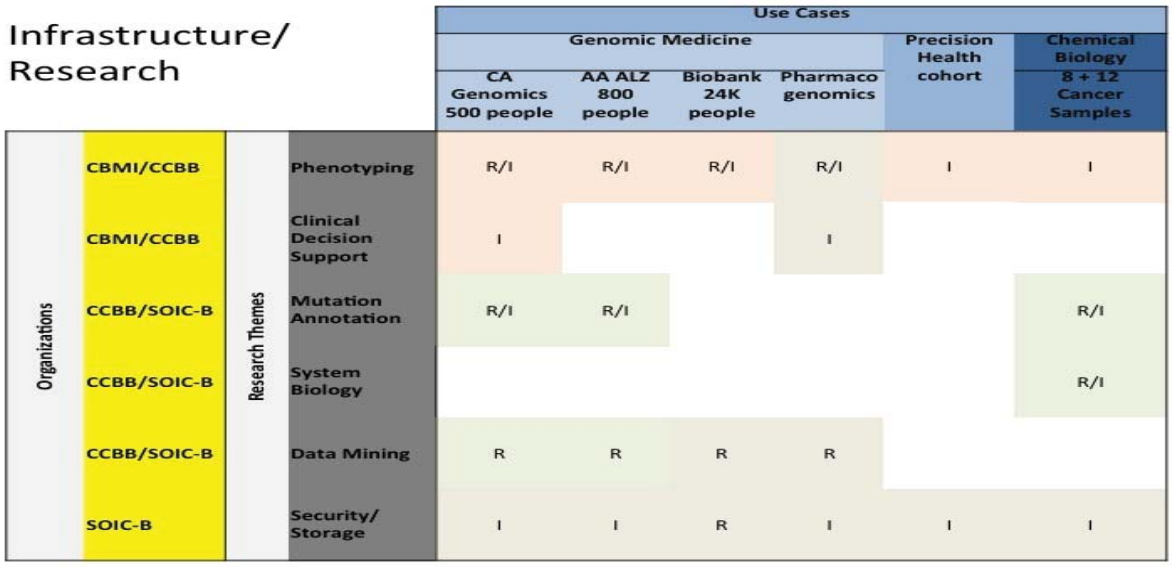


Figure 7: Informatics Research and Infrastructure Plan: Cross-Cutting Themes and Use Cases. Center for Computational Biology and Bioinformatics (CCBB), Center for Biomedical Informatics (CBMI), and School of Informatics and Computing in Bloomington (SOIC-B). "R" stands for research activities and "I" stands for the infrastructure development.

2. Themes for Research and Infrastructure Development

Advanced Phenotyping for Precision Health. Phenotyping refers to the characterization of a population of interest based on clinical, behavioral, social, economic, or other non-genotypic features. Recently, in the realm of research using electronic medical records, phenotypes imply a well-specified characterization of a patient cohort of interest (e.g., patients with a particular disease or having received a particular treatment) using explicit concepts such diagnostic codes,

medications codes, laboratory values, or other standardized data. Over the past five years, clinical phenotyping has evolved in two important ways. First, there is now wide recognition that a given clinical entity may be defined in a number of ways, and the choice of definition greatly impacts a study's outcome. For example, one definition for Congestive Heart Failure (CHF) may be highly specific while another is highly sensitive—both are valid but the choice of which to use for a given project will depend on study objectives. The other major change is the evolution of *deep phenotyping*, which reflects the rapid growth in diversity of data types (e.g., sensor data) as well as machine learning techniques that can cluster patients into a common phenotype that may not map to a known clinical entity (e.g., diabetes) but nonetheless represents a meaningful set of patient characteristics in relation to, for example, responsiveness to treatment or other clinical outcome. The phenotyping will benefit all use cases in the precision health grand challenge. Drs. Duke and Grannis from CBMI propose phenotyping infrastructure for a large research initiative support (1) storage of phenotypes in a standard syntax; (2) evaluation and documentation of phenotype performance (e.g., precision and recall on a particular dataset); (3) versioning of phenotype definitions to track changes over time; (4) a mechanism for sharing phenotypes across projects and investigators; and (5) a system for tracking which phenotypes were tracked on which projects to maximize transparency and reproducibility of research.

Clinical Decision Support. Precision health will soon exceed human cognitive capacity by orders of magnitude, removing any doubt that health care's future is entwined with computers and software. The great majority of Indiana clinicians currently use electronic health records (EHRs) in their clinical practice. Leveraging EHRs with integrated clinical decision support (CDS) will be vital to achieving important goals of this proposal, including the creation of a Precision Health cohort, expanding the Biobank with subjects who meet particular study criteria, creating a research pipeline to medical providers across Indiana, and catalyzing highly competitive precision medicine research. We propose to build an overarching, reusable precision medicine CDS framework, capable of integrating with Indiana EHR systems (including patient portals) and alerting both providers and patients to relevant research studies. We seek to create a precision medicine CDS system that can be trivially configured for an individual research project, helping IU researchers meet their study recruitment goals and consequently compete for national funding opportunities. Given that CDS support for precision medicine is universally at a very early stage, we anticipate that creation of such a framework will very much push the limits of existing EHR functionality, and consequently present multiple Informatics research opportunities. We also anticipate great value to building CDS capacity to deliver clinical recommendations based on a patient's "omics" and related clinical data, capture provider or patient input that clarifies eligibility for a particular study, transmit alerts to research assistants, and potentially randomize patients. To ensure maximal alignment with the needs of these future precision medicine researchers, we will restrict all CDS development to only those efforts that further the goals of active precision medicine projects. For these same purposes of alignment, Drs. Barnett and Dexter from CBMI will act as "embedded Informatics partners" to identify opportunities for Informatics to assist research groups achieve their goals, coordinate all CDS development efforts through IU/IUH's joint existing Clinical Research Informatics committee, initially focus on the IUH system where a majority of IU investigators conduct their research, develop a CDS strategy that maximally leverages existing EHR CDS systems (e.g., Cerner PowerTrials at IUH), and develop methods to ensure EHR CDS logic can access all clinical and research patient-specific "omics" data. At all points in the development process, we will seek to develop CDS-related policies and methods that will ultimately allow for expansion of research activities beyond the IU Health network. On the Bloomington campus, Drs. Natarajan and White will provide leadership in developing advanced machine learning methodologies for rigorously exploiting multiple modes of data in order to create user-friendly and interactive clinical decision support systems. Drs. Connelly and Siek will lead the collection and analysis of lifestyle data from wearable devices.

Functional Annotation of Mutations. People's genomes differ at millions of sites; interpreting how this variation affects phenotypes and disease risk is extremely challenging. Given the increased capacity for identifying genetic variants using high-throughput sequencing technology, a lack of computational and experimental approaches in interpreting genetic variation data is already a bottleneck in Precision Health. While Dr. Li is organizing the existing functional mutation annotation pipelines to fill the needs of precision health; Dr. Liu from CCBB and Dr. Radivojac and Hahn from SOIC-B will lead all initiatives focusing on novel genome interpretation.

a. **Coding and Noncoding Variant Function Prediction:** Dr. Radivojac's lab has a long-standing interest in understanding the function of biological macromolecules and how they impact organismal phenotypes. Dr. Liu's lab, on the other hand, focuses on variant functions that controls gene expression and splicing. They will initiate large-scale computationally driven approaches towards understanding specific molecular mechanisms consequent to genetic variation. They will work with the Chemical Biology pillar (Dr. Dann, Dr. Giedroc at IUB Chemistry) on approaches to experimentally validate and then treat the offending mechanism either by drug re-purposing or the development of new molecules through *in vitro* and/or *in vivo* (long-term, mostly federally-funded) techniques.
b. **Genetic Basis of Mutation Rate Variation:** *De novo* mutations passed from parents to offspring are the source of hereditary diseases, while somatic mutations occurring during an individual's lifetime are the cause of cancer. This project will use multiple non-human primate species as models for the study of variation in the mutation rate; these species differ in their generation times and the time spent pre-puberty and will be used because similar studies are extremely challenging and expensive to conduct on humans. Dr. Hahn's team will conduct whole-genome sequence multiple multi-generation families within each species to identify de novo mutations among the offspring, and whether they are of paternal or maternal origin. Dr. Hahn and Dr. Radivojac will be able to create novel predictive models of how mutations accumulate with age, and how this accumulation is affected by the length of the non-reproductive (pre-puberty) period. Such a model can be used to provide patients with improved information about the risks of genetic disease in their children. We will apply our computational algorithms to all use cases in this grant challenge, and demonstrate the utilities of our mutation accumulation prediction.
c. **Genetic Basis of Mutation Rate Variation:** *De novo* mutations passed from parents to offspring are the source of hereditary diseases, while somatic mutations occurring during an individual's lifetime are the cause of cancer. This project will use multiple non-human primate species as models for the study of variation in the mutation rate; these species differ in their generation times and the time spent pre-puberty and will be used because similar studies are extremely challenging and expensive to conduct on humans. Dr. Hahn's team will conduct whole-genome sequence multiple multi-generation families within each species to identify *de novo* mutations among the offspring, and whether they are of paternal or maternal origin. Dr. Hahn and Dr. Radivojac will be able to create novel predictive models of how mutations accumulate with age, and how this accumulation is affected by the length of the non-reproductive (pre-puberty) period. Such a model can be used to provide patients with improved information about the risks of genetic disease in their children. We will apply our computational algorithms to all use cases in this grant challenge, and demonstrate the utilities of our mutation accumulation prediction.

Systems Biology and System Pharmacology. Complex diseases have more than one molecular mechanism. This heterogeneity exists not only in a disease population, but also in a single patient. Using omics data, the heterogeneous disease mechanisms can be characterized at the system level, i.e. "systems biology." This systems biology theme has an enormous impact on genomic medicine, cell and gene therapy, and chemical biology components. Dr. Li from CCBB and Dr. Radivojac from SOIC-B will integrate both commercial databases and public-domain resources in molecular pathway, drugs, and drug targets. They will also assemble public-domain omics data for

data integration and computational model development. The following are two proposed innovative projects:

a. **Cancer Systems Pharmacology for Single Drug and Drug Combinatory Effect Predictions:** Tumor heterogeneity is the primary reason that a single drug is often not sufficient for cancer therapies. Dr. Li's lab will develop systems pharmacology models to predict single drug and drug combinatory effects. These models shall translate the cancer cell drug responses to the patients. (1) A novel gene regulatory network model is constructed under the statistical causal inference framework. This model will be used to identify common drug targets among a particular cancer patient population. (2) A translational model is under development to match the tumor with the cell lines. It is a combination of network models and bi-clustering. (3) An essential network model is being developed to capture the network topology to predict the single drug and drug combinatory effect.
b. **Integrative Multi-Omics Analysis in Cancer Genomics:** In addition to the typical omics data that will be collected by the PHI, IU Bloomington's Department of Chemistry has planned to expand on proteomic and glycomic data generation from these patients. Because of these mass and heterogeneous omics data, sophisticated computational methods are required to novel drug target and pathway identifications. SOIC-B faculty Drs. Sahinalp, Tang, Ye, and Radivojac will develop a suite of tools: (1) characterizing gene fusion events and other aberrant structural variants from cancer genomic and/or transcriptomic sequencing data, and validating these findings using proteomic data; (2) detecting heterogeneity and clonality from time series tumor genomic sequence using the single-cell sequencing data; (3) identifying and quantifying protein signatures associated with complex disease, in particular for the signature of structural variants and post-translational modifications (e.g. glycosylation); (4) identifying microbiome-associated features associated with complex disease through the comparative studies of metagenomic, metatranscriptomic and/or metaproteomic data, acquired from the microbiome of disease patients and control individuals; and (5) identifying and quantifying metabolomic features associated with complex disease by using metabolomic data acquired from disease patients, and associate these features with genomic and/or transcriptomic signatures. This well aligned with the omics data acquisition planned by IUB Chemistry and IUSM within the scope of the proposal.

Integrated Health Record/Omics Data Mining and Literature Based Discovery are the primary challenge when precision health data are collected and integrated. Selecting the significant genomic and clinical predictors is the key step to translate them to their clinical utilities, or validate them in biological experiments. All CCBB, CBMI, SOIC-B, and SOIC-I will dedicate significant amount of effort to address this research theme. This research theme will impact almost all of the disease and therapeutics areas. The following are seed research projects:

a. **Drug Interaction and Pharmacogenomics on Adverse Drug Events (ADEs):** This project will establish a hypothesis generation link between drug-interaction induced ADEs and pharmacogenetics research. Dr. Li and Dr. Duke's labs will collaborate on this project. Dr. Li's lab will be responsible for developing statistics tools to mine the drug interaction signals from medical record databases, assess these drug interaction signals' molecular mechanisms, and generate and test pharmacogenetics hypotheses using the Indiana Biobank data. Dr. Duke's lab will prepare and generate deep phenotypes for the patients. These phenotypes include adverse drug events and disease morbidity. This project will use Biobank samples for generating and validating genetics and drug interaction hypothesis.
b. **Combinatory Drug Safety Evidence Discovery from the Literature:** To move the drug combinatory therapy from preclinical to clinical, one of the primary challenges is the lack of

the drug safety data for drug combinations. Dr. Li and Dr. Palakal's lab will collaborate on literature based drug safety discovery project. (1) Dr. Li's lab will develop corpus for drug combinatory safety studies; i.e., manually curated golden standard abstracts on drug interaction safety data from the PubMed. (2) Dr. Palakal's lab will develop a text-mining tool to automatically extract the drug interaction safety information from the literature. The data generated from this project will help precision medicine clinical trial.

Advanced Mining of Electronic Medical Records Using Statistical Relational Learning: Our grand vision is to use our research in statistical artificial intelligence to build clinical decision support systems. There are two key research questions for the clinical decision support system a team lead by Drs. Natarajan and White of SOIC-B propose: (1) To investigate the presentation of knowledge to the clinician (say, at a point of care), we need to consider what the algorithms can effectively learn as well as what would be useful to the clinician. (2) The second key challenge is what can we learn from this high-dimensional medical record data? We propose to use reinforcement learning algorithms to learn policies using clinical decision-making data, and directly learn a policy mapping attribute information to a distribution over actions. Our goal is to develop robust and interpretable learning algorithms and to provide trustworthy support and understandable decisions. Furthermore, as the projects progress, several research groups will collaborate to develop and characterize algorithms that can learn and reason from clinical, genomic, and lifestyle data combined.

Privacy, Security and High-Performance Computing

a. **Privacy-Preserving Computation Technologies:** High throughput data, such as next-generation sequencing (NGS), are critical for precision medicine. A practical hurdle for its management is the data privacy. Loss of privacy and anonymity in high throughput data reflects a realistic threat. Dr. Tang's lab has developed privacy-preserving techniques to analyze and share sensitive human genomic data without undermining the participants. He and Dr. Sahinalp will develop more efficient methods to achieve these goals, and also extend these techniques to the analysis and sharing of other types of biomedical data, such as imaging and omics data.
b. **Secure Data Storage and Computation:** All prominent computing organizations are having difficulty securing sensitive data (Apple, NSA, Sony, and etc.), and the health sector is no exception (Anthem, Virginia Department of Health, etc.). While fully homomorphic encryption and secure multi-party computation is promising in theory, it is far too inefficient handling precision medicine data. Dr. Myers' group will use the Secure eXtension SGX technology to develop a practical (parallelizable) security platform. All data will be encrypted using a form of encryption that is many orders of magnitude faster than those supported by fully homomorphic encryption. This research direction is composed of three stages: (1) Encrypt and store data; (2) Develop federated exchange and API-framework to allow computation; and (3) Extend the API-framework to support cloud computation.
c. **High-Performance Computing:** Drs. Fox and Lumsdaine are international leaders in high-performance computing and they propose to design and prototype the necessary hardware and software for the PHGC. They will be dtransited to UITS for production deployment and support. SOIC-B will build its software according to HPC-ABDS or the high performance computing (HPC) enhanced Apache Big Data Stack (ABDS) where we have identified over 350 software packages that have been systematized into 21 functional areas. Here we propose that SOIC-B resource team be funded to develop, test, and deploy the prototype PHGC-ABDS or the Apache Big Data Stack configured and enhanced to support the Grand Challenge. This will be performed on test clusters located in data center but managed by SOIC-B. It is composed of optimized data management system and a closely linked system for data analytics. Our particular tasks include: (1)

Managing and supporting research clusters; (2) Gathering requirements from IUSM and UITS; (3) Identifying key benchmarks (CREST, SOIC-B); (4) Modifying HPC technologies for PHGC-ABDS; (5) Designing data management component of PHGC-ABDS; (6) Software hardening for analytics invoked by PHGC-ABDS); (7) Integrating and testing PHGC-ABDS; (7) Transfer to UITS with evaluation and feedback.

B. Educational program

Develop a Biomedical Ph.D. Training Program

The mission of this Ph.D. program is to train next generation informaticians in academia as well as the health care, biotech, and pharmaceutical industries, who will go into precision health related research and service. The following are specific considerations:

1. **Program Scope:** This Ph.D. program will be developed in the Indiana University School of Medicine. It will be a Ph.D. program shared by all the basic science and clinical departments.
2. **Development Process:** We will construct a biomedical informatics curriculum, which will leverage existing informatics curriculum in the SIOC-I and IUSM. Then, the curriculum will be approved by the SIOC-I faculty, before it is submitted to the corresponding authority for accreditation. The following are specific considerations.
3. **Focus on the Novel Precision Health Science:** This program will take advantage of existing strength of CCBB and CBMI in the IUSM, such as genomic variant function prediction, system pharmacology, data mining, phenotyping, and clinical decision system. This program will also grow under the emerging new areas such as chemical informatics and immunology bioinformatics.
4. **Integration with Precision Medicine Clinical and Basic Science Research:** This program will fill the needs for the translational research in the precision medicine. In particularly, this program needs to support the bioinformatics expertise in precision medicine clinics and basic science research in the IUSM.

C. Resource and Infrastructure

Executing precision health methodologies depends on a number of novel approaches, and also novel infrastructures to collect, manage, and analyze large, heterogeneous, and rapidly changing data. This infrastructure must also allow researchers, care providers, and patients to interact with the data, and with each other, in novel ways. The infrastructure described here will be: (1) flexible to manage a wide array of data of many different formats described in different ways; (2) powerful and able to scale to manage large data sets and complex analyses; (3) accessible by investigators, care providers, and patients; (4) integrative to support broad new applications and uses as described in earlier sections. The informatics Infrastructure will have the following components:

1. **The Precision Health Data Commons.** Based on a high throughput spinning disk array, the data commons will be the infrastructure for collecting, describing, and managing data that are collected by PH activities, be they contributed by researchers, care providers, or patients. This will initially be scaled at 2 Petabytes, but as large data sets, particularly genomics, are increasingly acquired, it can grow to 20 Petabytes by Year 5. It will be able to store any data collected through the PHI program, and will support many data formats, such as structured data (in database platforms such as Oracle or MySQL), data such as genomics data collected and managed as files, and Big Data repositories such as Hadoop Distributed File Systems (HDFS). It will be architected as a Virtual Logical Data Warehouse that allows data to be brought in and described in their native format, with the ability to create additional descriptive layers and logical linkages amongst diverse data sets for integrated analyses. As a high throughput disk system, it will allow direct computation of large data, heterogeneous sets, HPC nodes, or via Hadoop connectors for Big Data Analytics. It can be isolated as a HIPAA-compliant data enclave, with fine grained authorization capabilities so that investigators can create patient cohort datasets in trusted environments. Included in this infrastructure will be

expert technical support to create databases and metadata, manage data and data security, and create virtual integrated data sets for research projects.

2. **The Precision Health Integration and Analytics Platform.** Composed of high capacity (256 Gigabit RAM) compute nodes and connected to the Data Commons at 40 Gigabits/second, this computational array will be the computational part of the secure PHI data commons. Beginning with 12 computational nodes in Year 1, it will expand 5-fold in subsequent years and incorporate larger memory (512 Gigabit or 1 Terabit) nodes for memory intensive applications such as genomics analysis, with some architectural features determined by the ABDS research of Drs. Fox and Lumsdaine by Program Year 5. This component of the infrastructure will also be responsible for data integration, that being the acquisition of data from instruments, public data sets such as The Cancer Genome Atlas (TCGA), patient registries, medical records data, biobank data, mobile health data, patient contributed data, and other data such as health geographics data as they become available. Integration and analytics support will provide data virtualization, data integration, and support the acquisition of data, creation of project specific data sets, and support for analytics, software applications, and workflows required for PHI research. It will also have connections to the IU Health electronic data warehouse and systems such as the OnCore Trials and Biobank management systems for recruitment, trials, and clinical decision support.
3. **Portals and Patient Engagement.** In part to support the Psycho-Social Core, but also to support portals (or integration with existing portals) for researchers, care providers, and patient engagement, the Infrastructure Program will support Web application developers to create means by which these communities can easily engage in the PHI program. This may include provisioning of patient data back to IU Health patient portals, collection of patient contributed data, and the ability of patients to engage more meaningfully in collection and validation of their data, participation in PH research or care, and more effective engagement with them regarding our research and care efforts.

X. Behavioral, Psychosocial and Ethics Cluster

Precision Health can only succeed with the active involvement of a wide swath of the population and with a research agenda that extends beyond biomedical science. First, precision health research depends on collecting biological samples and phenotypic information from thousands of people and following them for years. Thus, studies must involve and educate people from all walks of life, answer their questions and address their concerns respectfully, and engage them over the long term.[45] Second, personalized medicine will enable improved identification of people at risk for major disease and improved treatments for those already diagnosed. Researchers must find ways to inform individuals about their health and motivate them to engage in behaviors to reduce risks and improve self-management of illness.[46] Finally, precision medicine will only work if personal information is gathered, stored, and shared effectively with healthcare providers and researchers.[47] Electronic and personal health records must do this while also protecting confidentiality and allowing individuals to access and control their own health information.[48]

The Behavioral, psychosocial-ethics core (BPSE) will support the precision health cohorts and develop externally supported research in the following three areas: (1) optimizing communication, participant engagement, and ethical conduct of precision health research, (2) using precision medicine to influence individual behavior and improve prevention and treatment, and (3) designing electronic and personal health records to protect privacy and allow individual access and control.

A. Communication, Participant Engagement, and Research Ethics: Over the last 50 years, important questions in communication, patient engagement, and research ethics have arisen in longitudinal research involving biosamples. These include: how to educate potential participants and obtain ethically adequate informed consent; how to involve participants and communities in the

research project and use of data and results; and when to return potentially useful information.[45] Failing to address these issues has led to public outcry, legal disputes, and unnecessary barriers to research.[49] Best practices in many areas have developed, though important questions and debates persist.[50,51] The BPSE core will support the precision health cohorts by working with researchers to optimize communication, participant engagement, and ethical conduct.

Where open questions about appropriate conduct of research or communication exist, the BPSE core will conduct research including ethical analysis and empirical methods such as focus groups, randomized trials, and public deliberation exercises, as appropriate. This research will serve as the basis for external grant submissions to NIH PAs such as: *PA-14-276: Ethical, Legal, and Social Implications (ELSI) of Genomic Research (R01)* and *PA-11-180: Research on Ethical Issues in Biomedical, Social and Behavioral Research (R01)*. Successful research in the three areas of the PSE core (A-C) will support a competitive submission for *RFA-HG-12-005 Specialized Center of Excellence in ELSI Research (P50)* in 2020. Investigators from the IU Center for Bioethics (IUCB), the Bioethics and Subject Advocacy Program (BSAP) of the Indiana CTSI, and the IU School of Nursing will lead these projects. The IUCB and BSAP have extensive experience assisting and educating investigators and developing institutional policies regarding communication with and engagement of research participants, and in the ethical design of translational and longitudinal biosample research. Investigators in the IUCB have written prominently on ethical issues involved in informed consent, patient decision-making, and governance in precision health research[52,53] and have conducted funded empirical research on public opinion, risk communication, informed consent, and patient decision-making.

B. Personalized Behavioral Interventions: Because optimal health requires active engagement of patients and families, personalized behavior change strategies that are innovative, cost-effective, and work in tandem with precision medicine therapies are urgently needed.[54] Studies consistently show the greatest opportunity to improve health and reduce premature death is by addressing health behaviors, which account for nearly 50% of all deaths in the U.S.[55] For example, patients need help understanding and managing risks, managing medications and side effects, and families need education and assistance in managing caregiving roles and the impact of a loved one's illness on the family.

Personalized behavioral interventions mimic the natural process of individualized consultation that takes place during face-to-face health care encounters, but at significantly lower costs and with greater reach.[56] Interdisciplinary investigators from Nursing, Medicine, and the Humanities on the IUPUI and IUB campuses have a long history of developing such interventions to promote health behavior change to prevent, detect, and manage illness. These interventions are highly individualized and provide personalized (precision) messages and content specifically designed to meet the unique needs of each user. Work in this area will draw on existing IU institutes and centers with potential funding sources including the following: NIH PAR-16-095 Basic biopsychosocial mechanisms and processes in the management of chronic conditions (R21); NIH PA-16-073 Behavioral and integrative treatment development program (R34); NIH PA-16-146 (R01) and 147 (R21) Population health interventions: integrating individual and group level evidence (R01); NIH PAR-15-048 Systems science and health in behavioral and social sciences (R01); NIH PA-14-114 Behavioral interventions to address multiple chronic health conditions in primary care (R01); and NIH PA-14-344 (R01) and 343 (R21) Self-management for health in chronic conditions.

C. Precision Health Information: Precision health information such as genetic sequencing will be an increasingly important part of electronic and personal health records, for researchers and healthcare providers.[57,58] The storage and use of such data raises concerns about privacy and confidentiality and about patient consent and access to health information. These concerns are

intensified for the precision health cores by the plan to collect advanced phenotypic information, for instance through digital wearable devices. Many experts, including leadership at the Office of the National Coordinator (ONC) for Health Information Technology, argue that patients and research participants should have access to and at least some control over their health information.[48,59,60] At the same time, it is not clear how to provide such access and control, and relevant tools do not exist. Further, limiting access for healthcare providers or researchers to personal health information could hurt medical care and research. Patients and research participants must be educated about the content and uses of health information, and options for control must be carefully explained and offered.[61,62]

The BPSE core will support the precision health cohorts by working with investigators and leadership to explain precision health information to patients and to obtain consent to its storage and use. The BPSE core will also conduct research on how to best provide patients or research participants with opportunities to access such data. This research will build on previous collaboration between the Regenstrief Institute and the IU Center for Bioethics, including a recently completed project funded by the ONC.[63,64] Work in this area will build on expertise and previous research at the IU School of Nursing, as well as the Center for Legal, Ethical, and Applied Research in Health Information (CLEAR). Investigators will submit proposals in response to the RFAs listed in section A above, but also to relevant PAs and RFAs from the National Science Foundation, the ONC, and the Patient Centered Outcomes Research Institute (PCORI).

XI. Precision Health Initiative Cohorts

Indiana Cohort Enhancement Study (MPC-IC*):

Overview: The U.S. is well-known to be the global leader in advanced medical research. At the same time, health indicators such as infant mortality and life expectancy reveal the US to lag far behind other countries, even beyond the Nordic countries to others such as Singapore. Within the US, the health of the people of Indiana routinely hovers near the bottom of national rankings. Recognizing this, important arbiters of American science and medicine such as the National Academy of Medicine, the National Science Foundation, and the National Research Council have called for novel, transformative approaches to change this national profile. The IU GC program aims to address such challenges at the state, national and global levels and the Precision Health Initiative (PHI) takes on medical care, primarily. The aim of this part of the PHI is to increase the immediate and longer term impact of the critical research in the proposed PMI genomic components. It does so by connecting the genomic pillars to the community, including current patients, potential patients and medical providers across the State. The MPC-IC* will 1) Create Indiana as a living laboratory to synergize research from genes to global culture by leveraging data in the IUSM Biobank and Regenstreif's EHRs but increasing its utility by including social, cultural, economic and geographic factors; 2) Serve as a major feeder into the PHI data to increase the representation of individuals throughout the state of Indiana, particularly the areas of greatest deprivation and racial/ethnic diversity; 3) Create an efficient, translational pipeline to the community by leveraging the ties formed during the field study, 4) Provide educational opportunities for students, research faculty and clinicians to understand the impact of context on health, medical care experiences, and treatment outcomes. Specifically, the MPC-IC* aims to:

1. **Use a novel theoretical framework, developed by IU researchers, to design and mount the first of its kind genes-to-global cultures fieldstudy to create a dataset available to all IU scientists, making them uniquely advantaged to discovery and funding.**
   1a. Respond to the IOM's (now the NAM) call to integrate the insights of all sciences that contribute to understanding health by using a network-based vertical integration framework.

1b. Provide an extraordinary public good, the 4k Hoosiers Study, that will be made available to all IU researchers to explore within and across discipline insights on health, health problems, health care use/non-use, and health care outcomes.

2. **Build a translational pipeline into the IUSM's MPC initiative to provide a more representative biobank of genetic information, especially from underrepresented groups in the State.**
   2a. Develop a representative sampling strategy to collect data on the current state of health, health care use, and health care outcomes for Indiana.
   2b. To provide a recontact platform for follow-up, subgroup data collection efforts on research questions from ethics to informatics.
3. **Build a translational pipeline to the community by engaging the people of Indiana in research efforts designed to improve the transfer, utility and ethical implementation of PHI discoveries.**
   3a. Provide a continuing link between the PHI, Indiana residents and Indiana physicians to facilitate exchange of information, perspectives and needs.
   3b. Strengthen the contributions of all IU health-related research at IU through targeted hires to fill gaps in expertise in sociomedical areas and support those in the information sciences.
4. **Strengthen education at all levels (Society & Health Minors, graduate and undergraduate; MD/Phd Program, IUSM), by increasing range of research options through the 4k Hoosiers Study.**

A. Significance: There is a broad consensus, across the landscape of science, that the nature vs. nurture debate is obsolete. As a result, there is a *significant knowledge gap* on how different levels of the body and of the environment, whether social, economic, cultural, technical or chemical work with or against genetic inheritance to keep people healthy, make them sick, and have them respond positively to medical treatments. We know relatively little about these complexities, to date, though early work has been very promising. A novel transdisciplinary, network-based approach holds the potential to break through the barriers to understanding the onset of complex chronic disease, the unwillingness of the population to use the medical care services that are available, and how the conditions in the community foster or retard the ability of medical solutions to translate into positive outcomes. Without these kinds of data, and a whole range of scientists outside medicine working on such a complex problem, we lack the necessary scientific foundation to implement PHI discoveries. Addressing the tailoring challenge in the community is as complicated as tailoring treatment to the genomics of the tumor. Personalizing medical care by adding consideration of individual environments will amplify the potential of genomic medicine, and may well prevent community conditions from undermining them. Providing cutting edge environmental (geographic, social/cultural, psychological) input for the MPC-IC, rounding out biobank data to represent the State's population, adding oversamples of critical subpopulations (middle-aged/elderly; regions of poverty; underserved), and collecting biomarkers and imaging data on select subsamples will result in a unique, value-added opportunity to do cutting edge research and policy planning.

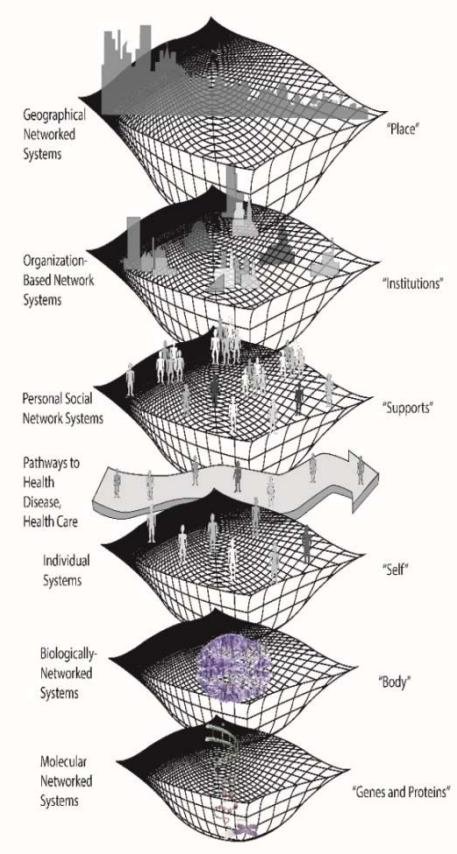
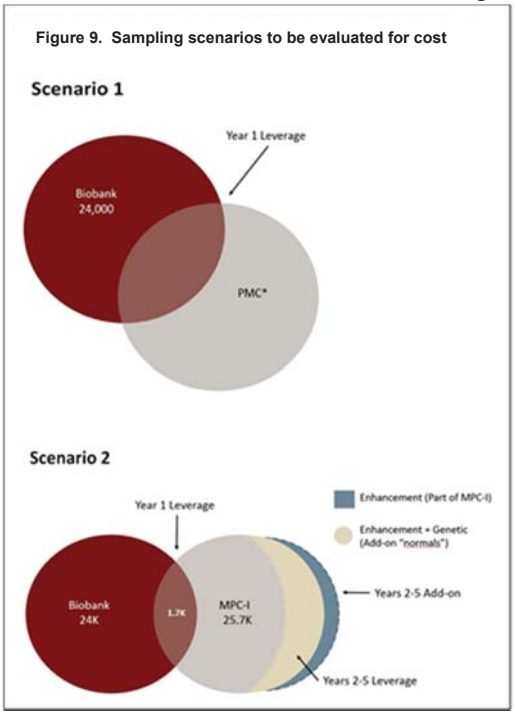


Figure 8. The Social Symbiome

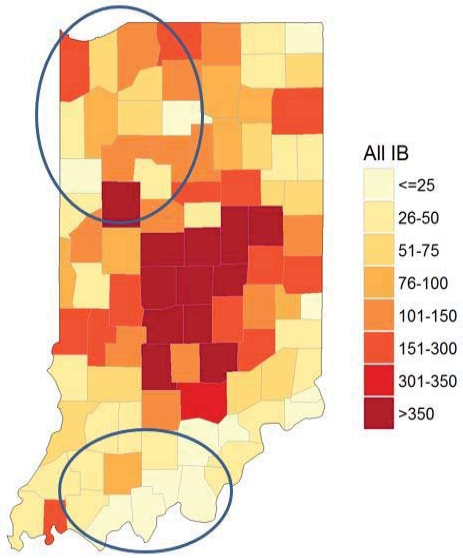
B. Innovation: The MPC-IC* Study is theoretically, methodologically, and analytically innovative. Arising, in part, from the successes and limitations of the Human Genome Project, axioms such as "helix to health," "bench to bedside", "neurons to neighborhoods," or "cells to society" have attempted to capture a new scientific vision that embraces the complexity challenge posed by complex diseases. The NIH, NSF, and the National Academies of Science, Medicine and Engineering have all concluded that we sit at a new, exciting and yet demanding crossroad. For example, recent research suggests that genetic risks are geo-located. That is, susceptibility to complex diseases, from cancer to Alzheimer's disease, result from a nonlinear interaction of genetic networks, age and environmental exposures. Theoretically, the approaches needed to cross into this new scientific vision represent a new generation of basic and translational science. Yet, as the IOM (2006) noted, existing frameworks fall far short because of the scores of influences that have been documented at each level. The Social Symbiome (Pescosolido et al. in press; Figure 8) provides one, innovative theoretical response by narrowing consideration to how network connections at each level operate. Based on three overarching principles – complexity, transdisciplinarity, and connectedness – it draws on an existing research base across the natural and biological sciences, a substantial history in social science and a more recent one in Network Science. Further, designing a fieldstudy to collect data to match the Social Symbiome requires a full complement of social, biological, informatics, medical and ethics scientists. By leveraging existing biobank data and working to enhance the Indiana component of the proposed Midwest Precision Cohort, the 4k Hoosiers data will be the first of its kind and unique among the PMC Initiaves or, in fact, any known data set on health and health care. Finally, analytically, these data will require new methods of data analysis to ascertain the effect of "networks of networks", among other complex statistical challenges. The innovations in the MPC-IC* will position IU researchers to apply for grant funding across a wide range of topics and from a wide range of sources because research questions and data can be focused on two levels or move beyond to three levels or more complicated nesting questions.



C. Theoretical Framework: The Social Symbiome offers a unifying mechanism of action — interactional dynamics shaped by network ties, structures, and processes. Health, disease and risk behaviors are conceptualized as a social process managed by social networks in the community and in treatment systems. Network ties serve as the mechanism linking influences within and across societal levels. At each level, a "safety net" tie structure exists with places of excess and deficiencies in connectedness and content. Poles indicate that extremes with under-production /absence represented by sparse network connections and over-production/presence by dense network connections. This safety net conceptualization (IOM 2002; Pescosolido 2011) allows us to move away from the tendency to think of social and biological structures as fixed or as having only linear effects. The Social Symbiome unites levels through network connections using Abbott's (2001) translation of mathematical fractal imagery for social structures and processes. The safety net is a complex but self-similar geometric shape repeated at many levels (i.e., fractal), with those in Figure 1 representing major units (Barabasi, 2009). The integration of those systems corresponds to layered networks, or "networks of networks", where each layer affects the processes occurring on other layers through feedback mechanisms and interlayer interactions.

Thus, most networked systems cannot be taken in isolation because they are mutually-contingent and reinforcing (Kivela et al. 2013). "Interdependency" is key to notions introduced by the Social Symbiome and levels represent the classic concept of *social embeddedness*, the degree to which actors (individuals or industries) are enmeshed in networks with variable structure and content (Granovetter 1983; Kawachi & Berkman 2001). Since individual's health and "illness careers" (the arrow, Figure 1) are highly social, research discussed above suggests that there are several networked social systems at work – geographic networked systems (i.e., "place" or physical location), organizational-based network systems (i.e., clinics, EHRs), personal social networks systems (or ego-centric ties), individuals risk factors (whether personality) or *biological embeddedness* (e.g., organ systems such as brain, protein-protein or genetic networks).

Figure 10. Heat Map of Sample Representation in the IUSM Biobank



D. Design: Ambitious recruitment of at least 4,000 Hoosier participants will use one of two strategies which will remain flexible until Pillar I is finalized and until the outcome of the MPC grant application is determined. As described earlier in this PHI application, IU led an NIH grant to develop the MPC, a 7-site, 8-state consortium recruiting 1,700 individuals in Indiana in Year 1 (leveraging the biobank) and 6,000 individuals/year in Years 2-5. In the event that MPC is ***not*** funded (Scenario 1, Figure 9), the MPC-IC* will evaluate 2 strategies and selection will be based on cost. The *first* strategy, will begin with existing data in the IUSM Biobank and the EHRs and develop a quota sampling procedure to bring the data to representativeness according to U.S. Census data. The *second* strategy will select a representative sample of Indiana residents and then go to the two existing data bases to search for individuals in the selected samples. In cases where data are existing, individuals will be recruited for a survey to provide additional social, demographic, socio-economic status, biomarkers (specifics in budget) and geographic data not found in existing data bases. In the likely event that MPC is funded, the strategy will be more complicated (Scenario 2, Figure 9). MPC-IC* will leverage from the 1,700 Indiana biobank cases in Year 1 using one of the two strategies from Scenario 1 to round out the sample. In Years 2-5, MPC-IC* will leverage from new MPC cases, similarly rounding out. Overall, these scenarios describe the most efficient way to leverage existing data but move to a sample of Indiana residents that represent the State's population as a whole. The MPC-IC* will include individuals who have a diagnosis but are not in treatment (i.e., those who have discontinued care, been denied care) and those who see themselves as healthy and not in need of treatment, whatever their health condition. Both of these groups are critical to understanding the how to improve the health of Hoosiers and the reach of current PM efforts. We will be able to understand pathways to health service utilization, adherence, and community-based outcomes that cannot be studied by only leveraging Biobank data since Biobank samples come exclusively from IU Health patients. In addition, given pockets of underserved populations throughout the State, we will oversample in two areas, the northwest corner (often referred to as The Region) and the southernmost counties as indicated in Figure 10, a "heatmap" (i.e., count) of the number of Biobank samples by county. In addition to opening up the data to researchers interested in these issues critical to health policy, selecting from these areas will provide more representative genetic data on Indiana residents.

Expertise, Data Collection and Analytic Strategy: The MPC-IC* will be conducted in close coordination with Pillar I leaders, particularly Dr. T. Foroud and include key faculty in epidemiology (Dr. Han, Dean, Fairbanks School of Public Health), health services research (Dr. B. Pescosolido, Medical Sociologist, Bloomington Campus and Co-Director, Indiana University Network Science Institute), ethics (Dr. P Schwartz, IUSM) and interventions (Dr. J. Carpenter, School of Nursing). In addition, relevant expertise from both Indianapolis and Bloomington campuses have been brought together to cover the key aspects of a genes-to-global cultures approach. They include, from the Indianapolis campus, Dr. Banerjee (Health Geography), Dr. L. Hulvershorn (Child & Adolescent Psychiatry), Dr. Sophia Wang (Geriatric Psychiatry), Dr. A. Saykin (Neurology, Alzheimer's Center), Dr. M. Salyers (Psychology), Dr. L.Shen (Computational Biology and Bioinformatics), and from the Bloomington Campus, Dr. B. Perry (Sociology), Dr. K. Simon (Health Economics, SPEA), Dr. B. D'Onofrio (Psychology & Brain Science), Dr. E. Pullen (IUNI), Dr. L. Rocha (Informatics & Computational Social Science), Dr. A. Krendl (Psychology & Brain Science), Dr. L. Rocha (Informatics), Dr. C. Taylor (Gender Studies & Sociology). Dr. W. Barnett will serve as the computational consultant. In addition, Dr. Irene Park, IUSM, South Bend will join the team. Dr. Virginia Caine, former president of the American Public Health Association and current Director, Marion Country Department of Health will serve as a major leader connecting these efforts to health departments statewide and Dr. Lee McKinley will serve as a major leader connecting these efforts to practicing primary care physicians in the State. Depending on the final choice of health conditions to be targeted in Pillar 1, additional expertise will be recruited as necessary.
Data collection will be guided by the recommended measurement tools in the PhenX Toolkit developed by the NIH's National Human Genome Research Institute. Each of the 27 domains contain 15 items or batteries. As a preliminary decision set, the team will review 6 health domains and 4 environmental domains as listed in Figure 11. Data collection will be done in face-to-face interviews, contracted through IU's Center for Survey research (budget estimate for interviews provided by the CSR).

Figure 11. NHGRI's PhenX Toolkit: Domains for Inclusion in MPC-IC* (in consultation with MPC investigators)

- Cancer
- Cardiovascular
- Diabetes
- Neurology
- Psychiatric
- Alcohol, tobacco, substance use
- Demographic
- Environmental exposure
- Psychosocial
- Social environment

To guide the analyses of data, we employ Network Science as our methodological base. Rooted in graph theory in mathematics and social network analysis in sociology, Network Science is a framework that allows transdisciplinary collaborations across diverse domains including biology, sociology, computer science, and public health (Albert & Barabasi 2002; Newman 2010). Shared methodologies and techniques in Network Science involve various centralities that identify key actors in the network (Wasserman & Faust 1994; Newman 2010), and community detection methods that identify social groups or functional modules from network topology (Fortunato 2010; Ahn, Bagrow, & Lehmann 2010). The team holds a great deal of analytic expertise in network methods but also in traditional statistical and advanced bioinformatics methods. All of these will be required to address the complexities of multi-level analyses using relational and standard individual data. To fill gaps in the theoretical, methodological/analytic and clinical application of the Social Symbiome and the living laboratory to improve the health of the residents of the State, we list the areas of expertise necessary. They are: organizational network scientists (2) for the EHRs component, a psychiatrist with expertise in health disparities among Hispanics and African Americans, a statistical sampling expert for the complex design that includes leveraging two different sources (particularly given the changing landscape of sample in the digital era), and a network community demographer to address the social network issues of areas. This component of the PHI will be physically located at IUNI, with its IT staff and UITS and CTSI collaboration, *however, given current success in securing funding for new, collaborative projects*, *there is insufficient space to house the project. The need for additional space is critical.*

XII. Personnel

The following faculty will be the key participants and members of the team that will execute the PHI programs detailed above. Details of their qualifications are provided in the attached biosketches.

Name	Role	Title
Anantha Shekhar, MD, PhD	Overall PI, Contact Person	Executive Associate Dean for Research, IUSM
Genomic Medicine		
Mark Geraci, MD	Team Co-Leader	Chair, Department of Medicine, IUSM
Tatiana Foroud, PhD	Team Co-Leader	Chair, Medical and Molecular Genetics, IUSM
Jamie Renbarger, MD	Key Team Member	Interim Director, Institute for Personalized Medicine
Bryan Schneider, MD	Key Team Member	Director, IU Health Precision Genomics Program
Cell, Gene and Immune Therapies		
Merv Yoder, MD, PhD	Team Co-Leader	Professor of Pediatrics, Director, Wells Center, IUSM
David Roodman, MD, PhD	Team Co-Leader	Chief, Division of Hematology Oncology, IUSM
Chemical Biology		
David Giedroc, PhD	Team Co-Leader	Professor, Department of Chemistry, IUB
Tom Hurley, PhD	Team Co-Leader	Interim Chair, Department of Biochemistry, IUSM
Jay McGill, PhD	Key Team Member	Senior Scientist, Eli Lilly & Co.
Data and Informatics		
Shaun Grannis, MD	Team Co-Leader	Professor, IUSM and IU School of Dentistry
Lang Li, PhD	Team Co-Leader	Director, CCBB, IUSM
Predrag Radivojac, PhD	Team Co-Leader	Informatics, IUB
William Barnett, PhD	Key Team member	CRIO, IUSM
Precision Medicine Cohort		
Janet Carpenter, PhD	Team Co-Leader	Associate Dean, Research, IU School of Nursing
Bernice Pescosolido, PhD	Team Co-Leader	Professor, Sociology, IUB
Peter Schwartz, MD	Key Team Member	Professor, Department of Medicine, IUSM
Jiali Han, PhD	Key Team Member	Professor, Fairbanks School of Public Health, IUPUI

XIII. Financial and Physical Resources

The initial resources to build the programs detailed above will come from the pooled Grand Challenge resources. As detailed in the accompanying budgets, IUSM plans to commit approximately $80 million over the next five years to this initiative. In addition, the Provost's office at IU Bloomington has committed 15 faculty lines and $20 M in cash to support the IUB components of this initiative. We are requesting that the President's Grand Challenge program provide an equivalent of 25 faculty line support (approximately $150K per slot/per year for 10 years) and cash resources to build out the informatics and high-end computational resources we need to successfully launch this scale of data science project. All of the itemized resources are fully detailed under the budget and its justification documents.

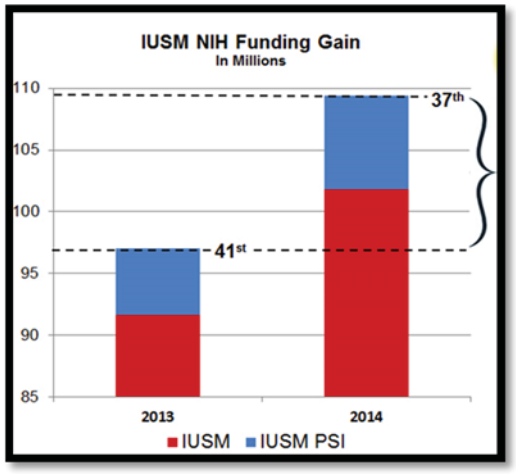
XIV. Management Plan

The full management plan for the PHI is detailed earlier in section IV under the **Administrative Core**. The PHI will have an administrative structure that has been highly effective in serving the mission of IU in similar initiatives such as the CTSI, Lilly Endowment funded Physician Scientists Initiative (PSI) or the IU Health funded Strategic Research Initiative (SRI). The overall management of PHI will be under the direction of Dr. Shekhar, who will be assisted by an **administration team** and a **Steering Committee** as detailed earlier in section IV, consisting of the leaders from the five PHI Clusters and Rick Van Kooten, PhD, the Vice Provost for Research at IU Bloomington. Robert Aull, MA, Director of Research Affairs Office, will assist in managing budgets,

grant accounts, program and pilot award accounts and will have general responsibility for all accounting and fiscal matters with partner institutions. Samantha Scahill, Administrative Manager, is responsible for the operations of the director's office, human resources functions of the PHI initiative, and planning PHI events and communications. Joe Hunt, MS, Evaluation and Metrics Specialist will be assisting the administrative team to make sure we collect accurate data and manage the initiative to deliver the expected results and make the right impact. Administrative Team will meet at IUSM biweekly for a 90 min administrative team meeting to discuss any operational issues of PHI, current recruitment activities of the cohort program, progress being made in the clusters, as well as strategic directions and tactical steps for operational success. The Implementation and strategic directions of the PHI will be enabled by a Steering Committee whose members include all the senior leaders representing the different components of the PHI proposal. The SC will review the overall progress of the PHI, plans for future recruitments and investments, and approve any major programmatic or funding initiatives. Funds will be approved by the SC similar to the 'council' model followed by NIH institutes. The meeting minutes will be recorded for each meeting. Additional oversight for the initiative will be provided by an **Internal Advisory Board** as well as an **External Advisory Board** as noted in section IV above.

XV. Sustainability

As is expected at the IUSM, all recruited faculty are supported at 100% for the first 3 years and are expected to require only 20% central support by the 5th year of their hiring. It is expected that these newly recruited faculty will join IU with significant extramural support and that additional support will derive from R01, P01 and U-based grant mechanisms as a result of new synergies catalyzed by this Initiative. The additional research staff scientists funded by PHI are expected to be supported by their PIs. The core staff will support their activities through extramural grant-support and/or through charge-back mechanisms from service activities for other funded work by the end of 5 years. The postdoctoral positions are seed positions strategically placed to generate preliminary data for new grant applications as part of a career development path for those individuals, and/or for use in existing or future granting mechanisms. This model of seeding exceptionally talented investigators with recruitment dollars and then expecting them to not only support themselves, but to also establish thriving programs is a well demonstrated model at IUSM. The most recent example of this approach is the Lilly Endowment funded $60 M Physician Scientist Initiative through which we recruited stellar, nationally recognized physician scientists from outstanding institutions like Stanford, Dartmouth, Emory, University of Colorado, University of Chicago, University of North Carolina, University of California at Los Angeles and University of Michigan who have substantially contributed to research funding growth at IUSM (see adjoining graph). PSI has also created many self-sustaining resources such as the Indiana Biobank.



Within the IUB component, faculty appointments will be pursued at all ranks, from new tenure-track Assistant Professors to mid-career Associate and Full Professors. Over the past six years, IUB Chemistry alone has hired ≈10 tenured or tenure-track faculty and research scientists (faculty or core directors) at all ranks, so the proposed hiring pace is possible. All recently hired biologically-oriented junior faculty have been remarkably successful, with one K99/R00 awardee, three 2016 NSF CAREER winners, one Cottrell Scholar, and one DoD Young Investigator Awardee. These honors are nearly always followed by significant support from the NIH, largely through the R01

mechanism. It is anticipated that this support will be enhanced by additional P01 and U-grant mechanism support as a result of collaborations made possible by the PHI and IUSM.

XVI. Partners

We have several corporate partners who are equally enthusiastic to join us and implement the precision health initiative. They all see the great value this will bring to their organization's missions, as well deliver benefit to the health of Indiana citizens and contribute to the economic success of the state. The following partners have joined us for specific components of PHI.

IU Health: IU Health is the largest health care provider in the state. This will be our statewide laboratory to implement the clinical programs proposed in the PHI as well as a vehicle for the cohort development and community outreach. We have included a support letter from Dennis Murphy, President and soon to be CEO of IU Health.

Eli Lilly and Company: Lilly is one of the top 10 big pharmaceutical industries in the world and has been a strong partner in multiple initiatives with IUSM. Within PHI, they are particularly excited to partner with us on genomic medicine and precision health cohort, as well as engaging in chemical biology programs. We have included a support letter from Dr. Andrew Dahlem, COO of Lilly Research Laboratories.

Roche Diagnostics: Roche Diagnostics is the largest diagnostics company in the world and has been a committed partner throughout the development of this proposal. They will bring to us novel genetic sequencing methodologies, unique companion diagnostic platforms and point of care tumor boards etc. We have attached a support letter from Jack Phillips, the CEO.

Cook Regentec: This is the latest company developed by the parent company Cook Holdings, and is dedicated to commercializing cell and gene therapies. We have executed an MOU for a partnership already with them to partner in this area. They are assisting us with the cGMP facility and will be our partner to commercialize any therapies we develop in the Cell, Gene therapy cluster. We have included a support letter from Rob Lyles, the CEO of Cook Regentec.

Regenstrief Institute: Regenstrief Institute is an affiliated organization with IUSM and the repository of international known medical informatics programs. It houses the Indiana Network Patient Care (INPC), unparalleled source deep electronic health records for most Indiana natives. We have a long history of partnering with them to conduct numerous informatics projects.

Deloitte: Deloitte is an international corporation that specializes in many different types of technologies, including informatics, computational tool commercialization and most recently in genomic sciences. They will partner with IUSM and Regenstrief in order to help develop the informatics tools necessary for precision health and if successful, commercialize them for us. We have included a letter from Juergen Schenk, their lead in the Informatics division.

XVII. Metrics and Timelines

1. Milestones and Metrics of Success for Genomic Medicine

Years 1-3: 1) Recruit physician scientists and scientific leaders in the targeted areas who can build upon existing IUSM strengths and build collaborative teams to expand and initiative new research programs. 2) Expand precision medicine clinics to include larger numbers of patients and expand current research efforts. 3) Implement uniform collection of family history information to inform subsequent efforts to implement genomic medicine in health care decision making.
Years 2-5: 1) Build new gene editing and sequencing cores that will support translational research allowing researchers to rapidly focus on the functional effect of newly identified genes/variants that affect the risk for disease. 2) Transform the exceptional genetic counseling program in Indiana to train a new breed of precision genomics counselors (PGCs) to meet the health care needs.

3) Develop innovative online certificate and CME programs

2. Milestones and Metrics of Success for Cell, Gene and Immune Therapies

Years 1-3: 1) Establish an exceptional human immunology research and therapy program at IUSM through recruitment and facility enhancement. 2) Build a Cell Good Manufacturing Practice (cGMP) facility to accommodate translation of results of cell, gene, and immunotherapy research to human subjects in selected clinical areas; 3) Recruit expert cell transplantation clinician scientists to facilitate translation of innovative cell, gene, and immune therapies into human subjects. 3) Provide increased educational opportunities and access to the cell, gene, and immune therapies program for physicians, patients and students in Indiana and beyond. 4) Begin to create cohorts of cell, gene, and immune therapy patients towards building comprehensive precision health cohorts.
Years 3-5: Begin to identify predictive markers for subjects who most favorably responded to such therapies and to examine the impact of the treatment on the patient's endogenous "omics" homeostasis.

3. Milestones and Metrics of Success for Chemical Biology

Years 1 -3: 1) Faculty hiring, acquisition of new instrumentation, and marketing, *e.g.,* development of website and other promotional materials, of the C2B2 will begin immediately; our first major milestone will be the successful recruitment of an internationally recognized C2B2 Director and appointment of an associated scientific advisory board composed of external academic and industrial partners. 2) A sustained increase in users by all major PHI participating core facilities, including the LBMS at IUB and the Proteomics and Chemical Genomics core laboratories at IUSM, particularly from samples originating from PHI-centered projects at IUSM.
Years 4-5: By the end of year five, we will have demonstrated proof-of-concept for the entire foundational concept of the Precision Medicine Pipeline (*Fig. 1*) in at least one thematic area (cancer or neurological disease), including the discovery of new molecular targets or biomarkers, followed by ligand optimization and the development of a new biotherapeutic(s). A proposed annual PHI C2B2 research summit and associated scientific symposium will function to publicize novel scientific advances being made across the entire Precision Health Initiative, while catalyzing the pace of discovery within the larger group.

4. Milestones and Metrics of Success for Data and Informatics Sciences

Years 1-5: **A.** Integrate precision health with the daily clinical workflow: (1) number of clinical facilities offering precision medical care; (2) percentage of patients diagnosed/treated using precision medicine approaches; (3) number of PH-focused clinical decision support alerts created, both for clinicians and for patients; (4) proportion of PH-focused CDS recommendations viewed, and followed or rejected; (5) number and type of clinical outcomes communicated back to researchers; (6) comparison of clinical outcomes of patients exposed to PM diagnosis/treatment with standard practice. **B.** Advance precision medicine data sciences: (1) milestones/deliverables achieved in building reusable research informatics infrastructure; (2) coverage of data in our system compared to data considered relevant for PH; (3) number of studies/grants using PH informatics infrastructure/data; (4) growth of collaboration with internal and external partners as evidenced by joint projects, grant applications and publications. Dr. Borner from SOIC-B will be involved in impact assessment of the PHGC scientific component. **C.** Biomedical informatics graduate program focused on translational biomedical research and biomedical data science: (1) establishment of training program infrastructure (director, coordinator); (2) number and type of applications over time; (3) applicants converted to trainees; (4) measures of applicant and trainee quality; (5) positions obtained by trainees after graduation.

5. Milestones and Metrics of Success for BPSE core

Year 1 -2: Establish the PHI behavioral, psychosocial, ethics (BPSE) core, engaging multi-campus, multi-school faculty experts. Recruit a faculty leader to manage the core. Provide support for creating the precision health cohorts
Years 2-5: Develop externally supported research in the following three areas: (1) optimizing communication, participant engagement, and ethical conduct of precision health research, (2) using precision medicine to influence individual behavior and improve prevention and treatment,

and (3) designing electronic and personal health records to protect privacy and allow individual access and control.

6. Milestones and Metrics of Success for Precision Health Cohort program

Years 1- 5: The MPC-IC* tasks, milestones, and schedule to accomplish the proposed aim are:

Pre-Grant Period (May 2016 – August 2016):	
• Select a sampling expert & negotiate contract or create new faculty position • Finalize sampling plan with IUSM • Obtain final cost estimates for survey fieldwork comparing internal (CSR or internally-staffed team vs external vendors, e.g., NORC)	• Decide on survey vendor and execute contract • Begin data acquisition for Aim 3 • Prepare position descriptions for Research Scientists – advertise and hire first position by Sept 2016 • Finalize faculty hiring strategy in conjunction with other funded GC's
Months 1-4 (September 2016 – December 2016):	
• Develop sampling plan with sampling consultant, biobank and PMI team • Select sample and oversample • MPC-IC* to develop instrumentation	• Begin search process for Organizational Network faculty hires and for Health Informatics faculty hire • Research Scientist prepares protocols and get IRB approval • Prepare marketing plan and draft project recruitment letters
Months 5-8 (January 2017 – April 2017):	
• Work with contracted survey organization to train interviewers and pilot test instrument and protocol	• Launch marketing plan • Plan data file structure and storage strategy • Send out invitation letters
Months 9-20 (May 2017 – April 2018):	
• Field Study, 1st set of data collection (N=1,000) • Search and hire 2nd Research Scientist to begin in at start of year 2	• Data entry and cleaning • Preliminary analyses • Send biomarker and telomere kits for analysis
Months 21-32 (May 2018 – April 2019):	
• Field Study, 2nd set of data collection (N=1,000) • Start neuroimaging subsample data collection	• Environmental add-on; Continue data entry and cleaning • Continue survey and biosample analyses
Months 33-44 (May 2019 – April 2020):	
• Field Study, 3rd set of data collection (N=1,000) • Begin planning T2 NIH grant application	• Ongoing analyses
Months 45-56 (May 2020– April 2021):	
• Field Study, 4th set of data collection (N=1,000) • Agree on aims for NIH grant	• Ongoing analyses • Prepare grant outline; draft application
Months 57-60 (May 2021– August 2021):	
• Complete NIH application	• Submit grant application (expected Sept or Oct deadline)

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