Advancing Precision Health at the University of Arizona

Recommendations from the Precision Health Advisory Council

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Executive Summary

Precision health has many definitions but boils down to two key changes in practice: 1) Better determination of the unique aspects of each individual and their individual disease process; 2) Delivery of specific treatments and preventative measures tailored to these unique aspects. It provides opportunities to revolutionize care in all areas of clinical practice. The University of Arizona has Precision Health initiatives already under way and opportunities to develop many others. Some result from our unique geography, demographics, and climate, while others reflect particular research strengths that already exist. Still others, undoubtedly, will emerge when the infrastructure and intellectual environment are further developed. Careful expenditure of resources is now clearly warranted to efficiently and effectively facilitate the advancement of Precision Health in the overall UA biomedical research and clinical practice environments.

Here we summarize the detailed findings of the Precision Health Advisory Council, appointed by Senior Vice President for Health Sciences Joseph G. N. “Skip” Garcia, reflecting its work January-March 2014. The report falls into three primary areas: 1) a SWOT analysis, including examination of the Grand Challenges in Precision Health; 2) specific recommendations for investing in infrastructure to support Precision Health at UA; and 3) criteria for launching an institution-wide process to select Precision Health initiatives that will leverage this infrastructure and propel UA to a national leadership position. Appendix A contains example initiatives—drawn from the council’s knowledge of current research strengths—for consideration as pilot programs during the first round of the proposed selection process.

SWOT Analysis

Strengths
Comprehensive training and research environment with five colleges, teaching hospital, research centers, and national recognition in several areas; aspects of Precision-Health infrastructure already in place, including the UA Genomics Core, computing infrastructure, and intellectual resources in bioinformatics. Weaknesses: A culture of silos hampering team science; lack of support for existing areas of excellence and for improvement in other areas; insufficient protected time for physician-scientists and nearly nonexistent career-development toward academic careers for physician trainees; weak clinical infrastructure both physically and for implementation of clinical studies. Opportunities: Unique environment and demographics of Southern Arizona providing research opportunities not available elsewhere; innovative genomics/bioinformatics provided by proximity to Translational Genomics Research Institute (TGen); TechLaunch Arizona for commercialization of intellectual property. Threats: Low and inconsistent support in state funding; intense competition from health provider systems locally and historic inability by UA to gain market share; strong competition for recruitment of physician-scientists by other academic institutions.

Recommendations

Infrastructure
We highlight five cornerstones of Precision-Health infrastructure and specific recommendations for implementation: 1) Clinical genomics and molecular diagnostics; 2) Informatics, including data acquisition, processing, and storage; 3) Biobanking and stem cell technologies; 4) Patient
management and consenting; 5) Digital health. Development of these infrastructural cornerstones will aid Precision Health in all areas and should be seen as the highest priority.

**Investment in areas of current strength**
Areas with well-developed Precision Health programs already in place are highlighted. Many of these will carry on without additional institutional support, while others are worthy of consideration for immediate support under a philosophy of playing to strengths as we move toward Precision Health leadership. 1) The lymphoma research group, which already carries out comprehensive bench-to-bedside Precision-Health research; 2) Pharmacogenetics/genomics: Several investigators are leaders in mechanism-based prediction of patient response to drugs; 3) Digital health and real-time monitoring of health status, a unique innovative collaboration between bioengineering and aging researchers; 4) Center for Clinical Genomics and Molecular Diagnostics, managing inherited disorders with a particular early focus on cardiomyopathies; 5) Genetics of diabetes in Southwestern Hispanics and Native Americans, combining research strength and our unique demographics; 6) Microbiome and virome research, impacting multiple areas of clinical practice and in which UA has several field leaders; 7) Pharmacodynamic analytics in skin cancer diagnosis and management; 8) Personalized radiotherapy and nanomedicine; 9) Institute on Place and Wellbeing, studying the impact of environment on health at the individual level; 10) Prevention and curing GI cancers; 11) Diagnosis, Prevention and Treatment of chronic liver disease; and 12) Valley Fever as a Precision Health Target.

**Campus-wide Precision Health request for proposals (RFP)**
Every area of biomedical research and clinical practice is amenable to enhancement under a Precision Health paradigm, and there are many areas of strength on campus not listed above. We therefore recommend a campus-wide Precision Health RFP to provide seed funding for projects with a long-term potential to become transformative research hubs in their fields.
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I. OVERVIEW AND CONTEXT

The era of Precision Medicine is here, and the University of Arizona (UA) is poised to take a leading role in advancing both research and clinical care. New sequencing technologies, along with developments in analytical methods, software tools, computational infrastructure, and wearable biosensors are the major drivers of this rapidly moving front. Researchers are now producing and analyzing ever-expanding databases of genomic and phenotypic data gathered from thousands of healthy individuals and those with a variety of disorders. In the next decade scientists will identify the genetic basis of most single-gene disorders and the molecular pathways that are disrupted in complex disease. The clinical areas in which UA has notable strengths relevant to genomic medicine are cancer, asthma, structural heart disease, and brain disorders.

Precision medicine, tailored to the genetic make-up of the individual and to the pathology from which they suffer is the emerging new frontier in preventive and therapeutic health care. Although some observers rightly point out that all medicine aspires to be Precision Health, there are three specific therapeutic arenas where these evolving tools are increasingly being applied: Mendelian disorder diagnosis, the characterization of pathogens, and cancer therapy. Overall these areas experienced a net growth of 14% in spending for molecular diagnostics and genetic testing between 2008 and 2010 (Figure 1), with predicted spending in 2015 being over $5 billion for Infectious Disease, $3 billion for Mendelian disorders, and $1.5 billion for Cancer [1].

Cancer therapy is the area where the most commercial focus has been applied. This is because cancer has the largest proportion of targeted therapies, which drives pharmaceutical manufacturer profitability, clinical trials activity, and accepted clinical practice. For example, hematology/oncology accounts for 38% of FDA approved drugs that target clinically relevant genomic factors (Figure 2). In the clinical trials arena, manufacturers know that targeted therapies have a higher probability of successful drug launch. UA’s trial aspirations require a spirited engagement with targeted therapy research. Academic medical centers across the US are increasingly aggressive in applying these tools, with an increasing number of “sequence every tumor” programs.

Precision Medicine requires a commitment to both cutting-edge technical and outpatient facilities and the specialties required to interpret and transmit the data to physicians and patients. For example, the use of genomic technology to resolve diagnostic dilemmas and guide therapeutic decisions requires interdisciplinary teams with expertise in genomics, proteomics, metabolomics, bioinformatics, clinical genetics, and genetic counseling. Medical centers offering clinical genomics require a hierarchy of capabilities, including (1) electronic medical records, (2) outpatient clinics, (3) genetic counseling, (4) CLIA-certified diagnostics laboratory, (5) informatics and analysis pipelines for the production and interpretation of molecular and imaging data, (6) medical review boards to oversee enrollment, casework and to discuss recommendations, (7) counseling services for...
families and patients, and (8) infrastructure for patient management and follow-up.

Other universities such as Duke, Vanderbilt, University of Washington, UCLA, Baylor, Harvard, Washington University, and a growing list of other institutions, are making great headway in the area of Precision Medicine. To meet the goals of our patient-care mission, to be competitive for funding opportunities (including private philanthropy), and to prevent falling behind the wave of advancement in clinical genetics and genomics, it is vital that the UA make critical investments now. The good news is that all of the components of a comprehensive Precision Health initiative exist at the UA. Our clinical and research enterprise demonstrates particular strengths in cardiology, pulmonology, neurology, and oncology. Indeed, these are the clinical areas that will yield the initial successes in the application of Precision Health. While already in place, existing infrastructure for Patient Management, Genomics and Molecular Diagnostics, Big Data Analytics and Computing, Biobanking, and Digital Health all need to be bolstered to support this effort. Despite our strengths, the UA has not yet developed a unified effort aimed at creating a powerful Precision Health enterprise. To meet this challenge, we need to develop a bold vision and create a plan to position the UA as a regional/national player in translating genetic and genomics research to the clinic, and ensure that patients and families in Arizona and the Southwest have access to the most recent innovations in Precision Health.

II. STRENGTHS & WEAKNESSES

The University of Arizona has a strong base on which to build a Precision Health program that would serve our community and state and garner national recognition. Our internal strengths include:

- **Arizona Health Science Center (AHSC)**, a comprehensive academic health center with presences in the state’s two largest cities (Phoenix and Tucson), five colleges, a teaching hospital, a growing number of health profession programs (including a partnership with Northern Arizona University), an Interprofessional Education and Practice Program, and more than two dozen research centers that focus on topics from rural health to integrative medicine.
- A growing partnership between AHSC and the University of Arizona Health Network, which recently launched the **electronic health record system EPIC**.
- Serving as the state’s Land Grant Institution with strong research and outreach programs (e.g., extension service) in Agriculture and Life Sciences (CALS).
- Prestigious, nationally recognized programs in optical sciences, environmental sciences, speech and hearing, and cognitive and behavioral sciences.
- Expertise in issues related to the Southwest environment and demographics (e.g., sun exposure, aging populations, border health issues, human health and climate adaptation); Concentrations of this expertise exist across campus in hubs like the Arizona Center on Aging, the Skin Cancer Institute and Partnership for Native American Cancer Prevention at the Arizona Cancer Center, the Southwest Environmental Health Sciences Center, and the Institute of the Environment.
- **University of Arizona Genetic Core (UAGC)**, a state-of-the-art molecular biology facility offering clinical genome sequencing featuring a proprietary software suite for germ line
disease, the **forthcoming CLIA/CAP certification**, and the partnership with Washington University for sequencing cancer panels.

- **The SWEHSC/AZCC Genomics Shared Service** – An NIEHS- and NCI-supported facility employing microarray and next generation DNA sequencing technologies for analyzing human exomes, transcriptomes, and epigenomes. The service is also a Life Technologies certified human exome sequencing center.

- **HOPE Research Center (Health Outcomes and PharmacoEconomics)**, which has served industry for decades in modeling economic and clinical impact of new technologies, such as drug treatments, clinical services, and devices.

- **Medication Management Center (MMC)** within College of Pharmacy, which serves over 6 million patients.

- **Relationship with Saudi Arabia’s Ministry of Health** and possible partnerships around pharmacogenomics and expansion of the MMC.

- **College of Medicine Phoenix’s Center for Applied Nanobioscience and Medicine** and its regional healthcare partners, which serve UA community with open source platform technologies and clinical resources for development through governmental and public-private partnerships with national and international activities in Personalized Health & Care (e.g. E.U. Horizon 2020 INTERPRISE).

- **Bio5 Institute**, which serves as a hub of interdisciplinary and translational research.

- **Medium overall size** (compared to other academic institutions), which affords opportunities for less red tape, better coordination, and more collaboration.

The UA has considerable expertise in many of the component elements of the most exciting health related innovations today. However, they exist within the individual labs and practices of specific physicians and researchers. Many of our greatest **weaknesses**, which need to be addressed in order to build a strong Precision health program, relate to bridging and then building upon pockets of excellence. These weaknesses include:

- A **culture of silos** and a lack of **true team science**, in which a group of leading scientists collaborate, more or less equally, toward the achievement of an objective about which they feel passionate, and to which they dedicate the lion’s share of their research effort. On the other hand, our numerous research centers bolster team science, and many researchers do indeed have collaborative, interdisciplinary attitudes and interests, However, **distribution of funding, credit, and other resources** almost exclusively via individual departments hinders teamwork.

- A **lack of centralized support** for areas of excellence. Institutionalizing areas of excellence requires long-term focus and the dedication of adequate resources—tissue banks, proprietary knowledge in the form of annotated clinical data, necessary technical equipment, multiple senior investigators, etc.

- **Lack of protected time (including a budget to cover release from clinical duties) for physician-scientists**, and a thus **difficulty in recruiting and mentoring** early-career clinical researchers.

- **Lack of comprehensive administrative and knowledge infrastructure to engage proactively with sponsors, to research and track emerging funder priorities and to launch targeted rapid responses** to new funding opportunities, especially for complex translational programs and diverse agencies and funders (e.g., industry, philanthropy) beyond the usual U.S. based governmental sources (e.g., Department of Health and Human Services).
• A weak clinical trial infrastructure, including challenges with study approval, recruiting, consent processes, biospecimen access, and data sharing.
• Inadequate bioinformatics infrastructure that currently does not leverage EPIC or allow for connection and mining of diverse data sets to yield new insights.
• Biobanks that are physically dispersed, not clinically annotated, and not widely or consistently available to researchers.
• Modest resources to support significant expertise and interest in issues of aging—an area where we could become an acknowledged expert with more investment.

III. OPPORTUNITIES & THREATS

To understand and strategically pursue opportunities in Precision Health, we must identify aspirational yet practical initiatives to adopt, and then pursue them with the resources and commitment necessary for their achievement. There is a very broad canvas that describes where UA might participate (Figure 3). Some of these are activities that we must adopt to keep up with what is expected of a competent Medical Center and Cancer Center. A subset of these—specifically those with a more specific and collaborative focus and where UA has significant reputation and momentum—represent initiatives where UA can realistically target uniquely innovative achievements.

From this perspective, opportunities include:
• Physicians and scientists working with TechLaunch Arizona to commercialize areas of research and care, which play to our strengths as an institution and which are not yet captured/saturated by other institutions—both within the Southwestern region and nationally.
• Building on our connections to the Translational Genomics Research Institute (TGen) in Phoenix and the Critical Path Institute (C-Path) in Tucson, the world’s leader in speeding and improving drug development in partnership with the FDA.

• Focusing our efforts on areas of research and care that are especially applicable to our local environment and demographics—such as health issues prominent among Latino populations or research on how arid conditions affect aging processes—but which are also of national and international interests (e.g., desert research and geo-medicine).

• Capitalizing on our opportune location in a relative void between other regional Precision Health players (e.g. Baylor, University of Utah, UCLA, San Diego Cluster).

Threats include:

• Fluctuating and relatively low funding from the State Legislature and shrinking federal government resources.

• A dearth of Fortune 500 companies driving the local economy in Arizona and suffering lower national average productivity limiting long-term research investment.

• Strong competition from other hospitals and health networks to serve the local population, in addition to uncertain change in national healthcare system.

• Strong competition from other academic institutions for recruiting physician-scientists at all points along the pipeline (Brain drain).

IV. VISION, CHALLENGES AND AIMS

The term “Precision Medicine” incorporates two important concepts: it conveys the idea of “tailoring medical treatment to the individual characteristics of each patient” [2], and emphasizes the need to obtain a more “precise classification of disease into subgroups”. [3] Precision Medicine is now thought of as a systems approach involving “the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment.” [4]

Ultimately the goals of Precision Medicine, and the broader realm of Precision Health, are to “discover and develop medicines and vaccines that deliver superior outcomes for patients, by integrating clinical and molecular information to understand the biological basis of disease.” This approach leads to better selection of disease targets and the identification of patient populations that will experience better clinical outcomes. The potential of Precision Health is that it will “yield treatments that deliver clinically significant treatment effects, with favorable safety profiles.” [5]

The University of Arizona view should take into account both:

• The broadest set of drivers of individual variability, including genetic, epigenetic, non-genomic, environmental, and behavioral differences and their impacts on disease susceptibility and resistance, and

• The broadest set of interventions with the potential to improve individual health status, including medicines, vaccines, surgery, cognitive and behavioral intervention, and environmental management.

A. Grand Challenges

The Grand Challenges of practicing Precision Health faced by all institutions and society at large include:

• Operationalize Precision Health in an academic setting by implementing new measures to translate discoveries in the research laboratory to applications in the clinic, by promoting
drug development efforts, and by creating innovative business plans that support sustainability and that make patient care cost-effective

- Develop the infrastructure to connect, mine, interpret, and utilize diverse datasets at multiple scales (e.g., genetic and epigenetic factors, individual health history, behavior, environmental exposure, and time and location information) to understand internal and external factors that affect an individual patient
- Integrate discoveries in basic research with those coming from clinical care of individual patients to aid in the development of a new taxonomy of disease
- Address the practical and ethical challenges involved in creating, linking, and making broadly accessible datasets
- Develop processes to interpret genomic and other molecular data and convey these implications to healthcare professionals and patients in an understandable manner
- Practice genuine team science and patient care that dismantles existing barriers—institutional, cultural, economic, and legal—between the biomedical research environment, the clinic, and the public and that encourages health professionals to work across traditional disciplines to achieve the best possible outcome

B. Aims

UA aims to embed Precision Health in every aspect of its human health-directed endeavors. To accomplish a successful Precision Health modality, the UA needs to:

- Develop a bold vision and create a plan to position the UA as a regional player in translating genetic and genomics research to the clinic, and ensure that patients and families in Arizona and the Southwest have access to the most recent innovations in Precision Health
- Adopt a collaborative, comprehensive model that engages health care professionals, researchers (basic and translational T1-4), consumers/patients, business executives, entrepreneurs, payers, and policy makers.
- Select a portfolio of opportunities within Precision Health that uniquely leverage current research, development and clinical strengths that, in aggregate, comprise a nationally recognized leadership position.
- Demonstrate the technological proficiency (e.g., next generation sequencing, micro-array, molecular imaging, proteomics, CLIA/CAP-certified genetic testing) and capability/capacity to develop products (diagnostic, therapeutic) that are safe and reliable.
- Develop the education and training capacities to produce the next generation of health professionals, genetic analysts, and genetic counselors that can interpret and convey Precision Health information to patients and the health care system.
- Encourage collaborations between basic researchers, UAHN and AHSC, and bring clinicians and researchers under the same administrative and/or physical structure
- Develop mechanisms to make health care professionals and patients aware of research programs and clinical trials, and facilitate patient enrollment to make UA more competitive for grants
- Commit to both cutting-edge technical and outpatient facilities and the specialties required to interpret and transmit the data to physicians and patients
- Develop the full potential of existing Biobanks to facilitate innovative translational research
- Link massive data sets from genome to exposome, including layering environmental data onto human health and well-being data in real time and place
V. RECOMMENDATIONS

Based on the SWOT analysis, the Council proposes two overarching objectives:

A) **Build the core infrastructure** necessary to sustain a successful Precision Health enterprise

B) **Develop and launch a cycle of specific Precision Health initiatives.** A menu of example initiatives to be considered as pilots is included in **Appendix A**.

Section A makes recommendations on how to support the necessary infrastructure upon which our successful initiatives will be based. Section B lays out criteria for choosing a set of initiatives that are practical to pursue concurrently given available resources.

A. Building a Precision Health Infrastructure

Building upon existing strengths at the UA in the following five major areas to accelerate UA’s advancement to next frontier in preventive and therapeutic health care, to meet the goals of our patient-care mission, and to be competitive for funding opportunities in clinical genomics and translational medicine. These five core areas represent the unpinning infrastructure to build Precision Health upon at the UA and are seen as essential to sustain a successful Precision Health enterprise.

1. **Patient Management & Consent**

**Center for Genomics and Precision Health**

We recommend the creation of an innovative Center for Genomics and Precision Health (the ‘Center’) as a collaborative effort between UAHN and AHSC to deliver personalized healthcare. The Center would serve to bring clinicians and researchers under the same structure with a focus on providing genetic and molecular profiling tools for diagnosing, predicting and treating patient specific disease to improve patient care, outcomes and costs. Founding partners should include the College of Medicine’s Departments of Medicine, Pediatrics, Pathology and Obstetrics & Gynecology, the College of Pharmacy, Bio5, the UA Cancer Center, the Center on Aging and the UA Vice President for Research and the CEO of UAHN. A strong established, visible, translational clinician-scientist should be named head of the Center, with responsibilities to assign heads of clinical, research and bioinformatics activities. Existing campus resources should be reassigned to the Center and a building made available for clinical and research activities.

The interdisciplinary structure of the center would in turn lead to the development of a **culture of clinical and medical research (Team Science)**, as well as allow UA to be more competitive for grants. The Center would focus initially on core areas such as cancer, aging, neurology, pulmonary and heart disease, and microbiome/virome, and eventually on other areas of UA excellence. It would provide patient services such as genomics testing and sequencing of tumors for each patient.

The Center would be responsible for organizing and staffing an outpatient clinic that cares for patients with genetic and genomic disease, as well as other disorders amenable to a Precision Health approach (e.g., Initiatives 1, 2, & 4). This clinic will serve the three purposes: 1) providing excellent patient care; 2) matching researchers with a patient base for enrollment in research
studies; and 3) providing the infrastructure needed to conduct clinical trials. To accomplish this
mission, Center leadership will require reassignment of and control over existing campus
resources:

- 2 MD geneticists
- 3 genetic counselor FTEs
- 7 offices and 6 research laboratories in the Angel Charity for Children ‘Wings for Genetic
  Research’ on the fourth floor of the Steele Children’s Research Center.

A budget must also be provided for additional infrastructure needs, including:

- Clinical space
- Administrative support (e.g. Billing Staff)
- Research & Clinical Nurses (patient navigation, consent, sample collection/archiving)
- Additional Genetic Counselors and Geneticists
- Marketing and community outreach
- A centralized and broad consent process supporting research as well as patient care
- Business/Market analysis

A plan must be implemented to maintain the Center’s long-term financial viability since genomics
and personalized medicine clinical services require explanation of complex medical and genomic
data during long (and relatively poorly reimbursed) patient visits. To maintain a vibrant clinical
service, a source of long-term funding in addition to billing receipts for clinical services must be
arranged. Other programs use a variety of sources to support clinical services: clinical laboratory
revenues (e.g. from an independent UAGC clinical genomics lab), state contracts for genetic
services (currently assigned to the Phoenix pediatric genetics group) and subsidies from high
earning specialties (based on the concept of “residuals” which is embraced in many non-academic
settings and leads to the success of places like Phoenix Children’s Hospital).

We recognize the need for updating genetic counseling training for interpretation and counseling
on genome-level data and recommend revitalization of a previously excellent genetic counseling
training program for this purpose. There are currently 32 Genetic Counseling programs in the US,
with only 6 in the western half of the country and none in Arizona, putting a UA program in an ideal
position to recruit diverse students and to retain them as providers within the state. A focus on
genomic data interpretation could attract outside genetic counselors willing to pay for updated
training. Financially, a program with 4 UA Genetic Counseling students for 2 years would bring
tuition payments (since many will be out-of-state students) of about $200K/year. Since UA policy
prevents return of tuition earnings to the specific programs generating them, some FTE equivalent
for the director of the program and long-term commitments for administrative support are needed.

Recommendations

- Ensure the timely hiring of a well-qualified pediatric/medical geneticist.
- Consolidate hiring and supervision of existing genetic counseling FTEs under a single
  administrative structure.
- Organize and run genomic and Precision Health clinics for general and pediatric genetics,
genomics, cardiomyopathy, neurology/neuromuscular disease, pulmonology and research
  recruitment.
- Develop a long-term business model for Precision Medicine as a necessary clinical service.
- Reopen the genetic counselor training program with a special emphasis on preparing
  graduates to interpret and counsel patients on genomic data.
- Build clinical services and move these (with other core facilities) to a single location where
  physicians, researchers and patients can interact.
2. Clinical Genomics & Molecular Diagnostics

a. CLIA/CAP-Certified Clinical Genomics Laboratory

We propose building on the strengths of the University of Arizona Genetics Core (UAGC) and scaling up its Clinical Services unit to support clinical, clinical trial, and research activities within the Center, as well as inpatient and outpatient diagnosis needs of physicians and researchers at UAHN and the UA Cancer Center. Over the past two years, UAGC Clinical Services has invested in becoming a CLIA/CAP certified facility specializing in high-complexity genetic testing and Next Generation Sequencing (NGS). Towards this goal UAGC Clinical Services also has received funds from the Office of the VPR to continue performing clinical case studies on a research basis (Initiative 2a).

This investment also has led to the development of a custom software suite that allows for the analysis of patient data and aids in the preparation of comprehensive reports to physicians (Figure 5). Ultimately the UAGC will provide complete genomic services that enable personalized and cost-effective patient care for the management of acute and chronic illnesses in a CAP/CLIA certified laboratory setting. The results will be accompanied by concise, expert interpretations from board-certified clinical genomicists. These and other genomic tests to be developed will be designed to return actionable genomic intelligence across a range of disease-relevant genes and will help ordering physicians stratify disease subtypes and identify optimal patient treatment strategies.

![Figure 5. Custom Clinical Genomics Software Suite.](image)

Together with the BCF and the support of the Office of the VPR, UAGC Clinical Services has developed a custom software platform. This software suite consists of five key components that power the clinically oriented pipeline from an initial intake questionnaire and coordination of a Medical Review Board (see below), through clinical sequencing, data analysis, and generation of comprehensive physician report. Extensive tracking, chain of custody, physician interfacing, and mechanisms to upload data to EMR with regulatory compliance features are implemented throughout.

UAGC Clinical Services will offer whole exome sequencing as soon as CLIA/CAP approval is obtained and validation is completed. This will serve many local clinicians (Initiative 2), including developmental pediatricians (S. Rice), geneticists (C. Laukaitis & TBA), neurologists (C. Scherer) and cardiologists managing cardiomyopathy (J. Tardiff). The next tests to be validated and released will include a tumor genotyping panel and a panel evaluating germ line (blood) samples for inherited cancer syndromes. Validation of the tumor genotyping panel benefits from an existing partnership with Genomics and Pathology Services (GPS), a clinical genomics laboratory at Washington University School of Medicine and is led by the lymphoma oncology and research group (Initiative 1). This test detects tumor somatic mutations in hundreds of oncogenes, tumor suppressors, and other cancer genes (42 of which are currently reported and reimbursed by third party payers), and assist oncologists with stratification of disease subtypes and permit tailoring of effective personalized therapies. The inherited cancer panel validation will be supported by an extensive database and bio repository collected by the UA High-Risk Cancer Genetics Clinic (Laukaitis, J. Jeter and S. Chambers) and by collaboration with the King lab at the University of Washington. A panel for pharmacogenomics should be developed in conjunction with Initiative 4.

Long-term financial viability of the UAGC core relies on it meeting the needs of local researchers and physicians through flexibility and responsiveness. This requires financial independence to support creation and validation of new test panels before their profitability is proven. Thus, UAGC
billing must remain independent of the UAHN and should be done by the Center for Genomics and Personalized Health (Core 1).

**b. Genomics Shared Service**

We propose greater coordination of services provided by the UAGC and the NCI- and NIEHS-supported Genomics Shared services in the Cancer Center. The primary foci of the Genomics Shared Service are human cancer, epigenetics, and molecular responses to xenobiotics. The Genomics Shared Service offers NGS for analysis of genetic, epigenetic, and transcriptomic changes in human systems, while Affymetrix and Agilent microarray platforms provide additional flexibility for comprehensive genome and epigenome analyses.

**c. Panomics Core and Mass Spectrometry Facilities**

Precision health consists of diagnosis and treatment, with treatment benefiting by ongoing monitoring of drug effectiveness. Panomic analysis of proteomic, lipidomic, glycomic, and metabolomic profiles will become a critical component of Precision Medicine in the future, and currently mass spectrometry techniques offer the most comprehensive and powerful approach to measure these profiles. The UA is not currently competitive in the field of biomedical mass spectrometry, both from the perspective of instrument development and bioanalysis, nor do we have the expertise in panomics that is needed to be a leader in the area of Precision Health and numerous other areas. Key faculty hires at the senior level in biomedical mass spectrometry are needed to augment our current expertise in Panomics and take the UA to the next level in Precision Health. To this end, a multimillion dollar university level recruitment package has been assembled with resources from the SVPHS, Director of Bio5, Deans of the Colleges of Science and Medicine, and the VPR, to recruit senior level mass spectroscopists with the academic accomplishments and leadership skills to lead this effort. Projected timeline: Initial roll out in years 1-2 is to recruit senior level analytical chemist with the needed expertise and leadership; years 3-5 yields big data from panomics that drive discovery.

**Recommendations:**

- Hire administrative staff to assist clients with insurance billing.
- Hire a genetic counselor to assist with patient navigation and data return.
- Hire a dedicated programmer to develop and maintain the custom clinical genomics software suite and to maximize its interface with the EPIC electronic health record and the data and informatics core.
- Support a search for a medical director for UAGC Clinical Services with ACMG molecular genetic board certification and research interests that complement the Precision Health mission.
- Develop a billing model through the Center for Genomics and Precision Medicine to support the administrative, counseling, programming and medical director positions.
- Support the research mission of the UACC genomics shared service in oncology and beyond.
- Support recruitment of a recruit senior level analytical chemist with the expertise and leadership needed to support panomic bioanalysis and/or instrument development.
3. Big Data Analytics & Computing Infrastructure

One of the most critical components of a Precision Health program is the computing and bioinformatics infrastructure necessary to integrate multiple "omics" datasets (e.g., proteome, genome, exome, transcriptome) with existing clinical data types (e.g., medical literature, electronic medical records, clinical trial data, histopathology), and to enable Precision Medicine at very large scales from the academic, industrial, and healthcare viewpoints. We believe discovery is best enabled through a centralized data and bioinformatics cooperative that can promote cross-disciplinary collaboration, ensure access to all UA scientists, and empower researchers with the tools and support they need to navigate the complex large scale data landscape. Such an organization will foster a new generation of Precision Health professionals that are equipped to harness rapidly expanding computational techniques and ever growing data sets. The recently established position of Associate Director for Data Science at the NIH (Dr. Russ Altman, Jan 2014) along with a series of BD2K (Big Data to Knowledge) initiatives, signals a new era of data-driven science and the need for institutions to fully exploit the potential of their institutional data repositories and interdisciplinary expertise.

The infrastructure described by the National Research Council’s Towards Precision Medicine (2011) serves as an instructive model (Figure 6). This infrastructure requires the establishment of an “Information Commons” in which data on large populations of patients become broadly available for research use and a “Knowledge Network” that adds value to these data by highlighting their inter-connectedness and integrating them with evolving knowledge of fundamental biological processes. Further there needs to be a paradigm shift towards establishing a big data technology infrastructure that exploits modern emerging concepts based on Hadoop and Map Reduce distributed and parallel processing frameworks instead of relying solely on high performance computing. The infrastructure should also embrace a vision for real time streaming, linking and processing of datasets including social media such as Twitter, and Fourssquare, Wearable sensors and the Internet of Things, as well as patient Electronic Medical records (EMR).

Strengths

- UA Research Data Center expansion with proposed HIPAA/Clinical data center extension
- UA High Performance Computing (HPC) capabilities ($2.4M/3 years)
- Early implementation of big data infrastructure at UITS (Technology stack and Hadoop based hardware and software ecosystem)
- iPlant Collaborative NSF funded ($100M/10 year) CI project with high throughput (1.2PB) data management capabilities, largest public cloud for life science researchers, 2000+ dedicated cores for HPC and 16000+ registered users.
- INSITE Research Center for Business Intelligence and big data analytics with an extensive history in developing scalable techniques for data mining, large-scale graph mining and big data visualization and analytics.
• Bio Computing Facility (BCF) with long standing history of utilizing cutting edge CI for projects ranging from mHealth to NGS based data mining.
• Faculty with active research projects in network analysis, cloud, big data, network security, encryption, imaging (Computer Science, ECE, MIS), natural language/text processing, information visualization (SISTA, CS, Linguistics, MIS), biostatistics (ABE, Bio5, Applied Math)

**Recommendations**

• Designate a leadership position with institutional support and resources, with earmarked pilot project/seed money to spur multiple investigators to write grants and carry out targeted data explorations.
• Establish a “Research Data Center” that is capable of providing the necessary security (physical, network, and information) to house the computing and data storage equipment in a manner that is compliant with PHI/HIPPA guidelines.
• Establish a Health Data Stewardship group [6] that facilitates the deposition and consumption of data while ensuring suitable safeguards and a research conducive data rich environment (http://www.ncvhs.hhs.gov/090930lt.pdf)
• Implement a “Biomedical Information Commons” that scales with the growing need of managing unstructured, semi-structured, and structured data from multiple data modalities including social media, and wearable sensors or Internet of Things, genomics, and EMR. This commons should have the ability to readily ingest data from repositories external to UA for facilitating further analysis (e.g., dbGap or subsets of TAGC) in a secure and compliant manner. [http://www.ncbi.nlm.nih.gov/projects/gap/pdf/dbgap_2b_security_procedures.pdf](http://www.ncbi.nlm.nih.gov/projects/gap/pdf/dbgap_2b_security_procedures.pdf)
• Utilize the Biomedical Information Commons and Health Data Stewardship framework to continually bring in data streams from EMR (EPIC) and other institutionally relevant data sources.
• Integrate scalable computing technologies that build upon and extend the UA HPC capabilities, including private and commercial cloud providers. This infrastructure should be capable of managing data streams from sensors to HL7 messages, from EMR and RIS (with heavy emphasis on preventing “data leakage”).
• Strengthen applied biomedical aligned expertise in the following areas:
  o Natural Language Processing
  o Large Scale Network analysis
  o Machine Learning/Predictive analysis/Data Mining/Modeling
  o Data encryption
  o Information visualization/Visual Analytics
  o Bio-statistics
• To meet the challenges imposed by Big Data, the University must maintain a strong, stable, centralized mathematical and statistical research community, which will serve both as research collaborators and core faculty of quantitative teaching and training of the medical community.
• Forge a software and data engineering team, with an emphasis on providing production grade services, developing middleware to connect open source, commercial and custom developed platforms, and managing analysis pipelines. This team will be responsible for leveraging computational and data infrastructure provided by the NSF and NIH for use by UA researchers.
• Create continuing education workshops to encourage adoption and utilization of this platform
4. Biobanking & Stem Cell Facilities

a. Centralized Virtual Biobank (CVB)

Access to biorepositories is one of the cornerstones of Precision Health. The need for biospecimens and associated clinical, molecular, and patient data requires a modern, sophisticated, and robust system for fast access to quality tissue and validated data. Adequate facilities, incorporation of standard practices in collection and management, and rapid access workflows are imperative. The new Centralized Virtual Biobank must also be flexible to allow for changes in regulations, data sources, vocabularies, research workflows, and research goals. The ability to perform “big data” research projects has driven the evolution of a new “research ecosystem” involving external collaborators, sites, sponsors, and other data vendors. Success in this new externalized environment requires new systems that incorporate patient protections (consent, compliance, and data security), future use accommodations, and secure linking of clinical and molecular data to tissue. Smooth information flow between external and internal systems requires biobank management platforms to face three major challenges: 1) subject consent & data acquisition; 2) informed consent reconciliation for regulatory compliance; and 3) standardized robust sample collection/management practices.

As biomarker-based research grows, traditional biobanks and software must reach beyond old sample-centric models to allow for linkage of specimens with clinical and molecular data. The new biobank model must meet the demands of a wide variety of researchers, with different projects, data and research outcomes. Current research silos have inherent inefficiencies and will not be able to support big data initiatives that link rich data sets to the specimens. The new CVB will have four key attributes: 1) harmonization of biospecimens with clinical and molecular information; 2) ability to generate scientific insights; 3) support for externalized collaborative studies, and 4) enhanced security and compliance. In order to gain scientific insights from the CVB, the plethora of molecular and clinical data gathered can be linked to create an information hub that CVB contributors across the research ecosystem can access, supporting rapid generation and testing of new hypotheses.

The full potential of UA’s large collection of specimens and associated clinical data can be realized only if we adapt to new biobanking models. As different departments have conducted their own biobanking efforts with biospecimens housed separately in many locations, centralized biospecimen storage in a single facility is not feasible, nor is it required. A new CVB, with its data processing and informatics pipelines, will allow investigators to access biospecimen samples and data from repositories across campus. Holders of biospecimens (e.g., frozen or fixed tissues, plasma, sera, DNA, RNA, etc.) will be invited and encouraged to add information from their holdings to the CVB. Web-based software platforms will link the data hub, and allow UA researchers to identify sample holdings, contribute samples and data, and initiate collaborative research. Current individual biobanks at UA include:

- **Department of Pathology:** >1.4 million paraffin embedded blocks and H&E slides plus >105,000 tissue blocks from autopsy specimens. Clinical data is currently accessible through Co-Path. The MicroBank which contains >8000 frozen bacterial isolates from diagnostic material such as methicillin-resistant *Staphylococcus aureus*.
- **UACC:** Multiple biobanks including the G.I. SPORE, Skin, Arizona Lymphoma, Prostate, UACC, and the Cancer Prevention & Control (CPC) Biorepositories. The CPC biorepository houses one of the largest colon polyp banks in existence, with more than 250,000 biologic specimens (urine, feces, blood, DNA, RNA and tissue). The Prostate Biorepository includes 700 prostatectomies with matching clinical data and long-term outcomes plus thousands of serum, plasma, and fixed tissues from large chemoprevention trials conducted over the last three decades. Specific information on specimens and
important de-identified clinical data is accessible through TissueMetrix software at http://biorepository.azcc.arizona.edu.

- **Arizona Respiratory Center:** 220,000 samples representing serum, plasma, breast milk, nasal aspirates, sputum, exhaled breath condensates, and saliva from over 28,000 individuals with many samples representing longitudinal collection. The Genetic Biorepository of the Arizona Respiratory Center (GBARC, 2012) manages all DNA samples. Custom integrated laboratory software manages samples, assays, data processing, and data export.

- **Department of Surgery:** 51 tissue samples from cardiothoracic surgeries in support of stem cell regenerative medicine efforts have been recently collected, including adipose, blood, heart muscle, sternal bone, tumors, and tracheal tissues.

b. **Induced Pluripotent Stem Cells (iPSC) Shared Facility**
Induced pluripotent stem cells (iPSC) generated from donor-patients offer a unique opportunity to archive and immortalize patient samples that can, depending on the tissue, be grown and differentiated into contextually relevant in vitro models in which to study the relationship between genetic/epigenetic variation and the resultant phenotype in a patient. We envision this as being incorporated as a combination of contracting out iPSC generation to a company with proven success at doing this reliably on a large scale (e.g., Cellular Dynamics International [CDI]), together with a local investment in banking, expanding, and differentiating iPSC. In the initial phase UA could focus on banking, and CDI could cover iPSC generation, expansion and differentiation; they provide this service routinely. This is the most rapid way to deliver patient samples to investigators with the expertise to do the functional experimentation. As the effort matures, UA could build capacity to assume some of the steps in this service.

**Recommendations**
- Tight integration with the other Cornerstones of the Precision Health Infrastructure, especially **Patient Management & Consent**, and **Data Center & Informatics**
- Appointment of a CVB Director with administrative support, coordinators familiar with human subjects protection regulations, data managers, and compliance personnel with space for data servers, file storage, and conferencing
- Systematic evaluation and acquisition of a flexible “Next Generation” biobanking software system for specimen and data management, consent management, data security, and data exchange (**Core 3**)
- Development of workflows and SOPs that incorporate NIH standard practices, comprehensive consent tracking, and sample management
- Development of metrics and dashboards to evaluate performance and value to the institution
- Development of front-door authorizations and compliance agreements with clinical partners and regulatory authorities
- Identification of centrally-managed physical space for freezers and room temperature storage of samples collected by investigators who do not otherwise have access to tissue storage facilities
- A centralized consent form that is broad and that allows for unrestricted future use of samples to avoid unanticipated issues in the future, and that allows for access to samples easier and reduce time spent on confirming specifics of consent for each type of study.
- Technical staff to manage storage and growth of iPSC at UA and to perform experiments to aid individual investigator’s research.
5. Digital Health & Biosensor Infrastructure

Wearable devices and sensors for healthcare applications are a fast growing field and UA has considerable strength in this area. The Arizona Initiative for Accelerated Biomedical Innovation (AIABI) has pioneered novel active flexible, stretchable and biodegradable polymeric electronic systems have been developed. These technologies are proprietary and have been configured to develop a series of skin patches, active tattoos, and other wearable external, as well as internal (stent and other implant) personal systems able to measure a wide range of physiologic variables, biomarkers and activity parameters. For example, a patch has been developed able to measure heart rate, blood pressure, ECG, 3° of motion as well as hydration status. Such devices may be utilized for general health assessment, performance with sport, training or rehabilitation, recovery from illness, or monitoring of heart failure. Similarly, the Interdisciplinary Consortium on Advanced Motion Performance (iCAMP) possesses unique expertise in the translation of wearable technology and embedded technology can be combined with other techniques to distinguish personalized health initiatives at the AHSC, providing real-life precise and accurate mobility measurements to enhance health status assessment of, and treatment efficacies in, patients in their natural environment where they're the most comfortable and active. Specific collaborations with the Arizona Center on Aging (ACOA), mobile health (mHealth) and other interdisciplinary teams are in progress and with the iCAMP growth and reach of Digital Health in other disciplines, the UA will be in a unique position to expand this area of research and become a leader in the field nationally and internationally.

Examples of projects that use these technologies, and which would be able to greatly expand their reach and funding, include, but are not limited to: (i) Inpatient population health; (ii) Personalized home monitoring - cognition and frailty assessment; (iii) personalized Exercise & ExerGaming; and (iv) Diabetes Care with research focus on diabetic foot ulcer, wound healing, and patient adherence.

Recommendations

While these teams have pioneered many innovative technologies and some of their bioengineering products have already led to patents and were translated to industries for commercialization, additional growth is needed to support true personalized health revolution in objective status measurement.

- Key hires: 3 postdocs, 3 nursing grad students, and 2 expert faculty
- Equipment such as motion tracking reference tools and telemonitoring technologies
- Seed funds for prototype device development and pilot studies, particularly in the area of bioengineering, cognition/brain and aging (Initiative 4).
- Centralized data center and bioinformatics capabilities (Core 3)

B. Proposed Criteria for Selecting Precision Health Projects

In this section we provide criteria for choosing a set of initiatives in a manner that is practical given available resources. It is better to start with pilots and grow the number of initiatives only after the initial selections are well on the path to success. Realistic and practical business plans will need to be thoughtfully prepared. Doing so requires us to view these opportunities within a larger context including factors in the University's physical, social, and political environment, as well as a survey of the Precision Health efforts of peer institutions and current market trends.

1. Sustainability in Precision Health Initiatives

- Applicability: The biomedical basis of the project should be applicable to current or near-term patient care needs. Not all basic discoveries or innovations are applicable to current medical practice or to the world market at large.
• **Expertise**: Solid research expertise should exist in the clinical area to which discovery will be applied. Much of the latest knowledge about the genetics of disease coming from genomic discovery will not necessarily result in a medical intervention, yet it will may to new scientific research opportunities.

• **“Market”**: There should be sufficient numbers of patients to apply particular clinical innovations, and 3rd party payers should have a history of paying (or payment is likely imminent) for such testing so as to make the endeavor self-sustaining.

2. **Capitalize on a cluster of unique UA attributes and existing infrastructure**
   - Engineering, bioengineering hardware and software, SISTA, Big Data Analytics, iPLANT
   - Device development e.g. that measure physical activity and physiological & biochemical biomarker data & connect this data to behavioral feedback
   - Exposome expertise: built environment & urban design; environmental expertise (IE); water; GIS; SW climate and environment, ecology

3. **Enhance existing Precision Health infrastructure**

4. **Tie closely to Arizona/Southwest environment and/or demographics**
   - Native American or Hispanic populations
   - Aging populations
   - Desert environment, urban heat island, climate change adaptability

5. **Impact**
   - Addresses Grand Challenges of Translational Precision Health
   - Capacity to fundamentally change concept of human health
   - Global Impact: potential for global applicability, translatable to global problems and populations
   - Potential to change/impact government policy in health or related domains
   - Potential for scalability and return on investment (ROI) – can it grow in multiples of the invested funds beyond standard grant size (R01)?

6. **Interdisciplinary characteristics**
   - Lays groundwork for future larger collaborative endeavors
   - Is cross-institution team-based science
   - Connects diverse data sets at multiple scales from genome to exposome
   - Encourages graduate training and interdisciplinary training and experiential learning.

7. **Business rationale**
   - Is attractive to funders and has potential to engage new sources of funding beyond health related government agencies, including private sector, foundations & philanthropy
   - Offers value to UAHN/health care community, e.g. competitiveness
   - Outreach potential: Is bold, attention-grabbing (media, public, philanthropists)

8. **Short timeline to implementation and results**
   - A previously proposed project that narrowly missed being funded, specifically due to infrastructure gaps
   - Builds upon ongoing IRB-approved studies
   - Enhances an ongoing project
VI. Expected Outcomes

Within three to five years of establishing a Precision Health program, expected outcomes will include the following accomplishments:

- UA will be recognized as a regional leader in Precision Health by operationalizing it within health care delivery systems.
- Precision Health practices will result in significant net new revenue/funding streams that support and stimulate growth in research and education at UA.
- Precision Health will be recognized as a key innovative health service that demonstrably benefits all citizens of Arizona and the Southwest in tangible and visible ways. (Impact overlay with Population Health/Health Outcomes)
- Leadership in Precision Health practices will distinguish the UAHN and other UA health providers as organizations with highly competitive assets in the regional market, and drive the financial success of the University and its human health activities to new levels.
- Outstanding Precision Health Graduate and Training Program(s) will be offered both as degree and certificate training for AHSC health professional students. This will help UA stand apart for training and attracting students and faculty, specifically because of it’s true inter-professional training program unlike any offered in the country.
- A biomedical enterprise promoting scientific discovery and facilitating clinical application to improve the health outcomes of individual patients: the needs of the patient will direct the emphasis of basic research, patient samples will provide the critical resource to investigate the basis of disease, and patient participation in clinical studies will generate the evidence needed to apply new drugs, vaccines and technology to the broader patient population (Figure 7).

Figure 7. Patient-centered biomedical enterprise promoting translational research.

Validated findings that emerge from the Knowledge Network, such as those that define new diseases or subtypes of diseases that are clinically relevant, would be incorporated into the new Taxonomy to improve diagnosis and treatment. The fine-grained nature of the taxonomic classification would aid in clinical decision making by more accurately defining disease.
Appendix A: Menu of Initiatives Recommended for Consideration as Pilots to Launch UA Precision Health

Here we describe several initiatives that exemplify the kind of team science that will allow the UA to make the greatest headway in Precision Health. Many of these initiatives are going forward independent of UA internal support, while others need funded pilot or seed support. The former will be rolled out in the very near future and demonstrate a strong potential for sustainability. These initiatives cut across multiple areas of existing expertise and have the potential for timely applications in Precision Health. The latter initiatives are more nascent, yet are worthy of consideration for immediate support under a philosophy of playing to strengths as we move toward Precision-Health leadership. This is not meant to be an exhaustive list of such projects at the UA, rather these initiatives are those that the council could identify with the above-mentioned characteristics within the timeline of their meetings. It is recommended that the SVPHS announce a Request For Proposal as part of its strategic planning to identify the most promising initiatives.

1. **Build on our reputation in Lymphoma to become the #1 center for challenging liquid tumor cases, with the eventual goal of sequencing every patient’s tumor** (Schatz, Rimsza, Puvvada)

Many academic medical centers are adopting this approach, primarily to create a better documented data (and tissue) based understanding of the segmentation of disease pathology, a subset also promise to use the data recorded to inform and guide donating patients therapy. No other institution is doing this in the southwest today, it is overdue and necessary for the support of research, clinical trials and cutting edge therapy for patients.

The lymphoma research group is one of the most comprehensive clinically oriented research programs at the university, covering the full spectrum of bench-to-bedside research, including genomics and molecular target identification, drug discovery and optimization, preclinical disease modeling and therapy evaluation, biomarker discovery, clinical assay development, and translational clinical trial development and implementation. Investigators already have taken major steps toward implementation of Precision Medicine initiatives, including whole-exome and targeted sequencing of individual patients’ tumor DNA for selection of therapy, transcriptome analysis in high-risk disease states with analysis by Dr. Yves Lussier, and implementation of biomarker-driven investigator-initiated trials. This research area is therefore a highly suitable area for early emphasis at the institutional level for Precision Health development efforts (Figure 8).

Current UAGC laboratory capabilities would have to be upgraded as the number of samples increases, and an interpretive service overlay added to integrate and then communicate results...
and implications for clinical physicians working with patients (surgery, medical oncology, and radiotherapy). The partnership with Washington University (see UAGC above) and the licensing of their Clinical Genomicist Workstation software will greatly facilitate both increasing throughput and efficiency in data analysis, as well as with automating the process of producing final reports and billing. These services should be designed to serve all of Southern Arizona/Sonora, especially including Phoenix College of Medicine and Cancer Center. After this effort is off the ground and self-sustaining, investment could be extended to other areas within the hematological cancers, perhaps starting with Multiple Myeloma, which has clinical overlaps with Lymphoma.

Recommendations

- Institutional support for designation as a research institute under the leadership of professor of pathology Dr. Lisa M. Rimsza.
- Support for program growth through recruitment of physicians, research nurses, and clinical research associates and seed investments in their research.
- Investment in clinical trials infrastructure including better access to walk-in facilities for research blood draws and other protocol-mandated evaluations.
- Funding for dedicated bioinformatics in conjunction with the Data Center and Informatics infrastructure initiative described above.
- Support to augment current grant funding of the Arizona Lymphoid Tissue and Blood Repository (ALTBR) to expand annotated tissue banking and extend its national and international reach.
- Facilitate further integration of drug discovery and development into the institute by working with Bio5 Oro Valley in collaboration with Pharmacology/Toxicology and Dr. Laurence Hurley.

Related drug discovery efforts (Hurley, Kendrick). As one specific example of our bench-to-bedside team approach, we have selected double hit lymphoma (DHL), which is a particularly refractory disease found in about 5% of lymphoma patients with a median survival of less than one year. For this disease the lymphoma group has identified MYC and BCL2 overexpression through gene expression profiling of individual patient tumor samples. In a separate and parallel drug discovery effort we developed novel ways of targeting MYC and BCL2 with small molecule inhibitors. This technology is licensed from the University to a start-up company and an SBIR was recently funded to optimize the BCL2 inhibitor. A second funding mechanism (STTR) is pending for the MYC lowering compound. Further preclinical development will be done in collaboration with the start-up company to bring these compounds into investigator initiated clinical trials at the University of Arizona Cancer Center.

2. Center for Clinical Genomics and Molecular Diagnostics

a. Clinical Genomics of Mendelian Disorders (Hammer)

While Mendelian diseases are rare, altogether they account for 1% of adult and 6% to 8% of pediatric hospital admissions. Many patients with genetic diseases are not given a specific diagnosis, which has adverse effects including failure to identify potential treatments, failure to recognize the risk of recurrence in subsequent pregnancies, and failure to provide anticipatory guidance and prognosis. The long search for a genetic diagnosis, called the “diagnostic odyssey,” negatively impacts societal medical expenditures, with unsuccessful attempts consuming limited resources.

Facilities nationwide offer genomic-scale testing for Mendelian diseases, however, there is no such testing facility in the Southwest. Building on strengths in NGS and a record of successful discovery of pathogenic mutations in young patients with undiagnosed disorders (>60% diagnostic yield), Michael Hammer and the UAGC facility have developed technical, bioinformatic, interpretive, and
validation pipelines to identify pathogenic mutations in patients with disease phenotypes such as intractable epilepsy, neuromuscular degeneration, hemiplegic migraine, severe hypocalcemia, Marfan's syndrome, skeletal dysmorphologies and hearing loss. See Core 2.

To continue and expand this effort, we propose the creation of a Clinical Genomics Center serving Arizona and the Southwest (Figure 9). This initiative would increase the geographical range, size and ethnic diversity of the patient population benefiting from next generation approaches to Precision Health. The UA has the clinical expertise to support these services, with strengths including neurology, cardiology, pulmonology, oncology, and pediatric and adult genetics. The clinical infrastructure outlined in the proposed Center for Genomics and Precision Health would support the clinical needs of the effort (Cores 1, 2). The patients cared for would provide samples for biobanking (Core 4) and could serve as subjects for clinical trials (Core 3; Initiatives 1, 3, 5, & 6).

**Figure 9. Clinical Genomics Work Flow.**

After genetic assessment and counseling patients are identified for clinical genomic services. Each case is reviewed by a Medical Review Board (MRB) comprised of board-certified clinical geneticists, genomicsists, cytogeneticists, genetic counselors, and/or informatics specialists. Tissue samples are submitted to the UAGC for genomic analysis, results of which are reported to the MRB. Variants are filtered for inclusion in a comprehensive report that is provided to the attending physician. The report includes variants that are likely to contribute to the patient’s clinical condition as well as medically actionable incidental findings.

**b. Diagnosis and Treatment of Cardiomyopathy** (Tardiff, Hammer, Laukaitis)

We propose to support Dr. Jil Tardiff’s efforts to diagnose and develop treatments that can lessen the impact of cardiomyopathy, a devastating disease often leading to heart failure and sudden death. Modern genetic approaches have provided key insights into the genetic basis of cardiomyopathy. With the plummeting cost of next generation sequencing technology, rapid progress is being made in identifying both the primary causative genes as well as secondary modifier genes. Importantly, the combination of clinical and genomic information has the potential to influence the care of each patient. However, implementing these advances to at-risk Arizonans has been limited by the lack of availability of diagnostic sequencing (Core 2), as well as the lack of clinical infrastructure for uniting researchers, clinicians, and patients (Core 1). Infrastructure is needed to recruit and enroll cardiomyopathy patients with extensive clinical data (Core 3), and seed funding is needed to sequence the exomes of those patients exhibiting a range of clinical phenotypes. If successful, we would develop the first genetic cardiomyopathy clinic in the Southwest and bring cutting-edge health care to the citizens of Arizona. The main focus of Dr. Tardiff’s clinic, hypertrophic cardiomyopathy, affects 1/500 individuals and there is a large unmet need for cutting-edge, modern therapy (based on the services provided by this proposal) for these patients and their families. In fact, even with minimal local outreach, the current clinic is growing rapidly. **Implementation of this initiative will make Arizona a leader in the diagnosis and management of families with genetic cardiomyopathies and establish the groundwork for translational ties to the world-class basic muscle biologists of the Molecular Cardiovascular Research Program at the UA.**
c. Inherited Cancer Predisposition and Cancer Prevention Efforts (Laukaitis)
We propose to build on the existing UA High-Risk Cancer Genetics clinic to expand cancer prediction and prevention efforts statewide. A collaborative agreement has created the UA Cancer Center at St. Joseph’s Hospital, Phoenix through which UA physicians (C. Laukaitis and J. Jeter) provide medical supervision for the St. Joe’s cancer genetic counselor. Experience with tele-medicine, including grant-funded testing of tele-genetic counseling will also serve this effort. We propose to offer physician consultations to guide cancer prevention therapy to patients from UACC St. Joe’s starting this year. We propose to expand to other facilities (Cancer Centers of Northern Arizona Healthcare, Indian Health Service, Gila River Health Care at Hu-Hu Kam Memorial Hospital, etc.) in the next 1-3 years. Billing and support (genetic counseling, nursing, tele-medicine set-up) for this effort should be administered through the Core 1. Samples will become part of the integrated biobank system (Core 4) and patients will be eligible for ongoing clinical trials (Core 3 and Initiatives 1, 3, 5, & 6). Implementation of this initiative will make UA the provider-of-choice for cancer prevention in Arizona.

Recommendations
• Announce the formation of clinics dedicated to diagnostic genomics, cardiomyopathy diagnosis and treatment and cancer prevention.
• Develop a billing plan creating a sustainable effort.
• Provide seed funding to sequence the exomes of 25 cardiomyopathy patients.
• Develop collaborative agreements between the UA and other Arizona medical facilities to support provision of state-of-the-art clinical services to patients statewide.
• Develop billing infrastructure for tele-medicine.
• Support the creation of additional physician and genetic counseling positions as outreach needs grow.

3. Genetics of type-2 diabetes and related complications in Southwestern Hispanics and Native Americans (Klimintidis)
Type-2 diabetes (T2D) is a growing global health threat that disproportionately affects Hispanics and Native Americans. Both genetic and lifestyle factors are known to play important roles in T2D and related health complications. The vast majority of research on the genetics of T2D has been performed on populations of European descent. However, research published within the last three months has revealed the existence of ethnic-specific genetic risk factors in the Hispanic and Native American populations that are absent in other populations, thus highlighting the need to increase research in the genetics of T2D in these high-risk populations. Although Hispanics and Native Americans make up a large proportion of the population in the American Southwest, this region and the UA are barely “on the map” in the field of T2D genetics.

To fill these gaps and advance the UA Precision Medicine initiative, we propose to build upon our current strengths in order to collect and analyze genomic sequence data along with lifestyle factors in the local Hispanic and Native American population in relation to T2D and T2D complications. Specifically, this project will build upon the existing strengths in statistical genetics and public health informatics in the Division of Epidemiology and Biostatistics. For example, Dr. Yann Klimentidis’ research has explored the genetics of T2D and related traits in various populations by applying methods for genomic risk prediction and uncovering interactions of genetic and lifestyle factors. We will also build on the strengths of the UAGC in generating and analyzing whole-genome sequence data, and help to support requested infrastructure in patient management and consent, biobanking, digital health, and informatics.

We plan for patient enrollment to take place at both UAMC and at UA South, where members of the Diabetes Program and the newly-formed ‘Collaboratory’ are based. We anticipate that a
minimum of 1,000 cases and controls will be needed to achieve sufficient statistical power to examine associations and interactions. The field of genomics is increasingly reliant on large consortia that combine data across studies; as such this project will require the integration of services provided by several of key the infrastructure cores. For example, our initial major objectives are to enroll local Hispanics and Native Americans with and without T2D, to obtain large-scale genotyping or whole-genome sequence data on these individuals (Core 2), to examine associations and interactions of genetic and lifestyle factors (Core 4), and to explore the integration of genetic data and biobanked specimens (Core 3) with centralized EMR data. Our secondary objectives are to join existing consortia (e.g., the Carlos Slim Initiative in Genomic Medicine, the Hispanic Community Health Study/Study of Latinos, and the eMERGE network), and to explore the use of digital health tools such as biosensors in the context of metabolic and cardiovascular health (Core 5).

4. Pharmacogenomics: Precision Therapeutics within Precision Health (Cherrington, Klimecki, Futscher, Wondrak, Hurley, Abraham)

Variable drug response exacts a substantial cost in healthcare dollars and societal burden. Reducing unintended drug response in patients is an essential focus of any Precision Health enterprise. Strong pharmacogenomics programs have focused efforts in clinical implementation of predictive and functional tests, discovery and validation of predictive biomarkers, and an analysis of the outcomes/impacts of pharmacogenomics on patients and on the healthcare system. Current strengths within the AHSC could be utilized to create an environment where academic medicine improves upon the current standard of care to make Precision Health a reality. The following three proposals are unified to coordinate an overarching approach to Precision Health from clinical use, to discovery and prediction, to outcomes assessment.

a. Mechanism-Based Prediction of Patient Response.

The ability to predict and adjust a patient’s response to the standard dose of any medication is a high-priority target in Precision Health. Giving the correct dose of an effective drug—rather than the standard dose—is one of the major objectives of personalized medicine. Research identifying molecular mechanisms underlying inter-individual variability in patient response has identified four key causation areas: drug metabolizing enzymes, drug transporters, the immune system, and drug targets. Of these, drug metabolizing enzymes and transporters are predominant and highlight the importance of pharmacokinetics and exposure. Patients who are unable to metabolize or eliminate a drug from their bodies are far more likely to have an increased risk of toxicity due to prolonged exposure to the drug. Identifying these patients prior to the initiation of therapy, and using this information to guide therapy, is a cornerstone of precision medicine. Pharmacogenetic, epigenetic, and physiologic functional testing can identify these patients.

A comprehensive assessment of the predictors of drug response represents a neglected research focus, and as such, a target of opportunity. There are no “Disease-Genetics-ADME Consortium Groups” or “Non-Genomic Research Networks.” Individual grass roots types of efforts have largely advanced this area of research. With the strong capacity that the UA has in both genetic and non-genetic modulators of drug metabolism and disposition, this should be one of our areas of emphasis. We are committing our resources on the promised future of predictive testing for therapeutics that will, in many cases, be a combination of genetic testing and functional
This is a unique niche that few programs are capable of occupying, and the UA would be missing a golden chance if it did not support this within a Precision Health effort.

**Strengths**

- The UAGC has developed genetic screening tests and has applied for CLIA certification to conduct genetic testing for a range of diseases.
- Clinical geneticists (Laukaitis), Human genetics researchers (Martinez, Klimecki, Hammer).
- Dr. Nathan Cherrington’s work linking a liver disease (NASH) with altered pharmacokinetics and drug toxicity.
- Two patents held by UA to diagnose patients with NASH (licensed and undergoing clinical trials) and to identify patients who are at greater risk of toxicity during standard drug treatment.
- Epigenetic-driven therapeutics, companion diagnostics, and biomarkers of disease presence and burden are being developed and implemented in the laboratory of Dr. Bernard Futscher.

**Recommendations**

- CLIA Certification for epigenetics, Analytical chemistry core for drugs/metabolites, E-records management of drug/test/test results flags, Seamless patient consenting and monitoring, Cost of non-reimbursed tests
- Clinicians (Physicians, Pharmacists, Nurses) with buy-in to this type of medical practice, Hospital “buy-in” also fits into this need. E-records management of drug/test/test results flags in routine patient care, Seamless patient consenting and monitoring, Cost of non-reimbursed tests.
- Additional clinical research capacity (research coordination etc. through CATS) for functional testing to identify patients that are at greater risk of toxicity prior to initiating therapy.
- Greater coordination with clinicians to alter the standard of care in response to the functional testing. A fully coordinated academic medicine approach could be used to deliver personalized treatment.
- A centralized drug metabolism and transport analytical facility is absolutely essential. The UA capacity in core-service, small molecule analysis in biological samples is currently inadequate to meet the demands of clinical pharmacokinetic analysis.

**b. Discovery of Drug Response Predictors.**

Diagnostics to identify patients outside of anticipated parameters is an important step in selecting and tailoring treatment regimens to individual needs. Research efforts directed on focused -omics analysis of human samples and experimental models of disease and response lead to the identification of these useful biomarkers. Coupling physiologic or metabolomic diagnostics with companion –omic predictors, microbiome analysis, epigenomics testing, or data mining of large records databases (MMC) has the capacity to complement conventional testing with physiologic probes.

Blood-based nucleic acid and metabolomic diagnostics. An easily accessible tissue that provides cost and time efficiencies when coupled with the power of NextGen Sequencing makes blood-based analysis of disease a potential area for growth and impact. Two nucleic acid approaches can be taken immediately: blood-based diagnostics to monitor cancer burden and/or therapeutic response by analyzing cell free DNA extracts using patient-specific epigenetic and genetic biomarkers, and to detect pathogenic bacterial infections.
**Discovery of Novel Predictive Biomarkers for Therapy Response.** Several researchers are making advances into the specific targets of toxicity in susceptible populations including Dr. Walt Klimecki examining genetic mechanisms of mitochondrial toxicity, Dr. Georg Wondrak investigating oncogene-driven redox dysregulation as a novel target for small molecule chemotherapeutic intervention in melanoma patients, Dr. Nathan Cherrington whose patent to identifying patients with NASH based on altered metabolism of a probe drug, and ANBM, which is participating in a BARDA sponsored consortium to develop genomic tests for dose response to radiation and proteomic-based assays for predicting radiation-induced late side effects in radiotherapy.

**Development of Novel Therapeutics: BIO5 Oro Valley.** A natural complementation with UA drug development programs exists in the Precision Medicine context. Most molecularly targeted therapies will require companion diagnostic testing to ensure the right patient is getting the proper-targeted therapy. Any investment in the basic system that we describe will be applicable to the rapid development and deployment of companion diagnostics assays. The drug discovery program jointly coordinated by BIO5 and the College of Pharmacy is focused on development of molecular targeted drugs and a new comprehensive program in development of the next generation Antibody Drug Conjugates. Companion diagnostics using techniques such as medical imaging to identify specific patients who will benefit from this type of therapy will be a critical component of this effort.

**Strengths**

- CLIA DNA testing lab (Hammer), Epigenetics testing lab (Futscher), Proteomics Core (Lau), Microbiome analysis (Futscher, Wing).
- “Gene by environment” researchers (Cherrington, Martinez, Klimecki, Hammer, Futscher, Vercelli), Epigenetics researchers (Futscher, Vercelli), Proteomics researchers (Lau).
- Dr. George Watts in the shared Genomics/Epigenetics Facility Core of SWEHSC and the Cancer Center holds a provisional patent for technology and software for the rapid DNA sequence-based analysis of the human pathogenic microbiome.
- COM-PHX Center for Applied Nanobioscience and Medicine (ANBM) has also pioneered and patented a rapid DNA analysis system leading to multiple platform configurations for nucleic acids-based assay diagnostics.
- Capability to develop both conventional molecular targeted drugs such as those targeting kinases, as well as drugs to target so call “undruggable targets” such as MYC, KRAS and hTERT through secondary DNA stuctures in the laboratory of Dr. Laurence Hurley

**Recommendations**

- Poor small molecule analysis resources, both –omics and focused (UA ALEC facility is inadequate), Clinical faculty commitment to clinical research.
- A critical mass of investigators involved in all levels of inter-individual variability of pharmacokinetics and drug response is needed. The College of Pharmacy is committed to developing this area of research. In fact, the most recent hire (2013) was directed to “Individuals with research interests broadly in personalized medicine (drug metabolism and disposition, epigenetics).” Assistance in building this area of strength is requested.
- Funding for dedicated bioinformatics in conjunction with Big Data Infrastructure (Core 3). Access to patient records will also be an important feature.

**c. Assessment of Drug Response Prediction on Healthcare.**

One of the great challenges to implementing pharmacogenomics into health systems is the lack of study on the utility and cost-effectiveness of defined programs. The goal is to obtain additional medical information via genomic sequencing that enables health care providers to provide higher quality health care at a much lower cost. We propose a portfolio of studies to document the incremental and critical value of clinical pharmacogenomics on improving patient outcomes at both
the individual and population levels. Guided by the empirical Arizona drug-related morbidity and mortality framework, this series of projects position pharmacogenomics as one of the essential moderators of clinical outcome and will be the beginning of a series of global efforts to accomplish this goal.

The College of Pharmacy has two major current activities unlike any other unit in the U.S. First, the Medication Management Center, a public-private partnership with Sinfonia Health, is the largest such patient care program whose sole purpose is to manage the appropriate and cost-effective use of medicines in over 6 million patients nationwide. The majority of these patients are elderly Medicare recipients. It is our goal to implement a series of epidemiological cohort and case control studies to assist in developing pharmacoeconomic and health outcome models for further application to health plans throughout the country.

Second, the Health Outcomes and PharmacoEconomic (HOPE) Research Center is in final contract phase as the major research, education, and innovation arm of the Ministry of Health for The Kingdom of Saudi Arabia. This is a country of 28 million diverse people with an epidemiological profile spanning from historical tribal homogeneity and differentiation to chronic illness morbidity associated with rapid economic development, prosperity, and lifestyle factors. The (pharmaco)genomic diversity of this population remains largely undocumented, offering a collaborative opportunity ranging from pharmacogenetic epidemiology, clinical pharmacogenomics, micro- to macro-level outcomes, and pharmacoeconomic valuation. Plans are in development to launch a series of studies that ultimately will engage the leadership of all Gulf states (Kuwait, Bahrain, Oman, UAE, KSA, Qatar) to countrywide efforts in the clinical pharmacogenomics, patient-to-population health outcomes, and pharmacoeconomics space.

Considering on-going discussions about medication management services to be provided by the UA Medication Management Center in Saudi Arabia, it will be possible to bridge the above singular efforts by our two centers into research and service models that will drive further development and innovation at the University of Arizona Health Sciences Center and enable the AHSC’s international leadership in accessible, responsible, and economical medication use.

Strengths
- Minimal input is needed as most of the private partnerships are already in place (e.g. Sinfonia, Gulf States, etc.)

Recommendations
- Additional “translational” scientists in health outcomes will be needed as these collaborations and contracts are extended.

5. Improving Healthspan and treating diseases through microbiome and virome (Nikolich-Zugich)

The microbiome is now recognized as a source of critical signals dictating normal gut development, but also as a powerful force modulating function of distal organs and systems and influencing systemic inflammation, aging, and diseases ranging from autoimmunity, arthritis and depression to autism. Parallel studies of virome are just beginning, but are likely to be similarly revolutionary. This initiative proposes to unify AHSC and UA strengths in fundamental virome and microbiome research with proven clinical strengths in respiratory health, geriatrics, psychiatry, arthritis, inflammatory bowel disease and GI cancers. Two or three teams in this area will coalesce around the fundamental hypothesis that manipulations of microbiome and virome can be harnessed to substantially improve human health across the age spectrum. Pilot studies will be initiated
immediately based on the existing cohorts, to provide preliminary data for strong program applications.

This initiative would leverage cross-campus investigator strengths and translation to human medicine and health. Specific areas of strength include the specific role of commensal bacteria, cutting-edge virome studies and recognized excellence in basic biology and immunology of aging. On the clinical side, strengths exist in respiratory health, geriatrics and clinical resilience research, psychiatry, arthritis, inflammatory bowel disease and GI cancers. Moreover, nutrition, metabolic research and climate/arid land angles could all be brought in to further enhance this program. Nationally, this initiative fills several gaps: virome research remains nascent, and there are very few, if any, national programs that have meaningfully linked basic microbiome and virome research to clinical manipulations and outcomes. This is an area with considerable long-term potential for NIH funding and for translation to human health, not overpopulated and with clear institutional base in research personnel and human studies cohorts. Unique angles of our collaborative approach will further distinguish it from competitors.

At a minimum, participant personnel will include, but not be limited to, Colleges of Agriculture and Life Sciences (Veterinary Sciences & Microbiology–Vedantam and Vishwanathan; Arid Lands-TBD), Medicine (Department of Immunobiology–Goodrum, Wu, So, Nikolich; Medicine, w/Geriatrics–Fain, Mohler, Pulmonary–Knox, GI–TBD; Rheumatology–Kwoh, Sarkar; Pediatrics–Kiela, Ghishan, and Psychiatry–Raison), Nursing–TBD, Public Health–Chen, and Science (Ecology & Evolutionary Biology–Sullivan; Molecular and Cellular Biology–Kaplan, Capaldi) and institutes and centers including the Arizona Arthritis Center, Arizona Cancer Center–Thompson, Doetschman, Gerner; Arizona Center on Aging and the Institute of the Environment. This initiative absolutely requires the proposed new infrastructure (Cores 1-5), including (i) Patient Management and Consent; (2) Specimen Biobanking; and (5) Centralized Data Center and Informatics), and may use Biosensors and Genomics and Molecular Diagnostics as it develops. Human cohorts would be contributed by the Department of Immunobiology and the Arizona Cancer Center, although other units may also have pertinent cohorts. 16S rRNA sequencing and high-throughput data analysis would have to be organized at a large scale via the UAGC and the informatics. Timeframe for implementation: 2 years to first R21/R01 support; 3-4 yrs to first P01 application. Final goal: Microbiome & Virome Translational Research Center (virtual or actual; $5M research budget; clinical applications by Y7)

Recommendations

- Recruit a strong figure in microbiome high-throughput research. Greg Caporosa from NAU should be our primary target (recruitable and affordable still).
- EPICS compatibility to pull human subject data (both parts of infrastructure).
- Recruit/free up Project manager through institutional resources.
- Pilot grant support to facilitate preliminary data gathering (salary for 2 graduate students or postdoctoral fellows for 2 years; supplies funds, animal per diem).
- Clinicians, clinical research associates and nurse partners should also be recruited.

6. Precision Health Pharmacodynamic Analytics and Innovation in Skin Cancer Diagnosis and Management at the UA Cancer Center Skin Cancer Institute (Alberts, Curiel, Stratton)

The intent of the Skin Cancer Institute (SCI) is to serve as THE model for community based skin cancer research and care. The Skin Cancer Prevention Program Project from NCI is the longest standing team science grant at AHSC (1980-2016) and has fostered many unique multi-disciplinary collaborations. Arizona has the highest incidence of skin cancers in the US, second worldwide to Australia and New Zealand. Advanced clinical/translational study of skin carcinogenesis, biology, and pathophysiology will help reduce skin cancer morbidity & mortality. Precision
pharmacodynamic analytics will use clinical, histopathologic, karyometric, and protein/phosphoprotein activation patterns associated with human skin carcinogenesis to develop and optimize use of new active drugs for cancer treatment and prevention. Exposure to solar-simulated light (SSL) in a controlled clinical environment followed by a small skin biopsy serves as a convenient clinical platform to demonstrate modulation of specific targets in cellular signaling cascades resulting in genotypic and phenotypic changes. Some of these changes appear highly variable in individuals regardless of skin type, and may predict response to selective tyrosine kinase inhibitors, which are becoming mainstays of cancer therapy. Target modulation by acute exposure of topical drugs may be used as a tool for combination therapy selection in consort with other ‘omic’ tools to develop a unique risk/response profile. Tools in development include 1) reflectance confocal microscopy with discriminative image-analysis software; 2) “skin chips” for mRNA expression arrays created directly from fixed tissue using a quantitative nuclease protection assay; 3) advanced reverse-phase protein microarray technology for molecular network analysis; 4) karyometric machine vision analyses for prediction of skin cancer outcomes; and 5) faster drug/target validation using “Phase 0” clinical trials.

In the last decade, tremendous progress in skin imaging is providing us with opportunities to apply these powerful technologies. Because of our institutional strengths in optical imaging research, specifically in confocal microscopy, spectropolarimetry, and image storage & analysis fields; combined with expanding programs in experimental, translational, and clinical skin cancer research; we have an extraordinary opportunity to establish a multi-disciplinary Skin Cancer Imaging Program. The use of non-invasive confocal microscopy and spectropolarimetry has the potential to spare diagnostic surgical procedures, accelerate diagnosis turnaround time, and guide the monitoring and surgical management of skin cancer. Imaging efforts will 1) optimize imaging technologies for clinical implementation, and 2) develop and evaluate methods for clinical application to increase quality of care and cost-effectiveness in skin cancer.

**Potential Funding Sources.** Grant opportunities, industry partnerships, clinical reimbursement, and philanthropy are all potential funding sources. The SCI is built on philanthropy and provides the basis for community development, but there are currently no UA funds that support the SCI. This initiative needs to be pursued to continue momentum in this area created by current levels of federal funding and the SCI. This is a priority research area for the state of Arizona, and the clinical volume in sun damage and skin cancer provides the patient base for research on precision diagnostics and individualized therapy. Other key reasons to pursue this effort now include: 1) The speed of evolution in the skin imaging field over the last 10 years and the natural fit of UA home-grown expertise in optics and skin cancer care; 2) the burden of skin cancer (5% of the Medicare budget is allocated to skin cancer diagnosis and treatment); and 3) the technology transfer opportunity for a high ROI. **Timeframe:** 1-3 years, building on current strengths

**Strengths**
- Leverages the well-established and internationally renowned expertise in cancer, optical sciences, bioengineering, and radiology.
- Concentrated, funded research in prevention and early detection makes one of the strongest programs in the UACC, and the multi-disciplinary Cutaneous Oncology Program at UAMC North is a national model for multi-disciplinary clinical care.
- Broad-based participation including Colleges of Medicine, Pharmacy, Nursing, Optical Sciences, Engineering, and Public Health (already working in an interdisciplinary P01 grant) along with the resources of the SCI and collaborative partners at the University of Minnesota and George Mason University.
- Primary resources to be provided include effort and clinical expertise of the faculty and post-docs through a collaborative set of pilot projects selected by a scientific committee.
• The UACC SCI is actively working to secure philanthropic funds to support gaps in FTE and other infrastructure resources.

Recommendations
• CLIA certification of the SSL research clinic and analytics lab
• Acquisition of a modern solar simulator and reflectance confocal microscope for clinical use
• Development funds for an experimental spectropolarimeter
• FTEs include a program coordinator (0.5), Post-doc support (3 x 0.5), and administrative support.

7. Integrated Genomic Characterization of Late Stage/Therapy Refractory Gastrointestinal Tumors For Novel Therapeutic Targets (Elquza, Patel, Nfonsam, Howell, Patel, Thorn, Nelson)

The mission of The University of Arizona Clinical Gastrointestinal Cancer Program is to provide state of the art preventive, diagnostic and treatment services for patients suffering from gastrointestinal cancers (i.e., malignant tumors of esophagus, pancreas, biliary tract liver, colon and rectum, and anal cancers. The Cancer Center’s Clinical Gastrointestinal Cancer Program is a multidisciplinary program that draws on the special expertise in gastrointestinal cancer pathology, molecular biology, surgical oncology, radiation oncology, pain management, nutrition, and psychosocial services. Approximately a third of patients with colorectal cancer and a large proportion of patients with esophageal, gastric, and pancreatic cancer present with advance, incurable disease.

New advances in drug treatment have enabled treatment of these cancers with targeted therapy which seeks to exploit an error in the normal functioning of a tumor, compared to other cells in the body, thus in principle allowing only tumor cells to be killed by the drug. The goal of this clinical research program is to comprehensively explore the genetic basis of late stage or therapy refractory G.I. cancers, with emphasis on elucidation of therapeutically relevant targets using integrated whole genome and whole transcriptome analyses of tumors from patients. After integrated analysis of a patient’s genomic and transcriptome data, subjects will be enrolled onto clinical trials with specific agents.

Strengths
• GI oncology clinical program has one the largest volume of patients at the UACC.
• The clinical team, led by Dr. Elquza (medical director of UACC), has access to novel therapeutic agents and currently enroll G.I. cancer patients onto clinical trials.
• Dr. Nelson has scientific expertise in G.I. cancers and analysis of tumor genomes.
• Dr. Futscher has equipment and expertise for the genomic analysis of tumors.
• UAGC has applied for CAP/CLIA certification as a high complexity clinical laboratory.
• This clinical research program can integrate into ongoing G.I. SPORE efforts.
• There is expertise in UACC and BIO5 informatics to develop the necessary bioinformatics pipeline.

Recommendations
• Support for Research coordinator and clinical research associates.
• Funding for dedicated bioinformatics in conjunction with the infrastructure described above.
• Access to sequencing equipment in CLIA approved laboratory setting.
8. Personalized Radiotherapy and the Advanced Particles Radiotherapy International Laboratory (APRILA) (Zenhausern)

APRILA is a UA-led consortium of interdisciplinary scientists, engineers and clinicians at international institutions investigating guiding personalized radiotherapy applications of a large spectrum of particle beams beyond conventional photons, in particular including hadrons and other particles. The consortium leverages existing international networks of hadrons therapy centers (6 centers in Europe and Japan) as there is no US-based infrastructure yet. The technology is targeting tumors more accurately and about 3 x more efficient than X-rays (photons) or even protons. In the case of rare or complex cancers, carbon therapy revealed up to 25% increase in survival outcomes using 4x less fractionation than protons therapy reducing secondary effects for the patients. The higher biological efficacy and ballistic accuracy of carbon ions result in low level of side effects so that treating tumors in complex microenvironments can be pursued (e.g. brain tumors, sarcomas). The UA team has entered formal cooperative agreement with the CERN and CNAO center as well as its E.C. sponsored network ULICE and ENLIGHT. APRILA consortium has also submitted a planning grant to NIH/NCI while 2 derivative proposals have also been submitted to E.C. Horizon 2020 program for joint funding. These programs will also enable other active initiatives for large funding renewals (e.g. NIAID Center for Medical Countermeasures Against Radiation U19; DHHS BARDA Biodosimetry) that will position UA in competitive lead while providing access to a large hub of specialized resources and infrastructure facilitating generating competitive datasets for a future local facility. UA researchers are also inventors on a few important patents related to the thematic domain.

APRILA leverages UA at large with strong expertise and resources from AHSC, engineering, physics and optical sciences as well as bioengineering and most departments of Life Sciences, as well as the AZ Cancer Center and most of the AHSC research and clinical capacity. Molecular radiobiology is a growing converging field of multiple disciplines from the state-of-the-art molecular biology techniques (e.g. NGS, Gene expression and meta-omics), immunobiology, to nanotechnology (e.g. nanoparticle-self lighting photodynamic therapy in combination with radiation therapy including particle/proton therapy for deep cancer treatment) but also to the development of dosimetry, studies of the exposome, next generation of accelerators and ancillaries. Medical disciplines related to radio-oncology but also broader emerging applications in cardiovascular diseases and other clinical applications will enable the program. Other non medical applications such as particle beam processing in materials sciences will also be leveraging the infrastructure and providing interdiscipliary research opportunities from NASA, DoD and other global industrial partners that are already cooperating on some of the largest UA programs (e.g. NASA – GODDARD OSIRIS-REX) and new campus-wide initiatives (e.g. Defense and Security Research Institute). At present APRILA team comprises about 20 principal member representatives of equipment manufacturers, medical centers, developers, academic and governmental institutions already committing significant assets and services toward the realization of an unprecedented interdisciplinary national facility. Considering 2/3 of cancer patients undergo some radiotherapy treatments (alone or in combination with chemotherapy), improving and guiding personalized treatments will revolutionize standard of care.

Recommendations:

- Promote international collaboration and faculty/students exchange for accessing existing specialized facilities and experts for leading UA implementation of biomarker-guided imaging and treatment of most common forms of cancers
- Develop financial model with economic experts at UA business school and local experts form government and industry to establish reimbursement model for US clinical services
- Recruit world-renowned physicians and physicists for leading innovative tool development and design of future UA facilities
Establish public-private partnership framework for capital investment development
Engage with a diverse pool of federal agencies for development of roadmap of future opportunities for sponsored research programs
Secure strategic support from partners for sustained healthcare delivery and research services while stimulating innovation and outcomes
Develop educational and professional training programs in advanced radiotherapies
Budget, recruit and hire faculty members across UA departments (5-8x) for startup phase

9. Institute on Place and Wellbeing (Sternberg)
Exemplifying an important grand challenge of Precision and Digital Health, the Institute on Place and Wellbeing’s research layers individuals’ time and location stamped biosensing and environmental data to address the impact of specific aspects of the built and green environment on specific aspects of human health and wellbeing. By collecting genetic and genomic material in prospective studies, this approach has the capacity to predict genetic factors that contribute to susceptibility and resistance to specific environmental factors, from genome to exposome. This research will create the next frontier of (1) person- and place-centered digital health and wellbeing; (2) green/sustainable design to include human health and wellbeing outcomes; (3) environmental health beyond removing toxins to enhancing support of human emotional and physical health. This highly interdisciplinary research leverages strengths across UA and UAHS: bio- and integrative medicine; psychology; biomedical engineering; Big Data Analytics; environmental sciences; architecture, urban planning, design. It attracts new granting sources beyond NIH, (DoD, DARPA, General Services Administration); new industry partners (GE, National Football League, Google, major architectural firms, developers), with potential for sustainable income to support core facilities through IPW consulting activities. Application of design interventions to create a healthy built environment will directly impact UAHN’s standard of care and market competitiveness. Relevant to Arizona-centric issues, including desert and climate adaptation, it is scalable and applicable worldwide in both the built and natural environments. UA is uniquely positioned to lead the nation in this new and emerging arena as new Federal guidelines are introduced including human health and wellbeing outcomes in green building and urban design standards.

Two sample research projects, in progress, are described in which biosensing data will be layered on environmental data using Big Data Analytics to measure the impact of specific aspects of the environment on individuals’ health and wellbeing. Project 1 applies this approach to the built environment, comparing workers in the sustainable/green retrofitted half of the Washington, DC Headquarters of the General Services Administration, to workers in the old/legacy half. Project 2 uses the same experimental approach to measure the impact of Southwest

Sequence & Timeline: Steps 1 & 2 can be accomplished in a 1 year period; Step 3 & 4 in a 2-3 year period, depending on numbers of subjects. ROI can be accomplished simultaneously in a 1-2 year period.
Tucson’s Tumamoc Hill natural desert sanctuary on health and wellbeing of community members in the urban heat island Barrio surrounding the Hill. Biomarker measures of allostatic load of stress, health and wellbeing include: psychological (smart phones momentary self-report assessments); physiological (Heart Rate Variability, activity, sleep quality – Najafi, iCAMP; salivary cortisol, sweat stress and immune biomarkers – Sternberg, AzCIM); social interactions (Electronically Activated Recorder “EAR”– Mehl, Psychology). Individual behaviors and space usage patterns will be tracked using digital health technologies. Environmental measures include light, sound, temperature, airflow collected with on-person and static environmental sensing devices (CAPLA). These and general health data will be used to calculate green/sustainable design’s costs and health outcomes Return On Investment.

Leveraging UA Big Data Analytics expertise, including iPLANT, Big Data Analytics (Ram, Eller College Management) and Geographic Information Systems (GIS), these massive data sets will be linked to relate environmental to health and wellbeing biomarker data as persons move through environmental gradients from urban heat island to natural vegetation protected area, or through the built environment. The health benefits of the natural desert environment on health disparities in the underserved Barrio will be assessed by comparing health outcomes in identical zip codes without access to a similar natural refuge (College of Public Health; CAPLA). The impact on allostatic stress load and the effect of integrative interventions e.g. mindfulness meditation, in chronically stressed caregiver populations who use Tumamoc Hill will be studied (AzCIM, Carondelet St. Mary’s). These methods will: be transferrable and scalable to other natural and urban settings and built environments; elucidate factors contributing to human climate change adaptability and resilience; address whether access to a natural environment with regular exercise, can counter negative effects on health of an urban heat island and socioeconomic factors in health disparities; inform design and policy decisions in all types of built and urban design.

Recommendations

- Improved server capacity for downloading, analyzing, and integrating massive data sets;
- Motion tracking reference tools for validation of wearable technology;
- Telemonitoring technologies;
- Improved mass spec facilities/equipment for proteomics and small molecule analysis (e.g. LC-MS MALDI-TOF) for further development of sweat biomarker analysis.
- **Analytics & Bioengineering Personnel:** Big Data Analytics, bioengineering including postdocs, graduate and undergraduate students to reinforce collaborations, collect/crunch data, algorithm design, develop sensors, reinforce clinical collaborations.
- **Immunochemistry:** Mass spec personnel.
- **Clinical Personnel:** Environmental psychologist; health outcomes expert; clinical trials personnel; MPH expert in underserved populations at an urban scale;
- **Design personnel:** GIS experts and students; architect/environmental psychology.
- **Support personnel:** full time administrator and grant writer – to coordinate grant writing and organize regular meeting and interaction between key investigators; business specialist to write business proposals to private sector and to monitor and follow-up on projects.
- Seed funds for prototype device development: Sweat biomarker discovery and sweat collection and mHealth device development.

10. UACC GI SPORE (Thompson)

The Arizona Cancer Center Specialized Program of Research Excellence (SPORE) in GI Cancers (P50CA095060) has been continuously funded for 10 years. On Feb 1, 2013, the leadership transitioned from Dr. Gene Gerner to Dr. Patricia Thompson (co-leader with Dr. Gerner for the past six years). The GI SPORE addresses problems associated with cancers of the colon, pancreas and esophagus. **The overall goal of our SPORE is to prevent and cure GI cancers.**
strategy has been to broadly apply knowledge of cancer biology and genetics to develop better methods of GI cancer risk assessment and treatment for patients with GI cancers or those at risk of GI cancers. Our project goals have been to develop tailored approaches for individual patients that will safely and effectively treat GI cancer risk factors.

During the prior two funding periods, the GI SPORE published over 250 publications reporting its scientific findings. In addition, during the most recent funding period (2007 - present), GI SPORE investigator research produced four patents and four invention disclosures. The GI SPORE Program has brought 25 million dollars to the U of A over the past decade.

Current Status: In September 2013, Dr. Thompson submitted a new GI SPORE application. The application is pending review by council, summary statements are not yet available. The team of investigators are actively preparing for a resubmission. As of March 2014, two of the four research projects have been submitted as RO1s, one is pending submission and one of the pilot projects has been funded through the provocative grants mechanism (PI Thompson).

The structure of the current proposal and FIVE-YEAR DELIVERABLES are:

Project 1.
- First preclinical mechanistic evidence for FXR agonists as prevention agents in obesity associated high grade Barrett’s esophagus.
- First clinical evidence for FXR as a prevention and possible therapeutic target in high grade Barrett’s esophagus; a precursor of esophageal cancer where rates have risen 400% over the past 2 decades

Project 2.
- First clinical evidence for minimally invasive metabolic profiling as a strategy for drug selection and drug response monitoring in pancreatic cancer
- Novel metabolomics strategy for preclinical screening of candidate anti-metabolites for use in pancreatic cancer treatment

Project 3.
- First clinical evidence for polyamines and prostaglandin inhibition as targets for inhibiting adenomatous polyp formation in adult FAP
- First clinical evidence for DFMO plus sulindac treatment in children as a therapeutic strategy to safely delay colectomy
- First preclinical evidence for polyamine transport inhibitors as co-drugs with DFMO to overcome metabolic rebound and drug failure with DFMO alone

Project 4.
- First mini-TCGA analysis of the clinical and histological presentation of non-familial, adolescent and young adult onset colorectal cancer in a diverse patient population
- Development of paraffin based genomic/proteomic platforms for diagnosis and treatment selection based on targets for the adolescent and young adult onset colorectal cancer patient.

Strengths
- At this point in time, we have the critical mass in terms of expertise and as of July 1, 2014

Recommendations
- Hire a senior, well-funded physician scientist in GI cancers to partner with Dr. Thompson through the multiple PI mechanism. This has to be a physician scientist with a history of and current RO1 funding.
- Gain a larger market share in Tucson of GI cancers, this is declining in real time.
- Continued support for preliminary data to enhance the level of scientific evidence and translational potential of each of the four projects
Continued support of the GI SPORE biorepository
- Support to convene our scientific advisory board in person in Tucson
- Continued administrative support for a resubmission and project management
- Program directed philanthropic support and institutional and statewide recognition of this exceptional and highly collaborative research team

11. The first state-wide treatment and research center of excellence in the diagnosis, prevention and treatment of chronic liver disease (Thompson)

Non-alcoholic steatohepatitis (NASH) is an obesity associated liver pathology that increases the risk for chronic liver disease, liver failure and hepatocellular carcinoma (HCC); all costly morbid conditions with high mortality rates. Asian, Hispanic and Native Americans are at significant risk for NASH. Until recently, there has been no effective treatment for NASH or for the prevention of NASH progression to fibrosis and cancer. This year, the FLINT Phase 2b Trial of the Farnesoid X Receptor (FXR) agonist Obetocholic Acid (OCA), product of Intercept Pharmaceuticals, for the treatment of NASH was stopped early for efficacy.

Given the growing burden of NASH and HCC in our community, we initiated a NASH/HCC working group that includes leaders from the Departments of Medicine (Dr. Tom Boyer), Radiology (Dr. Diego Martin), the Arizona Cancer Center (Dr. Patricia Thompson), Dignity Health St. Josephs Medical Center (Dr. Richard Mansch) and Intercept Pharmaceuticals. This group of investigators brings together expertise in liver pathogenesis, advanced imaging and expertise in FXR agonists, bile acid biology, metabolomics and pharmacogenetic determinants of OCA response as well as expertise in special populations research.

Where this fits in the larger landscape. Chronic liver disease and non-viral HCC are among the most rapidly increasing fatal diseases in Texas, New Mexico, Colorado, Arizona and California. These increasing rates reflect a high burden of risk factors and high susceptibility in individuals of Hispanic and American Indian ancestry for NASH; an active epidemic in the population. Action NOW would allow us to LEAD the field in research and clinical management of liver pathologies arising from the obesity epidemic.

Strengths
- At this point in time, we have the critical mass in terms of expertise

Recommendations
- Recruit a nationally recognized research Hepatologist
- A fatty liver disease research clinic
- Resources to shore up our clinical coordination to enhance accrual of NASH patients to an open and active protocol for the development of non-invasive for diagnosis of NASH and NASH staging using MRI.
- Resources to test the efficacy of OCA and timing of intervention for the prevention of NASH-associated HCC in mouse models.
- Resources to test the role of metabolic tracer studies to identify individuals most responsive to OCA (identify response phenotype) considering to what extent the genotype explains the variance in response. (Does genotype or phenotype best predict response? This study will then allow us to conduct dose finding studies based on phenotype/genotype profiles.

12. Valley Fever as a Precision Health Target (Gagliani)

Coccidioidomycosis (Valley Fever) is the most important orphan disease to the state of Arizona. Although only 20,000 infections were reported to the CDC in 2011, 16,000 of these came from Arizona. Seen another way, at least a third of all Arizona community acquired pneumonias are
Valley Fever infections. Between Arizona and California, the economic impact (inpatient, outpatient, lost productivity) is easily $0.5 Billion dollars annually. Even so, nationally and worldwide, Valley Fever is a rare disease and, as such, is neglected.

Within the estimated 150,000 annual human exposures, less than a third become ill and less than 1% have the fungal infection extend beyond the lungs, perhaps 400 to 800 per year in Arizona, producing debilitating, even life-threatening morbidity. All evidence to date indicates this broad spectrum of health outcomes is the result of genetic differences in people, the basis of which has only barely begun to be understood. For example, persons of West African or Filipino ancestry appear to have a many fold increased risk of wide-spread infection, but the genetic basis for this is unknown, primarily because the problem has not been studied with the informatic tools that are now available.

In 1996, the Arizona Board of Regents approved the Valley Fever Center for Excellence at the University of Arizona. Since its inception, the Center has sponsored and encouraged research by scientists from the Colleges of Science, Agriculture, Pharmacology, Public Health, and Medicine. This has resulted in discoveries toward the impact of weather on infection rates, improved diagnostics, and preventative vaccines, one of which is currently headed for clinical trials in dogs. Also, the UA is the sponsor of an active FDA drug development program for a potentially curative Valley Fever antifungal drug. In 2012 the Center, along with the College of Medicine in Phoenix, partnered with St. Joseph’s Hospital to establish a clinical center to serve as the hub-of-the-wheel for improving clinical care for patients with Valley Fever throughout the state. As recognized by ABOR, it is extremely appropriate for the UA to undertake this responsibility given the impact of Valley Fever on this state more than any other.

The Valley Fever Center for Excellence is an excellent target to develop Precision Health.

- Better understanding of the interface between increased urbanization and the acquisition of coccidioidal infection could lead to prevention by reduced exposure.
- Establishing metrics for the best outcomes in clinical management of early coccidioidal infections could lead to right-sized care and reduced costs.
- Using the increased susceptibility of African Americans as a probe, first genetic markers of risk and eventually responsible genetic polymorphisms could be identified, further improving risk stratification of the consequences of infection.
- The early successes in developing diagnostics, drugs, and vaccines for Valley Fever are opportunities ripe for rapid translation into clinical practice.
- In Valley Fever, we have the paradox of a “rare disease” being very common in a very small geographic area.
References


