

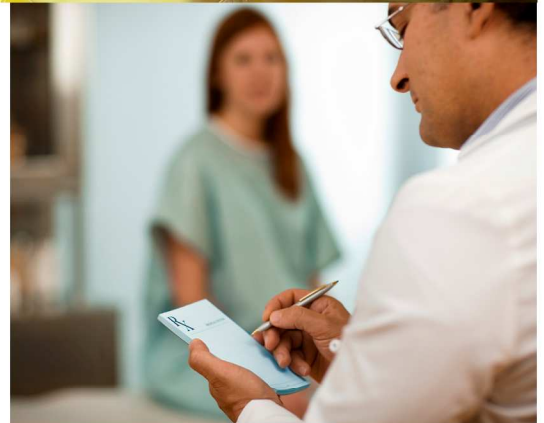


February 2010

# *Briefing Report on Framework for Understanding Personalized Medicine Opportunities for Arizona*

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*Prepared for: Flinn Foundation*



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## Experts Herald in the New Era of Personalized/Individualized Medicine

*I see a dramatic shift to individualized medicine—the ability to deliver therapeutics on an individual basis through molecular phenotyping of disease subtypes and to predict both patients’ therapeutic and side effect responses to drugs...Understanding the molecular biology of an individual’s disease by using early diagnostic testing and genetic profiling will allow therapy to be selected with a greater expectation of benefit.*

Arthur D. Levinson,  
Chairman & CEO, Genentech, the nation’s first and one of the most successful biotech companies, from Ernst & Young’s 2001 Annual Report on Biotechnology

*The old paradigm in medicine is a series of actions: observation of a disease condition and action to treat it; an observation of a response; and then a correction if the desired response is not achieved immediately...There is a new paradigm for personalized medicine, however, one in which complex testing (some of which is genomic, some of which is proteomic, and some of which is other technologies) plays a central role in linking observation to tests and therapies. In such a paradigm, observation is followed by a test that provides specific information for better decision-making.*

Brad Gray, President of Genzyme Genetics  
Diffusion and Use of Genomic Innovations in Health and Medicine,  
National Academy of Sciences, 2007, page 39

*In the last few years, personalized medicine—using genetics or other molecular biology-based diagnostic tests to customize treatment for a particular patient—has emerged as a powerful new tool for healthcare. Therapy guided by genetic testing has proven highly successful in treating some types of leukemia and breast and lung cancer. Similar “personalized” therapies are on the horizon for other types of cancer, as well as diabetes, heart disease and other deadly disorders.*

G. Steven Burrill  
CEO, Burrill & Company  
Biotech 08: Life Sciences A 20/20 Vision to 2020, 2008, pages 45

*In five years, we predict there will be numerous new companion therapies and diagnostic tests—that is, drugs whose prescribing information is linked to the results of a molecular diagnostic test. There will be incremental progress. In 15 or 20 years, I’d like to think that we won’t be talking about personalized medicine at all. It will just be the way medicine is practiced. The patient will ask the physician ‘will this work for me?’ and the physician will have various tools in his or her arsenal to find out.”*

Edward Abrahams, Executive Director, Personalized Medicine Coalition  
US News and World Report –The Future of Medicine, August 2009, p 35

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## Executive Summary

The genomics revolution is shaping and advancing medicine in the 21st century from being an inexact science of detection and treatment to one of prediction, prevention and strategic intervention or what is more popularly referred to as “personalized” medicine.

One of the first applications of personalized medicine already advancing in health-care treatments is the use of genomic information to more precisely prescribe medications based on an individual’s genetic ability to metabolize drugs, a growing field referred to as “pharmacogenomics.” Over time, pharmaceutical and biotechnology companies will be able to develop drugs that are more specific to the genomic variations in diseases found across sub-population groups. And with improved understanding of genetic variation and the interaction of genes and the environment, it is expected that individualized wellness treatments involving exercise, diet and lifestyle will be commonplace based on our risk profiles.

The rise of personalized medicine is of particular importance to states and regions focused on biosciences development. Personalized medicine has the potential to be a disruptive force in biomedical development that can allow emerging bioscience states, such as Arizona, to leapfrog the competition and emerge as a national leader.

Personalized medicine is not a “one-trick” pony. The emergence of personalized medicine is expected to offer multiple opportunities for development. The advancement of personalized medicine is not simply a phenomenon of generating basic research discoveries. Instead, it touches all aspects of translational research from basic discovery through drug and diagnostic development on to pre-clinical and clinical research and finally to health-care delivery and public-health interventions. A state, through its

research institutions, health-care providers and industry, can be positioned to gain a foothold in personalized medicine in specific niches.

For Arizona, the interest and focus on personalized medicine grows out of the emergence of **molecular therapeutics, vaccines, and diagnostics** as a signature opportunity area in biosciences research for the state. As detailed in the January 2008 update of Arizona’s core bioscience research competencies prepared by Battelle for the Flinn Foundation, *Arizona’s Bioscience Roadmap Toward 2012: Progress and Directions for the Future*, Arizona’s growing strengths in molecular therapeutics, vaccines, and diagnostics involves:

- **A growing capability in molecular and genomic sciences**, which represents 25 percent of Arizona’s competitive research grants in the biosciences awarded to Arizona universities, nonprofit research organizations, hospitals, and industry from NIH, NSF, USDA, and ABRC from 2000 to 2006. Arizona’s strengths in basic molecular and genomic sciences range from basic genomic sciences involved in genomic mapping, epigenetics, and gene regulation, to more applied research into human diseases involving high-throughput genotyping and gene sequencing, major NIH grants for studying molecular processes in heart development, asthma, and nervous system/neural development, and advances in new technology platforms of biosignatures, glycomics, and bionanotechnology to Arizona.
- **Supportive core-research competencies in bioimaging, bioinformatics and vaccine technology** offer important advanced-technology strengths for advancing solutions to personalized medicine.

- **Multiple disease focus areas.** In addition to a long-standing focus on cancer disease research, Arizona has growing disease-research efforts in cardiovascular disease, neurosciences, asthma and inflammatory processes, and diabetes that are oriented towards application of more genomic and personalized-medicine approaches.
- **Rising industry strengths related to molecular therapeutics, vaccines, and diagnostics.** The research-and-testing sector of the biosciences industry is expanding dramatically in Arizona, growing 27 percent in number of establishments (up by 67) and 21 percent in employment (up by 1,171 jobs) from 2002 to 2006. Compared with the industry nationally, it is also the most specialized non-hospital bioscience sector in Arizona. Furthermore, an analysis of Arizona's biosciences patents, which are dominated by industry, reveal clusters related to arrays and assays, drug development, imaging, and protein chemistry and molecular biology. A leading firm in the application of genomics to human diseases is Ventana Medical Systems, which was recently acquired by Roche Holding AG, and is now becoming home to all of Roche's cancer-diagnostics products. Other leading firms in the application of genomics to diagnostics and targeting drug development include High Throughput Genomics, CARIS/MPI, Applied Microarray, Intrinsic Bioprobes, and Chromosome Labs.

***In light of the growth potential, disruptive nature, and growing Arizona competencies related to personalized medicine, the Flinn Foundation determined it was critical for Arizona to take stock of its position in personalized medicine and to chart a pathway for realizing Arizona's potential to take a leadership role in specific areas of personalized medicine.***

## **APPROACH TO THE BRIEFING REPORT DEVELOPMENT**

The focus of this briefing report is to set out a framework for better understanding the issues and prospects for personalized medicine and its implications for Arizona. The specific questions for this briefing report to consider are:

- What is the trajectory of personalized medicine's development and its potential niches?
- How is Arizona positioned today?
- What specific opportunities is Arizona best positioned to capture?

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### ***The key sections of the Briefing Report include***

**Part I** – A Closer Look at Personalized Medicine and the Promise of 21<sup>st</sup>-Century Medicine

**Part II** – The Research and Technology Challenges for Personalized Medicine

**Part III** – Benchmarking National Leading Organizations in Personalized Medicine

**Part IV** – Arizona's Position in Advancing Personalized Medicine

**Part V** – A Recommended Pathway for Arizona in Personalized Medicine

**Appendix A** lists Arizona's specific research and health-care assets to advance personalized medicine.

**Appendix B** lists Arizona bioscience companies with capabilities to contribute to personalized medicine.

**Appendix C** lists Arizona-based interview participants

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To bring this analysis together, Battelle conducted an extensive literature review, including:

- Department of Health & Human Services, Realizing the Promise of Pharmacogenomics: Opportunities and Challenges, March 23, 2007
- PriceWaterhouseCoopers Report on Pharmacogenomics: Personalized Medicine. The Emerging Pharmacogenomics Revolution.
- Burrill Report: Biotech 08: Life Sciences A 20/20 Vision to 2020, 2008
- Pharmacogenomic Perspectives
- Stephen C. Schimpff, MD, The Future of Medicine: Megatrends in Health Care, first published in 2007
- Numerous scientific and news articles, as well as market studies, which are cited throughout the document.
- Interviews with Arizona-based investigators (see listing in Appendix C)
- Interviews with directors and investigators of leading programs around the nation, including University of North Carolina, University of California, San Francisco, Vanderbilt University, and St. Jude Children's Hospital

## Recommended Pathway for Advancing Personalized-Medicine Development in Arizona

Personalized medicine's development will come in waves and there is no one-size-fits-all roadmap to success. Indeed, as Table 1 suggests, personalized medicine extends across the translational-research paradigm from bench to bedside.

The best practices of leading academic programs from around the nation suggest that it is critical to:

- Bring together multi-disciplinary teams involving both basic scientists and clinicians;
- Be organized to ensure the needed hand-offs and integration across the translational-research paradigm;
- Have committed leadership, since it can take many years to bring together a high-functioning initiative; and,
- Start in the clinic to access patient populations and, then, work backwards to the genetics.

Battelle's assessment of Arizona's position suggests:

- Arizona starts with many of the prerequisite competencies—in high-throughput genomics, proteomics, molecular and genetic basic research, along with focused technology strengths in bioinformatics and bioimaging—to become a nationally-recognized player in targeted areas of personalized medicine. Arizona seems well-positioned to have leading research niches in epigenetics, diagnostics technologies, and pharmacogenomics with continued investment, particularly in faculty recruitment.

But Arizona's personalized-medicine pieces are relatively small, fragmented across institutions, and lack the committed leadership and coordination on a comprehensive, statewide level to be successful. Arizona must address the critical resource gap to succeed in personalized medicine—a lack of an integrated clinical research enterprise capable of tapping Arizona's patient

population at the scale required to inform and foster personalized-medicine development.

A unique, statewide collaborative initiative is proposed to advance Arizona's position in personalized medicine, as summarized in Table 1 (next page).

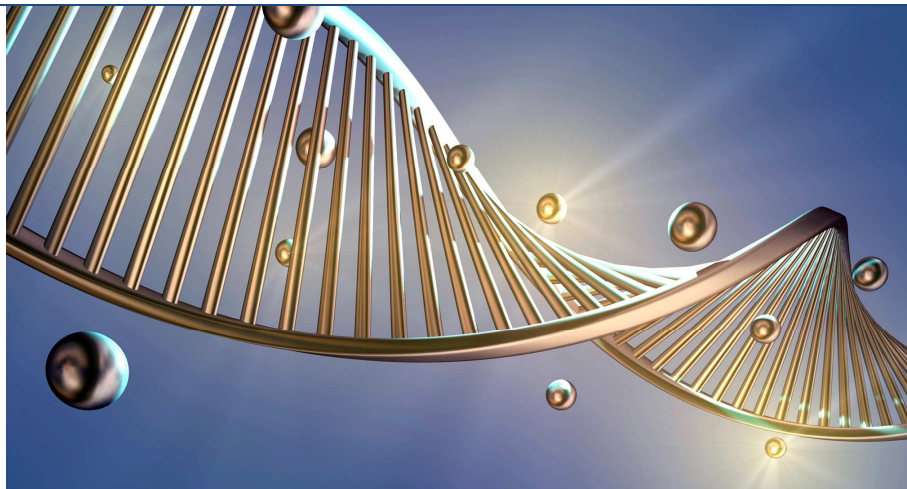
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For Arizona to advance, and realize its potential in personalized medicine, Battelle recommends:

1. *Establish the facilitative and coordinating mechanisms for advancing multi-disciplinary research projects in targeted disease areas.*
  2. *Focus on a set of specific disease areas that can bring together existing resources across institutions in Arizona.*
  3. *Engage Arizona's broad biomedical community to pursue an approach that works from the clinic back to the research lab.*
  4. *Spur the investment in modern translational-research infrastructure needed for advancing personalized medicine, including biorepositories, population databases, and epidemiology and biostatistics. In addition, evaluate more closely the infrastructure for a health-informatics system(s) that would enable integration of personalized medicine and personalized health care.*
  5. *Establish a focused storage and analytic center with the capacity to service the large pharmacogenomics datasets developed by investigators in Arizona and their collaborators.*
  6. *Establish a diagnostics-development center to support the academic and industry partnerships involved in the discovery, development and validation of biosignatures, biomarker molecules for gene-based diagnostics.*
  7. *Develop a new and innovative medical and pharmacy curriculum that incorporates the importance of pharmaceutical, genomic, proteomic, information technology, and other biomedical innovations in order to assist physician acceptance of personalized medicine.*
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**Table 1: Summary Framework for Understanding Personalized Medicine**

	Basic Discovery	Drug & Diagnostic Development	Pre-Clinical Studies	Clinical Research	Clinical Adoption	Public Health
Key Activities	Basic research into genetic variations in disease processes	High-Throughput Screening, In Vitro Assay Development	Testing for Pharmacokinetics, Metabolism, Mechanism of Action	Clinical trials	Prescribing treatments for an individual's disease or condition	Broader population-based interventions
Role of Personalized Medicine	Involved in identifying biochemical pathways and related biomarkers of genetic variations that help diagnose and target candidate pathways for particular therapeutic interventions, as well as consider drug metabolism and response to new therapeutic interventions.	More mechanistic approach, using predictive information, for developing safer and more effective drug therapies for treating particular sub-population groups.  Use of biomarkers for toxicity assessment based on genetic variations across population groups.	Open up a new era of Phase 0 trials in which micro-doses are used to study the biology and pharmacology of new drug candidates.	Design a clinical-trial approach around targeting of specific sub-groups.	Improve the targeting of specific drugs and dosing of those drugs based on an individual's genetic make-up.	Advance a more molecular-based understanding of health disparities.  Address cost-effectiveness of drug treatments.  Mitigate adverse drug reactions.



## Part I: A Closer Look at Personalized Medicine and the Promise of 21<sup>st</sup>-Century Medicine

A closer look at personalized medicine suggests there is much substance, but often also major hype and misunderstanding about what it is and how it can contribute to advancing medicine in the 21<sup>st</sup> century.

### Not Really Customized to an Individual... More Mass Personalization

One common misunderstanding about personalized medicine is that it is focused on developing customized treatments for each individual. Rather, personalized medicine is about using the population categories related to genetic make-up into which an individual falls to inform treatment.

We are learning that many common diseases are actually syndromes—that is, collection of different diseases with similar appearance, but involving different genetic causes. This is true, for instance, for breast cancer, which has already been identified to involve at least three different disease states related to different genetic variations. Understanding which genetic causes of disease apply to an individual is critical for identifying an effective treatment.

Moreover, genomic variations across population groups also lead to different ways in which individuals metabolize drugs. Individuals are already known to have different abilities to absorb drugs, such that normal doses can lead to unexpectedly low or high drug concentrations in the blood, causing ineffective therapy or severe toxicity. In particular, genetic mutations in liver enzymes associated with the cytochrome P-450 system have been found to determine how the body will metabolize or break down drugs. The use of a simple test for cytochrome P-450 enzymes is already in use to prescribe the level of

antidepressants like Prozac and Zoloft for individuals.<sup>1</sup>

A more accurate way to think of personalized medicine is more akin to mass personalization, in which individuals are biologically sub-classified based on what population groups they fall into related to their genetic make-up.<sup>2</sup> The implication of mass personalization is that personalized medicine will be about population studies and stratifying population groups according to how their disease functions, how they metabolize medicine, and how they interact with their environment.

### Many Identified Benefits from Personalized Medicine

There are well-recognized and documented benefits that personalized medicine, particularly involving the first wave of pharmacogenomics, can deliver, particularly:

- **Improved patient safety** – It is estimated that underdosing, overdosing and misdosing of medications cost more than \$100 billion dollars annually, and can be considered a leading cause of death in America.<sup>3</sup> Annually, approximately 3.1 billion prescriptions are issued in the United States, of which approximately 2.1 million result in an adverse reaction. One million prescriptions from this latter

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<sup>1</sup> See Schimpf, pages 19 to 21 for a good discussion of how cytochrome P-450 enzymes work.

<sup>2</sup> See Burrill, page 95

<sup>3</sup> Roland Valdes, "Introduction to Pharmacogenetics in Patient Care Conference by American Association of Clinical Chemistry, Nov. 6, 1998.

group may result in hospitalization, and of these, more than 100,000 patients may die.<sup>4</sup> The problem is that prescribing medications today is based on a trial-and-error approach. Often, doctors will have a choice of drugs to treat patients and will try to apply one after another until they find the one that works best for their particular patients. The point of pharmacogenomics is to get the prescription right the first time.

- **Increased effectiveness and cost efficiency of treatments** in light of the varying response rates to drug treatments based on genetic variations. Studies have shown that of 14 major drug classes, seven have shown less than 50% effective-patient-response rates<sup>5</sup>...suggesting significant gains are to be made by diagnosing which patients will respond effectively to what drug dosages.
- **More cost-effective development of drugs** – Through the use of pharmacogenomics tools, it will be possible to target new investigational therapeutic agents to patient subgroups and so reduce the risk of failures in clinical research. Without a doubt, the fact that a clinical trial includes individuals predisposed not to respond to the drug—either because of the genetic variation of their disease or their ability to metabolize the therapeutic treatment—adds cost, delays and even the risk of failing to demonstrate efficacy.

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<sup>4</sup> Mancinelli et al., “Pharmacogenomics: The Promise of Personalized Medicine,” AAPS PharmSci, March 7, 2000, page 10.

<sup>5</sup> See DHHS, page 16 cites Garrison LP Jr. Austin MJ. Linking pharmacogenetics-based diagnostics and drugs for personalized medicine. Health Affairs 2006;25(5), 1281-1290 and Spear BB, Health-Chiozzi M, Fugg J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7(5);201-204

## The Promise of Personalized Medicine is Falling Short of the Reality

Industry analysts heralded personalized medicine as changing the face of medicine. However, much of the growing market for personalized medicine is more about research tools and less about changing the practice of medicine. As Patricia Danzon, chair of Health Care Systems at the University of Pennsylvania Wharton School, explains: “Back at the time of the mapping of the human genome, people were talking about developing pharmacogenomic tests and really personalized drugs. That has not come to fruition ... Where we are right now is that there are a very small number of drugs on the market for which there is some sort of test as to whether or not that drug is appropriate for that patient.”<sup>6</sup> This view is echoed by the 2007 Department of Health and Human Services Report on Realizing the Promise of Pharmacogenomics: “In the 1990s, a widely held vision of pharmacogenomics innovation promised a new paradigm in health care. Although a small number of important pharmacogenomics products have reached the market, these early expectations for the field have not been realized. While the push for innovation and demand for truly personalized medicine remain, new products face careful assessments of benefits, risks and costs.”<sup>7</sup> There are a number of issues that will need to be addressed as the move towards personalized medicine continues. The lack of standardization—of biospecimens, of processes and procedures, of interpretation—is a huge potential barrier to acceptance and utilization of information. The implications for potential harm resulting from commercial companies providing direct-to-consumer genetic

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<sup>6</sup> “Getting Personal: FDA’s Plan to Save the Drug Industry,” FDABeat, September 2006

<sup>7</sup> DHHS, page 18

information before the field is mature cannot be minimized.<sup>8</sup>

There are a variety of reasons why pharmacogenomics—and particularly companion diagnostics—have been slow to grow in the marketplace:

**Pharmaceutical companies are concerned about their markets being constricted in size by the narrowing of the definition of the disease or its indication.** Many pharmaceutical companies are still pursuing a one-size-fits-all, blockbuster-drug business model. Having the ability to classify diseases into distinct molecular subcategories for treating patients goes against this traditional model and drug companies do not always view using this ability as in their interest. As PriceWaterhouseCoopers (PwC) explains: “... the pharmaceutical industry is not prepared to abandon the blockbuster approach in favor of pharmacogenomics. Companies have built considerable infrastructure, staffs, and capabilities in the past 40 years that support the blockbuster model. And the pharmaceutical business is still among the most lucrative in the world and has historically realized double-digit returns on investment.” So PwC concludes that it is “expected to take another decade for pharmacogenomics to be an accepted and integral part of mainstream healthcare.”<sup>9</sup>

**Cost Reimbursement remains a major stumbling block.** Payers are understandably concerned about making sure that, as these additional tests are performed, there is actually a reduction in cost or an improvement in outcome (such as reproducible predictive value) that appropriately compensates for the additional expense. In particular, Medicare, as the largest single health-care payer in the U.S., presents real limits today in

advancing personalized medicine. The Department of Health and Human Services Report on “Realizing the Promise of Pharmacogenomics” explains that “In order for Medicare to cover screening or preventive interventions, Congress must pass new legislation, as it has in such instances as screening mammography, prostate specific antigen (PSA) testing, and bone densitometry for those at risk of osteoporosis.” In addition, Medicare clinical-policy bulletins limit the ability to perform pharmacogenomic testing even among patients known to have a particular condition if the value of the test has not been demonstrated.<sup>10</sup>

The ability to demonstrate the value of pharmacogenomics testing through rigorous evidence-based medicine analysis is still a work in progress. AHRQ recently released its report on ovarian-cancer detection and management. The agency concluded that while “research remains promising, adaptation of genomic tests into clinical practice must await appropriately designed and powered studies in relevant clinical settings. So, it may take years for more complex population-based usages of pharmacogenomics to prove themselves in clinical settings.”<sup>11</sup> It is uncertain how the push for health-care reform and its emphasis on comparative-effectiveness measures will impact the development of personalized medicine and particularly whether molecular diagnostics will be approved for reimbursement. Dr. Francis Collins, the new director of NIH, is concerned that personalized medicine will be stifled because of the focus on comparative measures,<sup>12</sup> while others reporting to the President see personalized medicine and

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<sup>8</sup> See Venter, J.D., et.al., *Nature*, online, October 7, 2009

<sup>9</sup> PwC, pages 22-23

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<sup>10</sup> DHHS, pages 60-61

<sup>11</sup> “Linda Bradley [geneticist with CDC] on Whether Paucity of Outcome Data is Holding Up Pharmacogenomics Adoption,” *Pharmacogenomic Perspectives*, Vol II, November 8, 2006, page 7.

<sup>12</sup> Dr. Francis Collins, *Genome Web*, October 27, 2009.

comparative effectiveness research as complementary.<sup>13</sup>

### **Intellectual Property for diagnostics is complex.**

Critical for companies to be able to advance genomic and biomarker tests based on personalized medicine is having clear ownership to intellectual property (IP). But the IP landscape for diagnostics appears to be highly complex. On one hand, there may be multiple patents ultimately incorporated into a single genomic or biomarker test. As Sudhir Srivastava of the National Cancer Institute explains: “With the diagnostics you’re not going to just have one marker or two markers, you may have more than one biomarker. Some of those biomarkers may be patented by private companies. How do you deal with those multiple IPs?”<sup>14</sup> On the other hand, there is also an uncertainty about what is legally patentable material and particularly whether actual gene variants identified for genomic and biomarker testing can be patented as products.<sup>15</sup>

### **Many physicians lack the science background and confidence that personalized medicine can be of benefit to their patients.**

Physicians are truly the gatekeepers to new therapeutic interventions, and many have an uneasy relationship with more sophisticated diagnostics, such as those being advanced through pharmacogenomics. Dennis O’Kane from the Mayo Clinic explains: “Physicians do not understand pharmacogenomics: one, what it is; and two, how to use it. And so, you’ve got a full generation-plus of new physicians to train in this area, plus you’ve got all the previous generations who are in practice who have to be

brought up to a certain level of professional understanding on this. That’s the major barrier. If you don’t understand how to use the test, you’re not going to order it. That’s number one.”<sup>16</sup>

The experience of Genzyme Genomics illustrates how difficult it is to overcome physician reluctance to use pharmacogenomics and diagnostics:

“In 2005 Genzyme Genetics made a significant push in the field of personalized medicine, focusing explicitly on tests that could be directly tied to a therapeutic intervention. The company was aggressive in licensing technologies with early but promising clinical data that had been published in reputable journals. The company then worked quickly to get those technologies into the marketplace, believing that physicians would be convinced of their value as the data grew stronger and that a test that helped determine the dosing of a therapy would be a compelling value proposition.

The experience, however, turned out to be quite different. Physicians said such things as, “I don’t need a test because I can start patients on irinotecan, and when side effects occur, I lower the dose, stop a cycle, or stop treatment,” or “I monitor bilirubin level, so do not need to test.”

Physicians who were willing to test asked what dose to use if the patient did have the polymorphism, because the dosage and administration section of the drug label did not offer details about what to do if a polymorphism was found. Some physicians decided that the specific polymorphism was fairly rare, so that it was not worth testing all patients.

From these experiences, the company learned that clinical-utility data are not sufficient to change clinical practice. Physicians will use work-

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<sup>13</sup> Report to the President and Congress, Federal Coordinating Council for Comparative Effectiveness Research, June 30, 2009.

<sup>14</sup> “Sudhir Srivastava on NCI’s PRIDE Initiative and Biomarker-based Assay Validation,” *Pharmacogenomic Perspectives*, vol III, page 11

<sup>15</sup> See DHHS report, page 28

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<sup>16</sup> “Mayo Clinic’s Dennis O’Kane on Clinical Assay Validation and Barriers to Pharmacogenomics, March 29, 2006, pg 5, vol 1 *Pharmacogenomics Perspectives*

around solutions when they are modestly effective. Additionally, the inclusion of a test or genomic information in a drug-package insert does not necessarily lead to testing. Finally, package inserts must be clear on the implication of the testing results for dosing, or physicians will struggle to interpret them.<sup>17</sup>

**Public concern surrounding genetic testing.**

Ultimately, patient perceptions will influence the extent and pace at which personalized medicine is advanced. Concerns remain among public-interest groups and individuals that the growing use of molecular-based testing will result in violating individuals' privacy and denial of services and access to health insurance, regardless of recent legislation. A recent article in Genetic Engineering and Biotechnology News gives voice to these concerns: "Currently the legal picture regarding medical privacy issues that may affect personalized medicine and companion diagnostics is a patchwork of federal, state and local laws. HIPPA notwithstanding, these offer various levels of protection against the misuse of genetic information."<sup>18</sup> The Department of Health and Human Services reports on the body of studies on public concerns: "Most patient preference research to date has generally shown that patient concerns about pharmacogenomics testing are focused on cost, lack of effective treatment options for those testing positive, privacy and discrimination concerns, limited predictive value and negative impact on quality of life."<sup>19</sup>

**Regulatory environment for personalized medicine is still evolving.** The regulatory environment, which helps to influence industry's decisions regarding investment in developing

personalized medicine, is a work in progress. In the mid-1990s, Congress noticed a rise in genetic testing, and started to call for greater oversight by both FDA and CMS to ensure the analytic and clinical validity of tests. But the approach taken by FDA created two classes of diagnostics, one not regulated and the other highly regulated. The unregulated path to diagnostics adheres if a lab is designing the test itself as a service to physicians—so-called homebrews or in-house-developed tests. In this case, no regulator looks closely at the test itself, though the lab needs to be certified as conforming to the Clinical Laboratory Improvement Act (CLIA) standards in performing the service. The more regulated path adheres if the pharmacogenetic test is performed using a 'test kit,' or *in vitro* diagnostic product; then FDA requires more regulatory reviews. Recently, FDA has begun taking a stronger position, requiring that any test that involves a combination of reagents or uses algorithms to interpret the results fall under regulatory review. Still, this is an emerging area of regulation, and there will be continuing guidance from FDA regarding data requirements, market clearance and post-marketing surveillance.

Because of all of these factors, industry is going much slower in bringing personalized medicine forward than might be expected, given its promise. Based upon its own experiences, Genzyme Genetics, one of the nation's leaders in the field, offers the following criteria for introducing new personalized-medicine products:<sup>20</sup>

- First, for the company to invest in a test, the test needs to represent the only reliable way to obtain information. When there are low-cost work-around

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<sup>17</sup> Brad Gray, President, Genzyme Genetics, in National Academy of Sciences, "Diffusion and Use of Genomic Innovations in Health and Medicine: Workshop Summary, 2007, page 41.

<sup>18</sup> "Pitfalls Undermine Promise of Theranostics," Genetic Engineering & Biotechnology News, September 15, 2008.

<sup>19</sup> DHHS, page 78

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<sup>20</sup> Brad Gray, President, Genzyme Genetics, in National Academy of Sciences, "Diffusion and Use of Genomic Innovations in Health and Medicine: Workshop Summary, 2007, page 43.

approaches, there is too much commercial risk to proceed.

- Second, clinical evidence is absolutely critical to driving adoption. If the company is going to pursue the innovation, there must be proof-of-concept data from inventors, or it must be feasible to run a decisive experiment at reasonable cost and in a reasonable amount of time.
- Third, because reimbursement in the testing sector of the health-care system has traditionally not been based on value but on activity-based costing, the economics must support investment in clinical and market development. The reimbursement path must be attractive, either by virtue of its intrinsic coding or because there is the possibility of making a compelling case to be reimbursed on a different basis than activity-based costs.
- Furthermore, the company will look for places to invest where intellectual property and know-how is available on an exclusive basis.

### Leading Edge of Personalized Medicine Will Come through Molecular Diagnostics and Related Pharmacogenomics

*“In five years, we predict there will be numerous new companion therapies and diagnostic tests—that is, drugs whose prescribing information is linked to the results of a molecular test. There will be incremental progress.”<sup>21</sup>*

As Janet Woodcock, Deputy Administrator of the Food & Drug Administration explains: “We’re telling everyone that we can tell that diagnostics are excruciatingly important—they’re actually the foundation of medicine, because you have to

know what the person has. And personalized medicine—sub-setting patients and everything—it’s going to be the future of medicine. We can’t do that without good diagnostics.”<sup>22</sup>

Depending upon one’s view, molecular diagnostics are integral tools for pharmacogenomics, or pharmacogenomics is a subset of the broader field of molecular diagnostics. Many existing genetic tests, however, are not focused on pharmacogenomics. Instead, they are used to determine the risk of developing a genetic-based condition or disease. More focused pharmacogenomic testing has a more defined purpose—identifying how genetic variations affect reactions to different drugs—can enable diagnostic tests to be established that can guide doctors to make more informed and cost-effective medication decisions for their patients.

And there is interplay between pharmacogenomic diagnostic testing and drug development. A better understanding of how genetic variations impact drug responses can also enable better, targeted drug design for specific population groups. Indeed, a new field that links diagnostics and therapeutics has arisen, known as “theranostics” or companion diagnostics. An August 2004 article in *The Scientist* explains the field of theranostics:

*“Drug companies and diagnostic test developers are increasingly teaming up to produce theranostics, a treatment strategy that packs a one-two punch: a diagnostic test that identifies patients most likely to be helped or harmed by a new medicine, and targeted drug therapy based on the test results.”<sup>23</sup>*

Recent examples of efforts in theranostics include:

- Bristol-Myers Squibb collaborating with Dako, from Denmark, to identify patients more likely

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<sup>21</sup> Edward Abrahams, executive director of Personalized Medicine Coalition. “The Future of Medicine,” U.S. News & World Report, August, 2009, page 35.

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<sup>22</sup> Interview with Janet Woodcock, Pharmacogenomics Perspectives, Vol I, pages 14-15

<sup>23</sup> *The Scientist*, August 30, 2004, page 38

to benefit from treatment with certain investigational cancer drug candidates.

- Merck entering into a collaboration with Celera from Rockville, MD to develop biomarker and pharmacogenomic tests for cancer patients.
- Eli Lilly teaming with GE Global Research to discover and develop diagnostic assays to predict response to targeted cancer therapies.

### **Personalized Medicine Will Depend Upon Broader Health-Care System Changes**

The market barriers to advancing personalized medicine suggest it will take more than just research advances and new product development to move personalized medicine forward. Over the longer term, personalized-medicine innovations appear to be enablers rather than drivers of more systematic health-care benefits. Many of the benefits from personalized medicine require systematic changes well beyond the purview of personalized medicine, such as ensuring that patients follow their course of treatment or addressing the causes of disparities in access to health care, even addressing the pharmaceutical-industry structure and its focus on blockbuster-drug developments. Physicians, pharmacists, and other health-care providers will be the ultimate drivers of personalized medicine. To help them understand the science and technology behind the new therapies and to understand the value to their patients and themselves, they must be provided with relevant educational training. Revisions to existing medical-school curricula will be needed in order to integrate the innovations of personalized medicine into an exceeding complex healthcare system.

The need for a more systematic health-care focus has led some commentators to question the use of the term “personalized medicine” as opposed to “personalized health.” Alan Louis, research director of Health Industry Insights, explains “the nature of personalized health is differentiated from personalized medicine, because personalized medicine is largely framed within the pharmaceutical or life-science part of the value chain ... We’ve coined the term ‘personalized health’ because we feel that the knowledge base actually goes across to the hospital information systems area, as well as in the payor reimbursement side.”<sup>24</sup>

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<sup>24</sup> Alan Louie, Research Director, Health Industry Insights, page 15, Vol II, Pharmacogenomic Perspectives

## Part II: The Research and Technology Challenges to Personalized Medicine

Along with the significant market challenges facing personalized medicine, there are many technology challenges. To become a widely used approach in medical and health-care treatment, personalized medicine will require advances in sophisticated genomic technologies as well as innovative medical therapies. As Hakan Sakul of Pfizer Global Research and Development states, the challenge of science and technology remains substantial: “If you look at any diagnostics [in a disease area], what you’ll find is science and technology are both evolving in that area. There isn’t something available. It isn’t so much the business being the barrier, but science is the barrier.”<sup>25</sup>

### Setting Out the Emerging Focus Areas of Research

The nature of the research and technology challenges facing personalized medicine are hard to classify. Some involve the nature of advancing understanding of diseases, others the need for better instrumentation and data-analysis tools, and still others involve advancing new fields of scientific research.

### Challenges in the Quality of Microarray Technologies

Pharmacogenomic and molecular-diagnostic tests frequently employ high-throughput technologies, such as microarrays or “gene chips,” that allow for the analysis of whole genomes or specific candidate genes or biomarkers for alterations in gene expression affecting drug action or activity. However, there is substantial concern about the

quality and reproducibility of microarray analysis, particularly across different platforms. In fact, FDA has an ongoing microarray quality-control (MAQC) project to address the variety of quality and information from different microarray platforms. A recent report explains the concerns leading to this project:

*“A gap exists between technologies in use today and the technological levels required for application during product development and regulatory decision making. For example, recent publications have raised concerns about the reliability of microarray technology because of the apparent lack of reproducibility between lists of genes (i.e., potential biomarkers) identified as differentially expressed from similar or identical study designs with different platforms or laboratories”*

The first phase of the MAQC project demonstrated the technical reliability of microarray technology in detecting differential gene expression. However, questions remain regarding the reliability of the technology in clinical applications such as disease diagnostics or prognostics, and for tailored treatment based on gene-expression profiles. To investigate the capabilities and limitations of microarray technology in such real-life applications, the MAQC Phase II (MAQC-II) has been launched to address technical and scientific issues involved in the development and validation of predictive signatures and classifiers. Multiple data sets will be collected and distributed to participating organizations for independent analyses with available algorithms. The resulting classifiers will be evaluated at three different levels: within a single data set via cross-validation, validation across multiple data sets from studies with the

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<sup>25</sup> Interview with Hakan Sakul, Senior Director of Molecular Profiling, Pfizer Global Research & Development Pharmacogenomic Perspectives, Vol II, page 4

same study objectives, and prospective validation with additional data from new samples. It is anticipated that the MAQC project, through the community's active participation, will help develop "best practices" for the generation, analysis, and application of microarray data in the discovery, development, and review of FDA-regulated products.

### Challenges for Genome-Wide Association Studies

A key tool for advancing personalized-medicine research is genome-wide association studies that examine genetic variation across the entire human genome. These studies are designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. Whole-genome information offers the potential for increased understanding of basic biological processes and improving the prediction of disease and patient care, and ultimately realizing personalized medicine's promise. In addition, rapid advances in understanding the patterns of human genetic variation and maturing high-throughput, cost-effective methods for genotyping are providing powerful research tools for identifying genetic variants that contribute to health and disease.

However, these studies are complex and difficult to undertake. Uncertainty remains about the reliability of genome-wide association studies, including concerns over sample size, collection bias, and the capacity for current high-throughput technologies to produce the necessary volume of data. Thus while these methods may still have considerable value in discovery, routine clinical applicability that involves affordable sequencing and storing of whole genomes still remains far in the future. The sequencing and use of whole genomes for medical decision-making may not be available for another 5 to 10 years and will require robust information-management systems and methods for genomic analysis. Some have also pointed to an essential need for more cost-

effective genotyping methods in genome-wide association studies.<sup>26</sup>

### Challenge of Interrogating Data

Personalized medicine requires processing of massive amounts of data and identifying patterns across patient groups on disease progression. Among the needs are improved methods for database management, data-mining approaches, and statistical analysis. As Anna Barker from NIH notes, "The issue is coming up with meaningful approaches to the data, and the algorithms that will be required to actually determine those that are most meaningful to [the progression of disease]."<sup>27</sup>

### Challenges in Connecting with Phenotype – Advancing Metabolomics

Dr. Dennis O'Kane from Mayo Clinic explains that "we're really just scratching the surface on pharmacogenomics. The genotyping part is easy... Correlating it to a phenotype is difficult and that's where I think a lot of work is going to have to be done in the next few years, to really further develop the phenotypes that go with a genotype. In particular, there are some drugs that may be metabolized very poorly by one genotype and yet the same genotype may metabolize other drugs on an extensive basis ... and that hasn't been sorted out. We need further phenotype development and correlation with the genotypes."<sup>28</sup>

One critical way to create this connection to phenotypes is through the use of metabolomics (also referred to as metabolomics), which refers to the study of metabolic responses to drugs, environmental changes and diseases. In more

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<sup>26</sup> See DHHS, page 22

<sup>27</sup> Interview with Anna Barker, Pharmacogenomics Perspectives, Vol 1, page 9

<sup>28</sup> Interview with Dennis O'Kane, Pharmacogenomics Perspectives, Vol 1, page 5

technical (and wordy) terms, metabonomics is the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification.

Laura Schnackenberg from FDA explains the relevance of metabonomics to personalized medicine: “What’s been found is that it’s not only the genotype, but the phenotype, and contributions to the phenotype come from health status and nutrition. We’re a very diverse population, which is why we need to take this all into account in moving toward personalized medicine. So, the phenotype information that you can get from metabonomics is really going to be very important in determining what course of action is best for one person versus someone else who has a different diet or maybe other pre-existing conditions that need to be taken into account as well.”<sup>29</sup>

### **Challenge of Systems Biology: Understanding Basic Disease Processes**

Deciphering the mechanisms of disease we now know requires a much deeper knowledge of how signaling transduction pathways operate. For pharmacogenomics, many different genes may be involved in producing enzymes that metabolize drugs in different ways, and each of these may be variable in terms of their activities in terms of their expression, as well as in terms of having polymorphisms that inactivate or partially inactivate the gene product.

As Lee Hood from the Institute of Systems Biology explains, “this points to the need for advancing systems biology to provide a clear logic for being able to get markers that are very, very powerful—that can focus in on particular organs and particular diseases. Most of the biomarkers that are out there are very non-specific, and if they

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<sup>29</sup> Interview with Laura Schnackenberg, Pharmacogenomic Perspectives, Vol II, page 8

change, you don’t know whether it’s because of Organ A or Organ B, and you don’t know if it’s Disease X or Disease Y. And these systems approaches give us a new logic and a new strategy for choosing markers that will focus on organs and focus on particular diseases.

For example: The simple idea is that there are molecules that are made by networks in all of our different individual organs that are organ-specific, and some of these are secreted into the blood. And there they constitute a molecular fingerprint that reports back the status of that organ, and only that organ.”<sup>30</sup>

### **Challenge of Epigenomics**

An emerging field of study that may have significant implications for personalized medicine is that of epigenetics. In biology, the term epigenetics refers to changes in gene expression caused by environmental factors, not by changes in the underlying DNA sequence. Today, an array of illnesses, behaviors, and other health indicators already have some level of evidence linking them with epigenetic mechanisms, including cancers of almost all types, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral illnesses. Being able to track an epigenetic changes may offer another critical insight for personalized-medicine interventions.

Of particular importance for advancing epigenetics is the need for improvements in tools and methods, such as high-throughput technologies, analytical techniques, computational capability, mechanistic studies, and bioinformatic strategies.

### **A Framework for Advancing Personalized-Medicine Research**

As we end the first decade of the 21st century, the promise of personalized medicine remains largely

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<sup>30</sup> Interview with Lee Hood, Pharmacogenomics Perspectives, Vol I, page 6

ahead of us. We now understand and appreciate both the market and research challenges that need to be addressed to realize this promise.

But how can strategic interventions and approaches best be considered to advance personalized medicine in what has become a very complex environment? We propose a translational-research paradigm to understand the benefits, challenges, and opportunities for advancing personalized medicine.

Translational research is a hot focus in biomedical research and is commonly referred to as connecting “bench to bedside.” More fundamental for advancing new therapeutics, translational research is the pathway for going from research discoveries to drug discovery and development to pre-clinical testing to clinical trials and finally to clinical adoption and public health improvements.

Remarkably, personalized medicine plays a role across the entire translational-research paradigm and is not just an output of effective translational-research activities. Indeed, the translational-research paradigm offers many insights toward discerning in what specific areas of advancement in pharmacogenomics Arizona can position itself.

Here’s a snapshot of personalized medicine’s role across the translational-research paradigm:

#### **In Basic Research:**

- Personalized medicine is involved in identifying biochemical pathways and related biomarkers that identify the genetic variations in diseases and help diagnose and target candidate pathways for particular therapeutic interventions. Personalized medicine also considers drug metabolism and response to new therapeutic interventions.

#### **In Drug Discovery & Development:**

- Personalized medicine provides a more mechanistic approach, using predictive

information, for developing safer and more effective drug therapies for treating particular sub-population groups. Already, the National Institute of General Medical Sciences is supporting a national Pharmacogenetics Research Network to create a repository of pharmacogenetics data on human gene variations that affect drug response.

- Personalized medicine is being used to predict how new drugs will work in cells. The Broad Institute and Harvard have developed a genetic roadmap that connects human diseases with potential drug to treat them known as the Connectivity Map (or C-Map). This C-Map is already being put to use to enable the discovery of mechanisms underlying novel drug candidates for prostate cancer.

#### **In Pre-Clinical Testing:**

Personalized medicine offers a revolutionary approach to pre-clinical testing that can actually precede or at least pro-actively inform drug development paths. Through a concept known as Phase 0 trials, small or micro-level dosages will be given to individuals to study the biology or pharmacology of the potential drug candidate, not its toxicity, as is done in Phase I trials. With advanced tools, such as microscopy or imaging, pre-clinical testing will be undertaken to identify which drug candidate has the most favorable receptor binding or kinetics or metabolism or even proof-of-mechanism studies.

#### **In Clinical Research:**

- Personalized medicine can be used to select participants based on their genetic predispositions to respond to certain types of therapies, resulting in more efficient, safer, less costly, and more rapid clinical studies. PWC estimates that the use of personalized medicine in clinical-trial design could yield as much as a three-fold reduction in clinical drug-

development time, from 10–12 years to as little as 3–5 years.

- A new approach to “adaptive clinical trials” is being advanced, where patient outcomes from early phases of the trial are used to adjust the trial’s allotment of future patients in subsequent stages.
- Personalized medicine offers an avenue for “rescuing” or reintroducing drugs that were found ineffective during previous clinical trials or had adverse drug reactions with a particular sub-group.

#### **In Clinical Adoption:**

- Personalized medicine will offer physicians a more targeted drug-therapy approach for treating their patients, particularly through the use of combination diagnostic-drug treatments.

- Advances in diagnostic technologies and the ability to demonstrate clinical utility will be key for moving personalized medicine forward.

#### **In Public Health:**

- Personalized medicine offers a powerful new approach for improving public health, including:
  - Advancing a more molecular-based understanding of health outcomes and disparities.
  - Addressing cost-effectiveness of drug treatments.
  - Mitigating adverse drug reactions across population groups.



## Part III: Benchmarking National Leaders in Personalized Medicine

Before considering Arizona's position and how best to advance personalized medicine in the state, it is helpful to learn about the best practices of leading personalized-medicine programs. Battelle identified several leading programs and interviewed four, including:

- **The University of North Carolina Institute for Pharmacogenomics and Individualized Therapy**
- **Vanderbilt University Pharmacogenetics Initiative**
- **St. Jude Children's Hospital**
- **University of California, San Francisco Center for Pharmacogenomics**

These programs were identified by investigators in Arizona and elsewhere as representing the best in the field. Three of the four benchmark institutions also participate in NIH's *Pharmacogenetics Research Network (PGRN)*, a nationwide collaboration of scientists studying the effect of genes on people's responses to a wide variety of medicines.

Below is a summary of key barriers confronted and lessons learned on how to establish leading programs in personalized medicine, along with brief vignettes offering case studies for each of these leading programs.

A top-level examination of NIH's *Pharmacogenetics Research Network (PGRN)* program reveals some important insights into the focus and development of leading personalized-medicine programs. Among the common characteristics of these PGRN teams are:

- Multi-disciplinary, multi-institutional teams of researchers involved in focused projects, with key core facilities and administrative support.
- Such teams often exceed 20 immediate investigators with additional collaborative partners.
- Focused projects range from disease orientation (cardiovascular–arrhythmia, oncology–breast cancer, respiratory–asthma) to mechanistic investigations (membrane transport on drug response, functional-polymorphism analysis in drug pathways). Investigative approaches range from basic science (membrane transport) to clinical evaluation (asthma treatment).
- Many studies are at the interface of clinical observations and basic science (membrane transport and drug responses).

### Leading Academic Programs

Discussions with directors and investigators of leading programs have provided information on the challenges many of these institutions have and are facing, as well as those best practices that have led to success. Interview participants of these programs have provided insights into the most important areas of investigation and key barriers in the field of personalized medicine. The case studies provided below summarize elements of the programs of the University of California - San Francisco (UCSF), Vanderbilt University, the University of North Carolina (UNC), and St. Jude Children's Hospital. (It is recognized that all of these institutions possess advantages that many Arizona institutions does not. Two are private institutions (St. Jude, Vanderbilt), three are or are affiliated with major research medical centers

(UCSF, UNC, St. Jude), but they have established programs that can provide lessons from which Arizona can benefit.) One of the benchmark institutions (USF) provided information related to the relationship of pharmacogenomics to the broader field of personalized medicine.

A brief summary of the key discussion points includes:

**Barriers:**

- A silo, single lab approach to personalized medicine research is almost certainly a predictor of failure. The complexity of data needed to generate basic knowledge is beyond the scope of any single lab and, realistically, beyond the scope of most institutions.
- The lack of standardization of treatment regimes and data collection will hinder data evaluation. Retrospective studies using many databases will be unsatisfactory due to the variation in record keeping of therapeutic regimes and outcomes. Future studies need to develop standardized and consistent methods and protocols to support rigorous data evaluation.
- Predictive diagnosis will be problematic due to the difficulty of developing predictive algorithms with the existing data sets and their limitations.
- The need for large patient numbers and samples for statistically significant analysis is a problem that is only partially solved with collaborative efforts.
- Biology is very complex; disease entities and drug responses are due to networks of genes, not single genes. Large, well documented studies will be needed to sort out which genes and/or sets of genes are causally important.
- The translation of research into practice will be difficult, requiring success stories demonstrating the value of personalized

medicine to the physician and patient. Incorporation into health-care practice will require retraining both physicians and patients.

**Lessons Learned/Commonalities**

**for Best Practices:**

- Committed leadership that can coordinate the activities of team members is important.
- A multidisciplinary team approach that unites basic scientists and clinicians, employing internal and external collaborations to work on a focused project, is most likely to provide tangible outcomes.
- Sequential participation in an organized and focused manner is the most effective and efficient way to involve multiple investigators and utilize scarce resources. “Be organized.”
- Infrastructure support that includes research facilities and administrative assistance. Key facilities cores include:
  - Genomics
  - Phenotyping
  - Biostatistics
  - Bioinformatics
  - DNA specimen bank
  - Epidemiology
- Outsource or collaborate on tasks and facilities that are financially onerous for the program. Certain technologies change rapidly and upgrades can drain resources needed elsewhere for the mission of the program.
- Start with the clinic/patient to identify projects that will provide results of clinical applicability. Work backwards to the genetics.
- Commitment of leadership and institutions is essential—it can take up to five years to build a smoothly operating program.

## Case Studies of Selected Programs in Personalized Medicine:

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### The University of North Carolina – Chapel Hill, NC

#### Institute for Pharmacogenomics and Individualized Therapy

Mission: to employ an interdisciplinary approach to tailor therapies and enable the delivery of individualized medical practice; to increase the ability to identify patients at risk for severe toxicity, or those most likely to benefit from a particular treatment.

Organization: Director – Dr. H. McLeod, plus five associate directors who are responsible for driving the particular research forward in collaboration with and in concert with the other disciplines, in a unifying programmatic structure.

A new statewide structure was developed that bypasses traditional project-oriented design, creating a unifying, programmatic structure that encourages and relies on a collaborative and interdisciplinary approach. The program was formed as a collaborative effort of the Schools of Pharmacy, Medicine, Public Health, and Nursing with substantial support of the Lineberger Comprehensive Cancer Center and the Carolina Center for Genome Sciences. The program also offers the services of core facilities in molecular genomics, cellular phenotyping, and bioinformatics to add to other core facilities already existing at UNC.

Key Elements: Financial Support: In addition to research awards, funding includes long-term funding provided by an endowment plus yearly determined spending line.

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### Vanderbilt University, Nashville, TN

#### Pharmacogenetics Initiative

Mission: the study of mechanisms underlying individual variability in response to drug therapy. This work reaches from basic science to clinical medicine, and includes studies of metabolism and transport of many drugs, as well as specific studies of diverse clinical settings such as arrhythmias, hypertension, autonomic dysfunction, psychiatric disease, cancer, HIV infection, and recovery from anesthesia.

Organization: Director – Dr. Roden plus 13 team members, with investigators brought in as needed to maximize utilization of resources.

Research centers with a special focus on pharmacogenetics and pharmacogenomics include: The Division of Clinical Pharmacology, the Vanderbilt-Ingram Cancer Center, the Center for Molecular Neuroscience, the Vanderbilt-Meharry Center for AIDS Research, the Division of Genetic Medicine, the General Clinical Research Center, the Center for Human Genetics Research, and the Center for Genetics and Health Policy. Vanderbilt participates in NIH-sponsored Pharmacogenetics Research Network.

Key Elements: Core support is crucial, but outsourced investigations require overly expensive technologies.

Sequential participation does not extend to communications—investigators meet and communicate even when not directly involved in a project.

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## St. Jude Children's Hospital, Memphis, TN

Mission: Innovation and discovery with a focus on childhood leukemias and the germ line variation in drug response.

Organization: Director: Dr. William Evans plus *many* multi-disciplinary team members: clinical and basic scientists, nurse practitioners, pharmacists, biostatisticians, epidemiologists, bioinformaticians. The standard method is to look at particular patient problem—an observed clinical toxicity or lack of response—and then work backwards to animal models and basic science to understand the context of the genetic variation.

Key Elements: St. Jude has the advantage of standardization in treatment application and in phenotypic measures. Upfront standardization provides non-genomic information and allows them to capture phenotypes.

They develop discoveries and then export to cooperative group to validate and extent discoveries. Only in larger context is information generated and the observation replicated.

Key cores: genomics, phenotyping, central DNA

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## University of California, San Francisco, CA

### Center for Pharmacogenomics

Mission: to discover the many “hows” associated with genetic response to medications and to use this knowledge to suggest more effective and safer prescribing policies. To improve drug development and research, and ultimately to design more effective drugs with fewer side effects.

Organization: Director: Kathy M. Giacomini with 21 faculty members and 7 affiliated members.

The Center is a major research partnership led by the UCSF School of Pharmacy's department of biopharmaceutical sciences in partnership with the Program in Human Genetics at UCSF's School of Medicine, and bolstered by collaborations throughout the state and nation.

Investigations include basic research [sequencing of drug response (membrane transporter) genes in large scale, multi-center genomic studies] to clinical research in large patient populations (genetic variation in the response to anti-depressants).

Key Elements: Multiple collaborations.

Start with the problem.



## Part IV: A Situational Assessment of Arizona's Position in Personalized Medicine

Several broad observations can be made about Arizona's current position to inform how the state should move forward.

Since 2002, Arizona has invested significantly in biosciences. Results include: the new centers of excellence being formed at the UofA's BIO5 Institute, ASU's Biodesign Institute, NAU, and TGen. At the same time, non-university bioscience research centers, including the Mayo Clinic, Banner - Sun Health Research Institute (SHRI), Banner Health, Barrow Neurological Institute, Scottsdale Healthcare, and the Veterans Hospitals in Tucson and Phoenix, continue to evolve and invest for the future. The establishment of the University of Arizona College of Medicine - Phoenix in partnership with Arizona State University creates another anchor for biosciences development in Arizona. The establishment of a UofA College of Pharmacy division in Phoenix provides another potential asset to research and healthcare institutions in Phoenix and to the development of personalized-medicine approaches in Arizona. Many of these investments are in programs directly related to personalized medicine.

Not only have these investments resulted, directly and/or indirectly, in increased research awards, jobs, and a growing base of innovation companies, they have also resulted in a core of research, technologies, industries, and personnel that are directly and indirectly involved in personalized medicine and can be leveraged to position Arizona in the field of personalized medicine. Other investments have provided a foundation of supportive expertise and infrastructure to advance initiatives in personalized medicine.

To assess Arizona's current position in personalized medicine, Battelle conducted over 20 interviews with Arizona-based investigators, seeking their ideas regarding opportunities for the state and its organizations, and examined many of the leading efforts in personalized medicine found in Arizona. In addition, a top-level examination of ongoing projects at Arizona institutions was performed via accessible documents and websites.

A summary of Arizona's strengths, weaknesses, opportunities and threats is set out in Figure 1 (next page).

### **A Considerable Research Infrastructure Is Already in Place**

#### **Translational-Research Pathway:**

Arizona has extensive assets across the translational pathway of basic research, drug discovery and development, pre-clinical testing, clinical research, clinical adoption, and public health. The industry presence in Arizona has programs in drug discovery, drug development, and services that could support small-scale manufacturing and molecule production. The bench-to-bedside pathway is highly reiterative and provided with the necessary environment and support, these assets can provide feedback data that will inform and refine the area of personalized medicine in Arizona. A more detailed inventory of Arizona's assets in personalized medicine is set out in Appendices A and B.

**Figure 1 Summary SWOT Assessment**

**STRENGTHS**

Significant investments in underlying technologies: genomics, proteomics, metabolomics

Interdisciplinary centers and institutes including: BIO5, Biodesign, TGen

Statewide consortia in neuroscience, evidence-based medicine, personalized medicine

Research strengths in disease areas of oncology, neuroscience and respiratory disorders

Personalized medicine is often driven from pharmacology departments. The University of Arizona has basic-research strengths in pharmacology and toxicology.

A growing bioscience industry base

Many leading healthcare institutions

**WEAKNESSES**

Limited patient base for genetic analysis

Clinical-research enterprise is underdeveloped

Geographic distances among statewide participants and resources

Dedicated funding to provide short-term and project-specific funding is limited

Shared skilled-infrastructure support is lacking

Academia-industry connections are rudimentary

Tissue banks are growing but still small compared to other programs

**OPPORTUNITIES**

Community-health institutions – Existing connections can drive early participation and lead to identification of relevant targets and implementation policies.

Molecular diagnostics – New approaches and policies can leverage the availability of C-Path.

Disease-based approach could leverage research excellence in oncology, neurosciences, respiratory disease, and diabetes in order to collaborate on a nationwide basis.

Epigenetic investigations could make unique contributions to genomic studies.

Pharmacogenomics - Strong pharmaceutical, genomics, proteomics, drug development, and pharmacoeconomics programs now supported with medicinal chemistry expertise could provide significant capabilities for a future role in pharmacogenomics.

**THREATS**

Leadership for a focused personalized-medicine program is lacking, threatening the ability of Arizona to mount a leading effort.

Loss of clinical investigators is common due to patient revenue pressures.

Institutions face decreases in funding needed for short-term, gap funding.

Lack of infrastructure support results in the loss of opportunities to be a national player.

The highly competitive environment in pharmacogenomics and personalized medicine requires the ability to focus and collaborate extensively.

*Basic Research projects and programs:* Major departments and programs are found at TGen, the Mayo Clinic, Banner-Sun Health Research Institute (SHRI), the Biodesign Institute at ASU and the BIO5 Institute at UA. Research at these institutions includes genetic, proteomic, metabolic, and environmental studies of cancer, neurological diseases, respiratory diseases, and type 2 diabetes. For example: The BIO5 Institute at UA is highly focused on personalized medicine, with research programs working to discover possible genetic bases of cancer and respiratory diseases. TGen, which has in place a multi-platform capacity for high-throughput genomic analysis, is now adding a high-throughput proteomics capacity focused on both biomarker discovery and validation, and is working to develop the linkages between genomic and proteomic analysis through its focused efforts in lung cancer. The laboratory of Dr. Serrine Lau (Pharmacology, UA) in collaboration with TGen and Dr. Raymond Nagle (Arizona Cancer Center, UA) is developing a global mass spectrophometry-based protein profiling and drug-imaging technologies that will enable the monitoring of prognostic biomarkers and therapeutic-target-protein interactions. The Biodesign Institute at ASU is also highly focused on personalized medicine, with recruitment in proteomics and construction of state-of-the-art laboratories for high-throughput discovery work in biomarkers complementary to the programs of TGen.

Statewide research consortia such as the Arizona Proteomics Alliance, the Arizona Parkinson's Disease Consortium, and the Arizona Alzheimer's Consortium provide a mechanism for coordination and communication on specific areas of basic and clinical research.

Collaborative efforts among multiple organizations and institutions require a standardized set of policies and procedures. The Arizona Biomedical Research Commission has provided support to the Arizona Translational Network (AzTransNet), which is promoting harmonization in clinical and

translational research through template forms and policy guidelines, has developed statewide collaborative IRB approaches, provides training for clinical researchers on topics such as patient registries and biobanking, and is currently working to develop policies, procedures, and infrastructure for a statewide virtual repository.

Through the Partnership for Personalized Medicine (PPM), there are also collaborations between TGen and the Biodesign Institute at ASU, and with national and international institutions and research groups. PPM is also tackling the issues of standardizing collection and processing in collaboration with the Fred Hutchinson Cancer Research Center in Seattle, WA.

*Drug Discovery and Development programs:* TGen, Mayo, ASU, NAU, and others are focused on translating basic research findings into drug targets, diagnostic tools, vaccines, and other therapeutic agents.

For example, TGen is working with Scottsdale Healthcare to develop targeted therapies for pancreatic cancer, and work on biomarkers by TGen and SHRI is being used to identify targets for drug development and/or diagnostics in diseases such as diabetes and Alzheimer's. NIH has recently awarded \$7.5M to TGen and the UA College of Pharmacy for a drug-development center that will enhance the capabilities of medicinal chemistry in Arizona to develop libraries of compounds for high-throughput screening for potential drug candidates. The Drug Discovery Institute at BIO5 is leveraging the basic-research programs to provide drug targets for Arizona's emerging biotechnology industry. Biodesign is working on the development of vaccines for cancer and infectious diseases. NAU and TGen are collaborating on the development of advanced diagnostic devices for pathogens. The TGen-Mayo Cancer Center Drug Development Laboratory collaboration is developing new technologies and integrated systems biology to translate genomic data into new compounds.

*Technology Development:* Toward incorporating personalized medicine into the health-care system, Arizona institutions are developing technologies and information systems to analyze and manage data in a cost-effective manner. TGen, ASU, and UA all have bioinformatics programs that can lead to technology product development and support ongoing and future research efforts. Biodesign is working to develop a more cost-effective genome-sequencing technology that is essential for widespread adoption of personalized medicine. Additionally, these programs are developing the means to analyze large data sets and translate the data into actionable knowledge.

Through the Partnership in Personalized Medicine (PPM), TGen is working with ASU's School of Engineering to develop a robotic system to address the key technical issue of reproducibility of proteins from plasma. In addition, TGEN is advancing a unique niche in high-throughput validation of biomarkers, which may lead to new tools, databases, and techniques in the use of biomarkers.

This is also an area of bioscience-industry strength in Arizona. A leading firm in the application of genomics to human diseases is Ventana Medical Systems, which was recently acquired by Roche Holding AG, and is now becoming home to all of Roche's cancer-diagnostics products. Other leading firms in the application of genomics to diagnostics and targeting drug development include High Throughput Genomics, CARIS/MPI, Applied Microarrays, and Intrinsic Bioprobes.

*Preclinical Testing:* The Critical Path Institute (C-Path) has demonstrated the ability to work with industry consortia to provide critical validation of diagnostic tests and biomarkers needed for the acceptance of diagnostic tests by regulators [The Predictive Safety Testing Consortium (PSTC)]. C-Path is now considering broader initiatives for a national biosignature laboratory that would offer validation services on a systematic basis.

TGen and Biodesign are also working to develop standardized procedures and infrastructure necessary for the validation of biomarkers by the FDA. The Pharmacodynamic and Pharmacokinetic Laboratory at the TGen Clinical Research Services at Scottsdale Healthcare studies drug absorption and distribution as a necessary step in developing individualized treatments.

*Clinical Research:* The clinical-research enterprise in Arizona related to personalized medicine is in the embryonic stage. This component of the pathway can be enhanced by closer interactions with the other aspects of the research pathway. Currently, the most applicable of current programs is the pancreatic-cancer program of TGen Clinical Research Services and Scottsdale Healthcare, which combines basic research and innovations in clinical trials-- a national need that will be especially necessary for the success of personalized medicine. With the recruitment of Dr. Joshua LaBaer and his team, Biodesign will be involved with a global clinical-trials program in lung cancer.

The ASU College of Nursing is developing an innovative clinical-trials program that could help Arizona become a leader in clinical trials in personalized medicine focused on evidence-based medicine.

The efforts of ABRC in promoting biobanking infrastructure in Arizona can be a key asset in advancing more personalized-medicine-oriented clinical research. ABRC is working to establish a virtual biospecimen consortium in Arizona with key investments in an information-technology infrastructure and development of a working consortium model.

The Partnership for Personalized Medicine has established a network of Arizona hospitals to collect targeted tissue samples in a standardized manner by recruiting and training a cadre of clinical-research nurses at each collection site.

In addition, there are a number of patient registries underway in Arizona that can be

leveraged for more personalized-medicine-oriented clinical research. Barrow Neurological Institute has been a national leader in this effort, supporting Multiple Sclerosis Registry and the Parkinson's Registry. The Arizona Alzheimer's Consortium oversees a fast-growing patient registry that now numbers well over 1,000 screened participants.

A unique and valuable resource for patient registries is the Arizona HealthQuery, developed by the ASU Center for Health Information and Research, which is a unique statewide community-health data system for assessing health status and health-care needs in Arizona. AZ HealthQuery routinely collects administrative data from employers, insurers, providers, and health-related organizations and links these data sources to create integrated health information for each person. Its database, launched in 1999, now follows over 9 million patients and over 200 health-care encounters from a wide variety of settings, including hospitals, clinics, physician offices, urgent-care clinics, pharmacies, home health facilities, labs, long-term care facilities (ALTCS), etc.

*Implementation:* Arizona seems to have key programs that can be positioned to help in the implementation and assessment of personalized-medicine approaches. ASU's College of Nursing, through its nationally-known Center for the Advancement of Evidence-Based Practice, can advance the patient-based clinical information needed to inform basic and clinical research. With the additions of Lee Hartwell and Michael Birt to its faculty in 2010, ASU will continue to build its programs in biomarkers health-care metrics and economics. The UA College of Pharmacy has the well-regarded Center for Health Outcomes and PharmacoEconomic Research, which can provide data and analysis needed for new policy decisions and development.

*Outreach and Public Health:* Arizona also has a substantial base of supportive institutions,

organizations and programs that complete the translational pathway and will be essential to the refinement of new therapies that have been or are being incorporated into the health-care system. Most of these programs are not yet formally involved in personalized-medicine initiatives but have the staff and infrastructure that can be leveraged when needed. Arizona has several well-recognized medical centers, community-based health-care systems, physician practices, and colleges of nursing and public health that can provide information and feedback from the patient-needs perspective. C-Path also works at the end of the spectrum that investigates patient response or non-response to drugs and other therapies. Studies conducted by these institutions can be linked with basic research into the genetic and metabolic causes of drug response variability. The AZ HealthQuery databases will provide a unique and extremely valuable source of ongoing data acquisition and utilization.

Statewide consortia such as the Partnership for Personalized Medicine and the Arizona Consortium for the Advancement of Evidence-Based Practice can interact on an ongoing basis to provide communication and evidence-based feedback that can refine research-and-development efforts. They are well positioned to conduct educational and training programs that will facilitate the acceptance and proper use of new diagnostics and treatment regimes.

**Disease-Based Strengths:** There also appear to be specific disease areas that offer opportunities for a focused approach to personalized-medicine interventions in Arizona, given existing research teams in place. These include neuroscience disorders, cancer, respiratory diseases, and type 2 diabetes. These disease areas have been identified as strengths in Arizona, as discussed in the recent update to Arizona's Bioscience Roadmap:

#### *Neurosciences*

The field of neurosciences, a well-established and broad core competency in Arizona, ranges from

leading-edge basic sciences to focused applications and specific disease investigations. Arizona's statewide consortia, including the NIH-funded Arizona Alzheimer's Consortium and the Arizona Parkinson's Disease Consortium, which recently received core funding from the Michael J. Fox Foundation, contribute to the state's prominence in neurodegenerative-disease research. Other neurological-related disease areas of note found in Arizona include multiple sclerosis and pain. UA stands out as a leading research university in basic neurosciences, including neurobiology, cognition, memory, and motor control. In application development, a major new thrust in Arizona's neurosciences research is the application of neurogenomics, led by TGen, including identification of biomarkers for Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and autism.

### *Oncology*

Cancer research in Arizona continues to be a robust focus of bioscience research. One anchor is the Arizona Cancer Center at UA, an NIH-funded comprehensive cancer center with numerous major center and program awards. Other leading anchors include Mayo Clinic, targeting cancer diseases and bringing NIH-funded major programs in cancer to Arizona, including specialized research programs in neuro-oncology and pancreatic cancer; TGen, whose specialization in genomic analysis provides Arizona with a key resource in cancer research; Scottsdale Healthcare, with an early-stage clinical trials unit in the Virginia G. Piper Cancer Center; and Barrow Neurological Institute, with a specialization in brain tumors. Finally, the Partnership in Personalized Medicine is mounting a major effort in lung-cancer research at this time. Biodesign has recently appointed to its faculty a physician researcher who will be bringing a large, global clinical-trials effort in lung cancer to ASU. The identified niches of Arizona in cancer research include gastrointestinal cancer prevention and treatment, skin cancer prevention and treatment,

cancer drug discovery and development, cancer imaging, and neuro-oncology. Recently, a major thrust in cancer research has emerged across Arizona in molecular-based therapeutics, vaccines, and diagnostics, along with a focus on early-stage clinical trials.

### *Respiratory Diseases*

The NIH-funded Arizona Respiratory Center (ARC) at UA is one of the nation's leading centers of excellence in asthma research, focusing on the cellular and molecular mechanisms of asthma by analyzing interactions between genes, the environment, and the immune system, as well as studying innate immunity in children and the influence of the maternal immune system on asthma development in children. ARC and other researchers in Arizona are examining the environment's contributions to asthma, including how genetic traits predict the severity of asthma and other respiratory diseases, the incidence of asthma, and the impacts of environmental exposure on risks of developing asthma. Along with the center of excellence in asthma research, Arizona has one of the nation's top respiratory clinical infrastructures, with three hospitals highly rated in treating respiratory disorders. Arizona also has a strong clinical-research capacity in asthma, including the NIH-funded Childhood Asthma Research and Education (CARE) Network and a strong epidemiology and health-outcomes resource in ASU's Arizona HealthQuery databases.

### *Diabetes*

Diabetes is a major health concern in Arizona, given its incidence among Native Americans and Hispanics/Latinos. Diabetes research demonstrates significant potential for growth in Arizona in large part because of the ongoing intramural research efforts of the Phoenix Epidemiology and Clinical Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Carl T. Hayden VA Medical Center. TGen also strengthens diabetes research in Arizona, particularly in

identifying genes and molecular pathways underlying susceptibility to type 2 diabetes mellitus and its complications to enable earlier diagnoses and targeted treatment and prevention.

Both ASU and UA have established major new research initiatives in diabetes. ASU is working closely with Mayo Clinic and has established a new joint Center for Metabolic Biology, headed by recent recruit Larry Mandarino, an expert on insulin resistance. The UA College of Medicine's recently established Diabetes Research Program is intended to serve as a statewide collaboration of investigators, educators, and health-care providers focusing on research, clinical care, and education in diabetes. The new program provides an interdisciplinary, collaborative approach with a focus on the genetics, physiology, epidemiology, and management of diabetes, linking UA's College of Medicine, College of Nursing, College of Public Health, College of Agriculture and Life Sciences, and BIO5; TGen; Phoenix and Tucson VA Health Care Systems; ASU; NIDDK; and AZ Telemedicine and Tele-Health.

**Industry Development:** Arizona has a growing bioscience industry base. Of particular relevance for personalized medicine is the development of a base of bioscience research-and-testing companies. A recent internal Flinn Foundation review of Arizona's bioscience commercial landscape, involving interviews with senior industry executives, found that these research-and-testing companies are actively involved in the development of biomarker-based diagnostic technologies. These companies' expertise lies in their abilities to design and utilize multiple technology platforms, such as microarrays, optically-based detectors, mass spectrometry, and in-vitro diagnostics. The Flinn interviews with these research-and-testing companies found that while many are in the early-development stages, a significant number had developed revenue-generating products and/or services (see Appendix B for a listing of many of these companies).

The niche(s) occupied by Arizona's research-and-testing companies suggest potential opportunities around detection and analysis of environmental molecules and biomarkers, along with a strong emphasis on applications related to cancer.

The Flinn interviews with research-and-testing companies identified that most were involved in collaborations with Arizona research institutions.

Of particular concern to these research-and-testing companies is Arizona's lack of competence in proteomics and the need to advance biospositories that are accessible for proteomic studies.

Another concern for research-and-testing companies is the ability to access funding, either federal grants or VC/angel investment, to support internal R&D activities, infrastructure support, and/or marketing.

And these research-and-testing companies echoed the broader concerns found across industry development in personalized medicine with respect to gaining acceptance for diagnostic technologies from the broader bioscience community and ultimately the medical community, and validating technologies.

## Challenges for Arizona

### Programmatic Needs:

With all of the many research projects currently in progress, among the Arizona investigators interviewed there was a strong consensus that Arizona has much of the research infrastructure needed to advance the basic research-and-development efforts in personalized medicine summarized above. This involves the infrastructure for high-throughput genomics, proteomics, and pre-clinical research.

The most common request from Arizona investigators was for pilot funding that was not dependent upon complicated, time-consuming funding mechanisms to help jump-start promising research ideas and develop more collaborative research projects.

There was also wide consensus on the need for more focused faculty recruitment. Skilled personnel, such as epidemiologists and biostatisticians are scarce across all research institutions in Arizona. With a few more targeted recruits in areas such as medicinal chemistry, epigenetics, and glycomics, Arizona could build national leading programs.

Even with all of the resources found in Arizona, there are still gaps for Arizona in the more focused area of pharmacogenomics. Pharmacogenomics involves the study of how genetic variations shape the effectiveness of therapeutic treatments and require large population studies as well as sophisticated information technology--capable of collecting, storing, analyzing, and distributing data--that is still not fully developed in Arizona. Certain of these needs, such as population studies, actually create opportunities for Arizona to engage in national and international collaborations. Others, such as information technology, will require future investment.

Continued investments in targeted faculty recruitment, such as in the area of epigenetics,

provides Arizona a possible niche opportunity for expansion into pharmacogenomics. Additionally, as discussed in the text of this document and summarized in Appendix A, Arizona has many programs and initiatives that can be leveraged for collaborative efforts with established pharmacogenomics programs. For example, the recent NIH award to UA and TGen for a comprehensive center of medicinal chemistry indicates recognition of the research in Arizona. The center will support many efforts in Arizona and provide the means to link promising genomic targets to optimal drug development.

### The Individual Pieces Are Small in Arizona

While Arizona has many of the needed technologies and enjoys the presence of significant collaborative research institutes and centers, the current footprint of researchers focused on personalized-medicine development remains small outside of TGen. Typically, research teams in Arizona working on personalized-medicine initiatives stand at 3 to 4 investigators, which is below critical mass compared to leading national programs. (This is beginning to change, however, as shown by the exciting interactions of PPM investigators—TGen and ASU—and C-Path.)

The smaller size of Arizona's research programs in personalized medicine has led Arizona to focus more on technology niches rather than being the leaders in broad areas of personalized-medicine research. For example, genome-wide studies that form the basis of pharmacogenomics are beyond the resources of individual Arizona institutions at this time. However, Arizona is contributing in this area via the program at the ASU that is developing cost-effective sequencing technology as well as the efforts to improve the standard collection techniques of proteins from plasma—each crucial technology improvements for the advancement of personalized medicine.

Finally, it is important to note that being small is not a complete deterrent to participating in pharmacogenomics and personalized-medicine

research. Being small does require being smart about choices and utilization of resources.

One way is to provide support for collaborative efforts that will effectively increase the size of research teams. Another approach is the utilization of outsourcing. UNC and Vanderbilt found that outsourcing certain tasks and technologies—especially where technologies and/or skills are too expensive or too rare to maintain in-house—provide the ability to invest in those components most relevant to their programs.

### **Geographic Dispersion**

One of the key weaknesses for Arizona in its initiative to have a competitive program in personalized medicine is the degree of geographic dispersion that confronts its investigators. The challenges of geographic dispersion in essence dilute the impact of its bioscience resources—not because the resources are weak but because collaborative efforts are difficult to initiate and maintain.

Yet to participate competitively in a multi-disciplinary program in personalized medicine, ongoing collaborative efforts among investigators is essential. Trying to make these collaborative efforts work is difficult even when on the same campus, let alone different cities. The need for top-level strategic coordination and front-line facilitation and assistance to organize these resources around a focused program must be addressed for Arizona to compete in and benefit from the national agenda.

### **Clinical-Research Enterprise Is Lagging**

Arizona does not, at present, have a robust academic clinical-research enterprise. Clinician researchers are underrepresented and face economic pressures that limit their ability to engage in academic research projects. It will be important over time to develop a pool of physician researchers both for discovery and for educational programs.

While the clinical-trials infrastructure in the state is being enhanced through efforts of the Arizona Translational Resource Network initiative (supported by the Arizona Biomedical Research Commission), most statewide clinical trials are not likely to enroll patients in sufficient numbers for many personalized medicine studies. This is not a problem restricted to Arizona. The large number of patients required is daunting to even larger research groups and represents a significant challenge to the translation of discoveries into practice. National and international collaborations will be necessary.

Arizona is particularly lacking in the size and breadth of its tissue banking—a critical resource for advancing personalized-medicine research. There are a number of high-quality tissue banks, such as Banner-Sun Health Research Institute’s brain and whole-organ bank and Barrow Neurological Institute’s tissue bank, but from a statewide perspective, tissue banking is quite limited in Arizona. The Arizona Biomedical Research Commission has a promising new initiative to create common infrastructure for hospitals to develop high-quality tissue banks. The Partnership for Personalized Medicine has developed a network of collection sites across hospitals in Phoenix, and is working to build capacity to collect in a standardized manner. More focused investment is needed in this area.

### **Statewide Committed Leadership and Coordination**

Although Arizona has all the parts, coordination and translation require full-time committed infrastructure and skills in order to create a whole greater than the sum of its parts. Collaborations and programs don’t just happen. An often expressed wish of Arizona investigators was committed full-time leadership to provide coordination, guidance and drive. The time commitment needed to maintain connections, timelines, research inputs, etc. can be significant. A concerted use of these “core” resources must

be aligned with investigators' ongoing responsibilities so as to be both time- and cost-effective. This requires someone with the time and resources to see the big picture and bring the details in alignment with goals. Best-practices benchmarking programs had directors, associate directors, core facilities, and support staff dedicated to maintaining the trajectory of the project, assisting in administrative duties, seeking funding and performing other sometimes mundane tasks. Both Vanderbilt and UNC stated that the coordination of participants—bringing them in as needed—was important to the success of their programs. This approach conserves valuable resources and allows investigators to contribute on realistic basis while meeting other obligations.

### **Incorporation of Personalized Medicine into Health-Care Practice**

Successful incorporation of personalized therapeutics and treatment regimes will depend upon the value seen by physicians, pharmacists, and other health-care providers, as well as how well they understand the scientific basis of new diagnostics and treatments. To assist physicians, pharmacists, nurses, and other providers, medical curricula will need to include instruction toward understanding of pharmacogenomics, proteomics, and other “-omics”-based therapies and molecular diagnostics. Without such an understanding, tailoring the treatment to the patient will be difficult at best. The relationship between these technologies and discoveries and their patients calls for a new paradigm of instruction.

### **Need for Shared Core Labs and Signature Centers**

In addition to a committed leadership, key service cores are needed to leverage and support existing resources throughout the translational chain and clinical implementation. These include biorepositories and centralized databases, along with continued focus on ensuring advanced information-technology infrastructure.

Two major signature-center opportunities also stand out in Arizona that specifically target emerging markets in personalized medicine in pharmacogenomics and diagnostics development:

#### *An Arizona Pharmacogenomics Center:*

Advancement of pharmacogenomics in Arizona will require dedicated core facilities. While there may be an opportunity to partner on specific requirements such as genomic and proteomic analysis, the effort must bring a unified, programmatic structure to focus on pharmacogenomic questions, whether through basic research-related genomic studies or more clinically-oriented large patient-population studies. Of particular concern is the capacity to undertake large-scale population studies in Arizona, involving the collection, storage and analysis of large data sets from multiple sources. This effort will require the creation of a dedicated pharmacogenomics (bioinformatics) service core. Data ranging from basic genomic studies to the patient data provided from sources such as AZ HealthQuery will present significant challenges in necessary expertise and time commitment and is best handled as a service core to benefit institutions in the state. In addition, there may be a need for other specialized cores to serve the needs for pharmacogenomics research in Arizona, including dedicated core facilities in molecular genomics and cellular phenotyping.

#### *Center for Diagnostic Biomarker Standardization and Validation.*

With the unique capabilities of C-Path and the academic–industry partnerships in place as well as the efforts of the Partnership for Personalized Medicine, the state has a unique opportunity to develop a niche in the standardization and validation of biomarkers and other biosignatures critical to moving basic-research discoveries into clinical research, and advancing the commercial-

zation of molecular-based diagnostics. A core supporting the efforts of C-Path, ASU, TGen, and others would position Arizona to be a leader in this area.

#### *Networked Health-Care Information Systems*

Looking forward, effective implementation of personalized medicine will require investments in wireless and network-enabled information technology in order for physicians, caretakers, investigators and others to access such information from multiple sites and formats and incorporate the information into medical practice.

## PART V: RECOMMENDED PATHWAY FOR ADVANCING PERSONALIZED MEDICINE IN ARIZONA

Battelle's assessment of Arizona's position suggests:

- Arizona starts with many of the prerequisite competencies in high-throughput genomics, proteomics, molecular and genetic basic research, along with focused technology strengths in bioinformatics and bioimaging, to become a nationally-recognized player in targeted areas of personalized medicine. With continued investment, particularly in faculty recruitment, Arizona seems well-positioned to have leading research niches in epigenetics, diagnostics technologies, and pharmacogenomics.
- But Arizona's personalized-medicine pieces are relatively small, fragmented across institutions, and lack the committed leadership and coordination to be successful on a broader national level.
- Arizona must address a critical resource gap to succeed in personalized medicine—the lack of an integrated clinical-research enterprise capable of tapping Arizona's patient population at the scale required to inform and foster personalized-medicine development.

To realize its potential in personalized medicine, Battelle recommends that Arizona:

- 1. Establish the facilitative and coordinating mechanisms for advancing multi-disciplinary research projects in targeted disease areas.**
- 2. Focus on a set of specific disease areas that can bring together existing resources across institutions in Arizona.**
- 3. Engage Arizona's broad biomedical community to pursue an approach that works from the clinic back to the research lab.**

- 4. Spur the investment in modern translational-research infrastructure needed for advancing personalized medicine, involving biorepositories, population databases, epidemiology, and biostatistics. In addition, evaluate more closely the infrastructure needs for a health-informatics system(s) that would enable integration of personalized medicine/pharmacogenomics and personalized health care.**
- 5. Establish a focused storage and analytical center with the capacity to service the large pharmacogenomic datasets developed by investigators in Arizona and their collaborators.**
- 6. Establish a diagnostics-development center to support the academic and industry partnerships involved in the discovery, development and validation of biosignatures, biomarker molecules for gene-based diagnostics.**
- 7. Develop a new and innovative medical, pharmacy, and other health-profession curriculum that incorporates pharmaceutical, genomic, proteomic, information technology, and other biomedical innovations in order to assist physician acceptance of implementation of personalized medicine.**

**Identify committed leadership and establish a facilitative and support core of resources for the management of multi-disciplinary personalized-medicine research projects.**

This action item is probably the first that should be tackled. Beyond the scientific and technology needs, a formal Arizona personalized-medicine

research initiative will require leadership and support as discussed above in order to coordinate, guide, and facilitate the many operations and connections within and outside the state if Arizona is to benefit and contribute to the field. One possibility is for the Partnership for Personalized Medicine to be the home base for such a coordination center.

Arizona investigators are seeking and developing collaborative interactions but have stated that optimal participation in personalized medicine requires committed leadership to guide and facilitate a “Manhattan Project” approach. The effort required to maintain momentum on even small collaborations can be significant. Collaborations on the scale needed for Arizona to participate in a statewide personalized-medicine research initiative require full-time facilitative assistance on scientific and administrative levels.

As noted earlier, the programs examined as best practices have designated directors and, in some cases, associate directors to provide leadership and direction. Arizona faces the challenges of geographic dispersion far beyond that faced by UNC, Vanderbilt and others. As a result, a designated leader supported by a facilitative organization is essential. The leader would be able to provide a comprehensive view of the resources available and those needed for a focused approach. Due to the level of personalized attention needed by participants, the leader would also require administrative and facilitative support.

Key tools for advancing the facilitation and collaboration environment needed in Arizona include:

- Program-coordination support;
- Funding for pilot projects to bring together interdisciplinary teams across institutions;
- Targeted, shared-use, core-facilities investment (should be highly leveraged by institutional and federal funding);

***The overriding problem of focus, coordination, and support of these projects could be addressed by developing a center for leadership and facilitation modeled on that of the CIMIT organization (Center for Integration of Medicine and Innovative Technologies), which is described on pages 33-34.***

### **Focus on Disease Areas with Existing Presence in Arizona**

Arizona does not have the breadth in its academic/non-profit clinical-research activities to risk being spread too thin in advancing personalized medicine. It would make sense for Arizona to focus on no more than two or three disease areas to build up a statewide collaborative personalized-medicine consortium.

As has been well-documented, Arizona has strengths in focused areas of disease research, including selected cancers, neurosciences, respiratory diseases, and diabetes.

Battelle recommends that by surveying members involved in disease research from across Arizona’s academic/hospital/non-profit institutions concerning treatment issues in these disease categories, an advisory board for the Arizona Personalized Medicine Initiative would identify potential projects. More-detailed assessment of the research implications, potential for collaborative efforts, and ability to connect with national databases and programs (for example, an affiliate membership in the NIH research network) would then designate 1–2 initial projects of greatest potential. A five-year NIH roadmap/business plan would identify the technologies, investigators, expected milestones and results and the timeline for collaborative input by various institutions and investigators. The plan would also provide input on opportunities for funding support.

Cancer is probably the most competitive area of focus nationally in advancing personalized medicine. Perhaps Arizona can stand out in a

specific cancer research area such as gastrointestinal or skin cancer, but might be better served working on respiratory diseases, neurosciences, or diabetes.

### Work from the clinic backwards

*"..most beneficial impact is derived when biomedical applications of modern technology are driven by clinical needs, not by 'technology push'—and thus fit into the context of clinical practice and meet the demands of patients' and clinician's daily lives."*

J. Parrish, Director, CIMIT

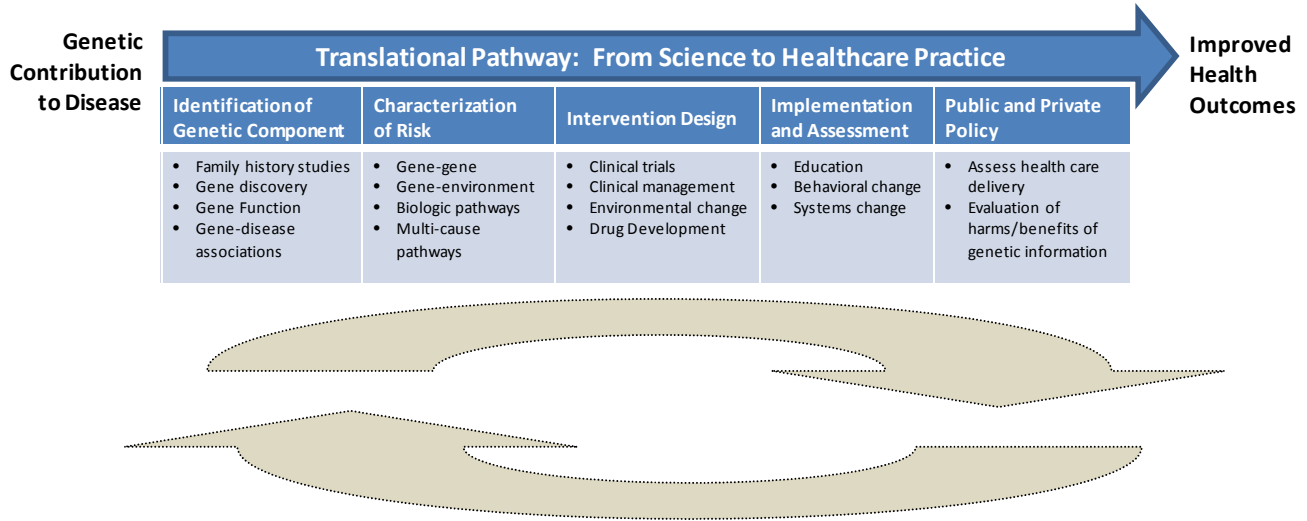
There are two broad approaches to working from the clinic/patient point of view:

- **Top Down:** work forward from data on genetic variation of patients to design drugs and therapies based on the functional consequence of the variation;
  - **Bottom Up:** work backward from data on patients demonstrating drug toxicity or non-response to a treatment to the identification of genetic variation followed by the development of therapeutic regimes, new drugs, and diagnostics.
- Result in a more-focused and clinically consequential research project;
  - Provide better therapeutic regimes for existing and future drugs of major significance to the local community;
  - Lead the way toward development of rigorous, standardized annotation and documentation procedures that will support subsequent genetic, metabolic, proteomic, and epigenetic studies;
  - Support parallel identification and development of policies and knowledge-management systems that will be needed to render findings clinically applicable; and,
  - Include health-care providers from the beginning, allowing the feedback and participation that will enhance the probability of successful integration of pharmacogenomics and medical practice.

Many leading programs have utilized the bottom-up approach as less risky and more likely to deliver tangible results and provide actionable information to the physician and patient.

This approach has several attendant benefits; it can:

Figure 2: Translational Pathway



From:Harrison TA, Burke W, Edwards KL. The asthma consultative process: a collaborative approach to integrating genomics into public health practice. *Prev Chronic Dis* [serial online] 2005 Apr. Available from URL: [http://www.cdc.gov//pcd/issues/2005/apr/04\\_0135.htm](http://www.cdc.gov//pcd/issues/2005/apr/04_0135.htm)

**Establish and/or invest in value-added core facilities:**

While Arizona has many of the core technologies and facilities currently needed to establish a personalized-medicine program, there are significant gaps related to more modern translational-research cores, including:

- A centralized DNA repository to complement existing tissue biospecimen banks. As stated by William Evans of St. Jude Children’s Hospital, a well-documented, standardized core of DNA samples will be necessary for future genetic studies, retrospective evaluations, and Phase III clinical trials that seek to segment patients on the basis of response, no response, or toxic response. Identification of patient segments that may not benefit from some drug therapies could allow pharmaceutical and piotechnology companies to save expensive drugs from oblivion.

- Centralized data archives. The amount of patient-specific data that will be generated is likely to be very large and the ability to access relevant data in support of a personalized-medicine health-care system will be key to successful implementation.

*“...before pharmacogenomics testing can be widely accepted, it must be considered beneficial in guiding therapeutic management and decision making. ...Moreover, since the variability one sees in patient response to drug therapy is a composite of genetic variation and environmental factors, genomic testing information frequently needs to be considered in the context of other clinical information, such as age, sex, weight, the effect of concomitant medications, including dietary supplements or even the patient’s diet. ... In many cases, software-based decision tools will need to be developed to aid in the*

*computation of such complex drug and dosage recommendations.*<sup>31</sup>

A center that begins to develop the knowledge-management and technological ability to manage Arizona genetic and health-care data will enable Arizona to link with and benefit from the impetus for nationwide electronic records.

- Consider advancing health-care information systems infrastructure: Future IT resources such as cloud computing will be needed to ensure the effective dissemination of information for patient care. There should be a focused effort in Arizona to assess the opportunity to develop this infrastructure in the state. A consortium of computer scientists and experts from engineering, medicine, nursing, pharmacology, and public health at institutions such as UCLA, the University of Southern California, the Argonne National Laboratory at the University of Chicago, and St. John's Health Center in California are currently focused on the development and application of "... wireless and network-enabled technologies integrated with current and next-generation medical enterprise computing" for future health-care services. Such cloud-computing health-information tool(s) will allow for the interaction of multiple systems and platforms and the maintenance of data ownership and confidentiality. In support of this development, UofA is currently exploring opportunities in this area in collaboration with MaryAnn Guerra of BioAccel, Patrick Soon-Shiong of Abraxis BioScience, and Denis Cortese of ASU.

It should be noted that the Arizona Biomedical Research Commission is already committed to seeing these types of core developments take

place in Arizona, and would be a critical partner for advancing these efforts in the state.

#### **Advance the state's capabilities in pharmacogenomics through a signature center.**

Personalized medicine will contribute to streamlined drug discovery, and minimization of adverse reactions through pharmacogenomics. While Arizona investigators can develop collaborations in order to participate in large clinical trials, it must develop the infrastructure to analyze the resulting data sets in order to participate more fully in pharmacogenomics. Arizona will need to develop both 1) the infrastructure needed for high-capacity storage, computing capacity, and bandwidth, and 2) the intellectual capabilities for data integration of multiple databases and analysis.

A core of specialists who can work with clinicians, and investigators to provide integrative analysis linking clinical data to -omics research would provide the most effective and efficient benefits to Arizona. A pharmacogenomics core would be positioned to link gene-expression data from multiple sources, platforms and studies with disease entities and link clinical data to therapies. In addition to its service function, the center/core would also perform research leading to new or modifications of storage and computing technologies to deal with the challenges of ever-increasing amounts of data in multiple platforms.

#### **Advance a signature center for diagnostic biomarker standardization and validation**

The search for biomarkers and other biosignature molecules is intense. The failure of many of these to move from "bench to bedside" is a major barrier in drug and diagnostic development.

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<sup>31</sup> Personalized Medicine: The Role of Laboratories. Victoria M. Pratt, S. Terence Dunn and Karen E. Weck. *Update* 5: 18-22, 2008.

A center that can collect and validate biomarkers would be a valuable resource to the academic and industry investigators in Arizona. In fact, Arizona has the components for such a center in place. C-Path, through its collaborations with the FDA, the Bill and Melinda Gates Foundation, and the pharmaceutical industry, provides a level of expertise unique in the field. Its collaborations with UA, ASU, Roche Ventana, sanofi-aventis, IGC, and TGen provide a statewide platform for future, enhanced developments. In

addition, the Partnership for Personalized Medicine is developing high-throughput screening capabilities in proteomics that can be a critical tool for validating biomarkers.

This signature center in the standardization and validation of diagnostics biomarkers would complement the broader development of molecular diagnostics and related technologies in Arizona, and be a global resource to spur the commercialization of biomarker discoveries in both academia and industry.

## CASE STUDY: A Model for Centralized Honest-Broker Leadership and Facilitative Support

### CIMIT – Center for Integration of Medicine and Innovative Technology

(based in Boston, Mass. as a component of Partners HealthCare)

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*MISSION: To improve patient care by facilitating collaboration among scientist, engineers and clinicians to catalyze the discovery, development and implementation of innovative technologies, emphasizing minimally invasive approaches.*

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**Basic Structure, Organization:** Promoting the acceleration of translational process and progress through the design and implementation of an organized, staffed, *facilitative* structure to provide support, mentoring, convening, and problem-solving consultative service to innovative investigators as well as to ensure the success of close collaborations across disciplinary boundaries.

The appointed leader is responsible for ensuring for the proper staffing, coordination, and progress of the facilitation process.

**Facilitation:** The process provides a project or project leader with the right help at the right time in the right place. This is a highly personal process that may include:

- Connecting project leaders or teams that need complementary skills. Bringing in appropriate industrial resources,

technologies, or prototyping skills at whatever stage they are needed;

- Guiding and supporting project leaders through the challenges of obtaining needed regulatory approvals and protection of any IP for subsequent licensing;
- Helping with obtaining needed follow-on funding for work beyond the pilot stage, including potential philanthropic support;
- Assisting with any needed business planning, reimbursement analysis, connections with licensees or investors, and other issues of actual launch of a given technology in health-care;
- Assisting in solving administrative problems with IP management, contract negotiation, grants administration, regulatory compliance, etc.

The leader is supported by a dedicated central staff.

*Staff:* The characteristics of effective central staff include experience working across boundaries, relevant communication skills to do so effectively; successful track record of relevance to tasks of “CIMIT”; readiness for the “give-back,” selfless portion of their careers; generosity of spirit in fostering collaborations without requiring credit; and passionate commitment to improving health-care.

*Site miners* – These staff members are: senior clinicians/scientists within an institution; multi-disciplinary; knowledgeable in the politics and networks of their home institution; still active in clinical/research work. They are key to penetrating the multiple isolated member institutions, and connecting people and ideas across the cultural walls of these institutions and even across the boundaries separating departments within them.

*Program leaders* – These staff members are clinicians and scientists with distinction and expertise within a specific scientific domain and serve a broad integrative role. They ensure familiarity with the general flow of ideas in a specific scientific or technical area in which a cluster of current projects fit.

*Industry Liaison* – A “CIMIT” office can also serve as a liaison to industry as a neutral third party—working closely with academic institutions and industry to bridge cultural and geographic gaps, thereby providing early support to an institution’s commercialization office.

The coordinating “CIMIT” office might also provide a mechanism for the rapid dispersion of small amounts of funding. CIMIT-Boston currently provides:

(1) Working Group Awards provide funds to gather a multi-disciplinary group together to focus on a vaguely defined clinical need and characterize that need with sufficient specificity and cleverness to allow clinicians and technologists to attack it effectively. CIMIT provides \$25,000 awards to cover such expenses as travel to other sites, focus-group expense, staff support for meetings, etc. to catalyze a group’s formation and support its work.

(2) Pilot or Gap research awards inject small amounts of funding at key points of need where other sources are not available for an exciting concept and team, and when progress depends on a special and rapid injection of support.

The Boston based CIMIT organization has grown to a level of research projects in 16 areas with 1 director, 21 program leaders, 10 site managers, 10 program directors and 10 facilitation leaders. The organization has an annual budget of approximately \$15M—of which \$1M is for administration, operations, finance and compliance; \$5.7M for project grants, \$3.2M for research services and \$2.6M for innovation leadership. CIMIT receives \$12.6M in funding from the federal government, \$1.2M from fund raising, \$0.2M from industry and \$1.0M from consortia members.

#### **SUMMARY OF NEXT STEPS AND INVESTMENTS NEEDED:**

**The top priority should be the establishment of a facilitative and coordinating mechanism(s) for supporting and advancing multi-disciplinary research projects in personalized medicine. Establishment of this mechanism will drive subsequent actions in a focused, coordinated, and productive manner.**

- A five-year roadmap/business plan should be developed by an advisory board that details the establishment of the coordinating center and its role in advancing these projects. The roadmap should detail the strategic, organizational, operational, and financial plans for the center. Expectations for governance and research priorities and milestones should be clearly defined. The plan would serve as ongoing decision support and as a communication document for funding agencies and other important constituencies.

**Focused faculty recruitment in the areas of medicinal chemistry, epigenetics, and glycomics.**

**Continued investments in shared core-lab resources, including biorepositories, centralized databases, and capacities in epidemiology and biostatistics. Consider future investments in cloud computing, linking health-care information and research activities.**

**Develop signature centers in:**

- Pharmacogenomics;
- Diagnostic biomarker standardization and validation;
- Health-information systems and applications.

**Create a revised medical-education curriculum that synthesizes the multiple components of personalized medicine to provide health-care providers with the ability to understand the research-and-technology basis of personalized medicine and the value of the new approach to their patients.**



## APPENDIX A: Selected AZ Resources Relevant to Personalized Medicine

There are many resources in Arizona that could provide value to a program in personalized medicine. The following list is not exclusive but is meant to summarize those institutions and programs most likely to be involved on a more dedicated basis.

Primary institutions and programs currently involved in personalized-medicine initiatives	
Academic Institutions: UNIVERSITY OF ARIZONA	
<i>Overview</i>	<i>Implication for Advancing Personalized Medicine</i>
<p><b>The Arizona Cancer Center</b> is a Comprehensive Cancer Center designated by the National Cancer Institute. The Cancer Center has five research programs (cancer biology and genetics; cancer imaging; cancer prevention and control; gastrointestinal cancer; therapeutic development) and two institutes (the Skin Cancer Institute and the Cancer Health Disparities Institute). The Cancer Center is the recipient of two SPORE (Specialized Program of Research Excellence) grants, including one of only five SPORE grants for research in GI cancer. The Cancer Center’s Lymphoma Research Consortium, in partnership with the University of Rochester, has also received a SPORE grant for research in lymphoma. The Cancer Center is a member of the Partnership for Native American Cancer Prevention (with NAU and members of the Hopi Tribe and Navajo and Tohono O’odham nations), which has received an NCI grant to confront cancer disparities among Native Americans.</p>	<p>Although the Cancer Center is not especially focused on personalized medicine, its programs in health disparities and its work with American Indian tribes and Latina women have potentially great value in targeting therapeutic treatments to these specific populations.</p> <p>Shared services include: imaging, proteomics, experimental mouse core, genomics, informatics/bioinformatics, molecular modeling and synthetic chemistry, tissue acquisition, and cellular/molecular analysis.</p>
<p><b>The BIOS Institute</b> – BIOS has several collaborative initiatives linked to personalized medicine, including: the Genome Structure and Function Consortium and the Drug Discovery Institute.</p>	<p>Shared cores include proteomics, genomics, genetically engineered mouse models, and the Arizona Proteomics Consortium.</p>
<p><b>College of Pharmacy -- Center for Toxicology</b> – The Center for Toxicology is the home for the research-and-training toxicology programs at UA. The center combines chemistry and biology to understand the processes by which chemicals affect people, to identify factors that influence those processes and to develop preventive or therapeutic measures to reduce any toxic effects. The center includes the Southwest Environmental Health Sciences Center (see below), and the U.S.-Mexico Binational Center for Environmental Sciences and Toxicology. The center also has a research-and-training program in toxicology and toxicogenomics and has been awarded a National Institute of Environmental Health Sciences (NIEHS) training grant in toxicogenomics.</p>	<p>The center serves as a significant site for the study of environment effects on population susceptibility to disease. Projects include leading-edge research in toxicogenomics and toxicoproteomics.</p>
<p><b>College of Pharmacy -- The Southwest Environmental Health Science Center.</b>, led by the University of Arizona College of Pharmacy, is an NIH-funded research center that studies how environmental factors are related to such diseases as chronic pulmonary disease and other types of lung problems, skin cancer, reproductive problems, and liver and kidney disorders, among others. Among its recent studies are an examination of the effect of high UV-light exposure on the various ethnic groups drawn to the Southwest and the potential genetic susceptibilities of these groups to a multitude of environmental pollutants.</p>	<p>The Center has core research facilities for genomic and proteomic analysis. Potential genetic susceptibilities of ethnic groups to environmental pollutants provides long-term opportunities for population-based diagnosis and treatment. With TGen, the College of Pharmacy has been awarded a \$7.5M grant for a drug-discovery and development center putting renewed focus on medicinal chemistry. Building a library of compounds via high-throughput capabilities will facilitate identification of molecules of biological interest in drug discovery and development</p> <p>The laboratory of Serrine Lau, in collaboration with the Arizona Cancer Center and TGen, has been awarded a GO award to develop global mass-spectrometry-based protein profiling and drug imaging on tissue.</p>

<p><b>College of Pharmacy – The Center For Health Outcomes and PharmacoEconomic Research</b> assesses health-care interventions from a clinical, economic and humanistic view. Research includes cost-effectiveness analysis, quality-of-life assessment, pharmaceutical policy analysis, and drug-use evaluation.</p>	<p>Economic analysis of potential treatments and therapies from healthcare provider perspective will help develop new policies and procedures and lead to the effective integration of personalized medicine into clinical practice. The Center’s assessments will be critical to the development of new policy guidelines and the acceptance of personalized medicine by government and reimbursement agencies.</p>
<p><b>The Respiratory Center</b> – An internationally recognized Center of Excellence comprised of physicians, scientists and scholars focused on research in basic science, clinical advancements, drug development, and alternative therapies, with emphasis on the biology, genetics, epidemiology, prevention, and treatment of respiratory disorders.</p>	<p>Research projects relevant to personalized medicine include work in functional genomics, biomarkers, cellular and molecular mechanisms, genetic basis of respiratory disease, and molecular and genetic epidemiology of respiratory diseases.</p>
<p><b>The Diabetes Research Program</b> serves as a statewide consortium of investigators, educators and health-care providers, focusing on diabetes research, clinical care, and education. The center will provide a collaborative, interdisciplinary approach based at the College of Medicine programs in both Tucson and Phoenix, with a focus on the genetics, physiology, epidemiology, and management of diabetes. Program partners include University Physicians Healthcare at Kino campus, University Medical Center, the Carl T. Hayden and Southern Arizona Veterans Health Care Systems, ASU, TGen, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).</p>	<p>Investigators at UA (BIO5), ASU (Biodesign), and TGen are working to discover biomarkers for diabetes that can be used to identify individuals with a predisposition for adult-onset diabetes. Results from the biomarker, genetic studies of diabetes can be used to determine the most effective treatments for segments of the population susceptible to the onset of diabetes.</p>
<p><b>The Arizona Center for Education and Research on Therapeutics (AzCERT)</b> is one of 14 national centers funded by the U.S. Agency for Healthcare Research and Quality to conduct research and offer educational programs to advance optimal use of drugs, medical devices, and biological products. The centers serve as a national resource for health-care providers, consumers, and others seeking to improve health through best use of medical therapies.</p> <p>The AzCERT is a collaboration between UA’s College of Pharmacy and the Critical Path Institute. Its goal is to improve, through research and educational programs for medical professionals and consumers, therapeutic outcomes and reduce adverse events caused by drug interactions, especially those disproportionately harming women. This goal, directed toward improving the safety of medical products currently on the market, is an excellent complement to C-Path’s mission to foster the safe acceleration of the process for developing new medical products.</p>	<p>The AzCERT fills a crucial gap in personalized-medicine research as a trusted source of research and information needed for optimal use of therapeutic regimens. Implementation of personalized medicine with targeted drugs and diagnostics will be worthless without education as to the effective use and the provision of a mechanism for providing feedback information on no or adverse reactions by patients. AzCERT will function as a valuable communication and research center for the refinement of existing therapies and the safe and optimal use of new therapies.</p>
<p><b>Academic Institutions: ARIZONA STATE UNIVERSITY</b></p>	
<p><b>The Biodesign Institute</b> – Research initiatives include: <i>Conquering Cancer</i> – development of vaccines in collaboration with the Mayo Clinic; <i>The Cheap Genome</i> –development of more cost-effective sequencing methodology; <i>Rapid Vaccine Discovery</i> system – rapid development of vaccines in response to rapidly emerging infectious diseases; <i>Doc in a Box</i> – developing technology linked to predictive biosignatures of disease.</p> <p>The Virginia G. Piper Center for Personalized Diagnostics, funded by the Partnership for Personalized Medicine, will utilize proteomics technology for biomarker discovery and validation.</p> <p>Other research centers include: the Center for Innovations in Medicine; the Center for Ecogenomics; Evolutionary Functional Genomics; Personalized Diagnostics; Environmental Biotechnology.</p> <p>To facilitate development of therapies, Biodesign has established the new Impact Accelerator – a separate entity that provides a unique incubator environment for ASU and Biodesign.</p>	<p>The Biodesign Institute has several major initiatives directly relevant to personalized medicine, with significant resources and cores to support collaborations with clinical entities. The hire of Joshua LaBaer adds expertise in functional genomics. In addition to basic research, Biodesign has investigators involved in the development of technologies crucial to the advancement of personalized medicine – for example, development of a more cost-effective sequencing methodology is often mentioned as a key element for incorporating personalized medicine into clinical practice.</p> <p>The addition of Lee Hartwell to ASU’s faculty will help Biodesign build its program(s) in biomarkers. Work on health-care metrics and policy will be performed Dr. Hartwell’s colleague, Michael Birt.</p> <p>Collaborations are in place with C-Path for developing validation procedures and policies for biomarkers to facilitate FDA approval.</p> <p>Biodesign is also working with the College of Nursing</p>

	<p>to develop the clinical research nurse workforce essential to performance of clinical trials related to personalized medicine.</p> <p>Participation in global lung-cancer trials has potential to add significant samples to AZ tissue repositories.</p>
<p><b>School of Engineering:</b> developing advanced biosensors, bioassays, and lab-on-a-chip tools for clinical diagnostics, biomedical informatics, drug-delivery systems, health-monitoring devices, health-care systems analysis and modeling, and bioinformatics.</p>	<p>The School of Engineering is involved in the development of key technologies necessary for the incorporation of personalized medicine into clinical practice, including biomedical informatics for integrative analysis of genomic data using biomedical-domain knowledge, as well as using bioinformatics to improve knowledge access, public-health informatics, and clinical diagnostics.</p>
<p><b>The Center for Metabolic Biology (ASU and Mayo Clinic Collaboration)</b> is an interdisciplinary group of basic and clinical scientists working together and dedicated to discovering the molecular mechanism underlying insulin resistance. Insulin resistance syndrome is an array of abnormalities comprised of insulin resistance, obesity, type 2 diabetes, dyslipidemia, hypertension, vascular dysfunction, and coronary artery disease. The center is investigating the underlying molecular mechanism behind the multiple manifestations of insulin resistance. The center embraces a strong translational-research focus, with involvement of basic-research departments such as chemistry/biochemistry, kinesiology, and the School of Life Sciences, as well as a dedicated clinical-research facility on campus and a strong relationship with the Carl T. Hayden VA Medical Center.</p>	<p>Many disease disorders are complex, multiple-disease states demonstrating variability among population segments. The Center for Metabolic Biology provides a cross-disciplinary group of researchers focused on underlying causes of a metabolic syndrome.</p>
<p><b>Independent Research Institutes: T GEN</b></p>	
<p>Genomic studies of cancer, neurogenomics and metabolic diseases (type 2 diabetes) include DNA sequencing and microarray analysis, and multiple collaborations with other Arizona institutions. TGen research centers include the Center for Proteomics. TGen Clinical Research Services at Scottsdale Healthcare is focused on pancreatic cancer, with the goal of developing new therapies. The organization at Scottsdale Healthcare includes the Genomic Medicine and Individualized Therapy Center and the Pharmacodynamic and Pharmacokinetic Lab for the study of drug absorption and distribution. The Cancer Drug Development Laboratory (in collaboration with Mayo Clinic) is developing new technologies and integrated systems-biology approaches in order to translate genomic data rapidly to new anti-cancer drug compounds. TGen also has significant collaborations with Biodesign and is working with C-Path on high-throughput biomarker validation. The recent collaboration with the College of Pharmacy to form the Southwest Comprehensive Center for Drug Discovery and Development will expand TGen’s work in the development of synthetic compounds to enhance large-scale screening efforts for compounds of interest for drug development.</p> <p>TGen is also partnering with 5AM Solutions as a “In Silico Research Center of Excellence” to investigate comprehensive genomic data on brain tumors.</p>	<p>TGen provides Arizona with a unique and highly specialized competency in genomic analysis with extensive expertise across multiple technology platforms in high-throughput genotyping and gene sequencing, as well as medicinal chemistry, proteomics with mass-spectrometer capability to advance studies in diverse disease areas from multiple types of cancer, neurodegenerative and psychiatric diseases, metabolic disorders, and pathogens. With the establishment of a macromolecular-analysis and processing center, TGen will be developing standardized protocols and will build the infrastructure needed for consistent data analysis of large amounts of samples. Without such standardization, validation of biomarkers will be very difficult.</p>
<p><b>Independent Research Institutes: C-PATH</b></p>	
<p>C-Path has focused its efforts over the past years on solving a critical gap in therapeutic development and utilization—the unbiased validation of diagnostic tests for verification of biomarkers to be used in diagnostic tests and target identification. The persistence of this gap prevents diagnosis and monitoring that would improve use of drugs and other therapies currently on the market. C-Path has established programs that examine drug safety and effectiveness by providing unbiased assessment and validation of diagnostics (especially biomarkers). Use of valid biomarkers can help identify safety problems before a product is on the market. C-Path is organized to be a neutral third party providing validation. In addition to its validation work, as a member of the Cardiovascular Disease Consortium, C-Path has collaborated</p>	<p>C-Path is involved in a number of initiatives of direct value to personalized medicine. C-Path will be a valuable contributor to the development of diagnostics and therapies for personalized medicine by validating biomarkers and diagnostic tests. Without such validation, incorporation of new drugs and diagnostics developed by research in personalized medicine into clinical utilization will be hindered. C-Path also brings experience in studies aimed at optimizing the use of existing therapies—a component of personalized medicine that has</p>

<p>on a study of warfarin dose levels and patient response. As a member of the Coalition Against Major Diseases (CamD), C-Path will collaborate in the analysis of data from clinical trials to better map complex-disease entities. The initial diseases to be analyzed are Alzheimer's and Parkinson's.</p>	<p>immediate application and value.</p>
<p><b>Academic Medical Centers: ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER</b></p>	
<p>St. Joseph's significant neurosciences initiatives include Barrow Neurological Institute (BNI), the Barrow Neuroscience Research Center, the Muhammad Ali Parkinson Center, and the BNI-ASU Center for Preclinical Imaging.</p>	<p>Neuroscience resources include tissue specimens (Barrow Neurological Institute) – another key element of research into the determination of causes of disease(s) and patient segmentation.</p>
<p><b>Academic Medical Centers: BANNER HEALTH SYSTEM</b></p>	
<p>Banner Health has studies in oncology, neurobiology and neuroengineering involving the Sun Health Research Institute with the L.J. Roberts Center for Alzheimer's Research, the Cleo Roberts Center for Clinical Research, the Napoleon Longtine Center for Molecular Biology and Genetics, the Roberts S. Haldeman Laboratory for Molecular and Cellular Neurobiology, the Ralph and Murial Roberts Laboratory for Neurodegenerative Research, the Laboratory of Neuroinflammation, the Civin Laboratory of Neuropathology, and the Thomas H. Christopher Center for Parkinson's Research.</p>	<p>Banner Health is a large healthcare system with significant presence and research in neurological disorders. Supportive technologies include medical imaging and tissue/organ banking facilities at Sun Health.</p>
<p><b>Academic Medical Centers: MAYO CLINIC</b></p>	
<p>Significant initiatives at the Mayo Clinic, Scottsdale, include the Cancer Center for translation of cancer biochemistry, molecular biology, cancer signaling and systems biology, genetics and genome studies in drug discovery and improvements in patient care. On-site collaborations include TGen's Drug Development Team and Drug Development Laboratory. Mayo is collaborating with ASU's Biodesign Institute on cancer vaccines as well as the Center for Metabolic and Vascular Biology. Other collaborative projects include: Alzheimer's and Parkinson's disease – genetics and biomarker identification.</p>	<p>Mayo has clinical resources and collaborations in personalized medicine in oncology and neuroscience with research projects in basic research (genetics and biomarkers) and drug/vaccine development that contribute to patient segmentation and drug development.</p>
<p><b>Academic Medical Centers: SCOTTSDALE HEALTHCARE</b></p>	
<p>Includes the Virginia G. Piper Cancer Center and the Scottsdale Clinical Research Institute (SCRI). The SCRI provides support and resources for collaborative partners, including TGen Clinical Research Services (see above), the Arizona Cancer Center, and the Biodesign Institute at ASU. A goal is the development of targeted, patient-specific therapies in the area of cancer, with plans for diabetes, cardiovascular diseases, and neurosciences. Work includes gene expression analysis of tumor tissue samples in collaboration with International Genomics Consortium.</p>	<p>Scottsdale Healthcare contributes clinical-research support and resources, as well as tissue specimens to the pancreatic-cancer program.</p>
<p><b>Supportive Institutions and Programs can provide valuable contributions</b></p>	
<p><b>UNIVERSITY OF ARIZONA</b></p>	
<p><b>School of Public Health</b> – includes projects in cancer prevention and control, chronic disease prevention and control (cardiovascular, diabetes), Hispanic and Native American health programs.</p>	<p>Patient-based public-health information and outreach, educational program development.</p>
<p><b>Advanced Research Institute for Biomedical Imaging</b> – established to promote interdisciplinary biomedical-imaging research and directly affect health care. The Institute involves work ranging from micro- to macro-scopic imaging.</p>	<p>Supportive technology of biomedical imaging for research support, product development and testing.</p>
<p><b>ARIZONA STATE UNIVERSITY</b></p>	
<p><b>College of Nursing</b> – The ASU College of Nursing includes the Center for Health Innovation and Clinical Trials, the Center for Improving Health Outcomes in Children, Teens and Families, the Center for the Advancement of Evidence Based Practice, and the Arizona Consortium for the Advancement of EBP.</p>	<p>The College is not currently focused on personalized medicine, but these programs will provide support for the translation of research initiatives into medical practice. For example, the interdisciplinary Center for Health Innovation and Clinical trials will participate in and expedite the process of bringing health-care products to market through clinical trials, product-development partnerships, and educational programs.</p>

<p><b>Arizona HealthQuery</b> – ASU’s Center for Health Information &amp; Research houses Arizona HealthQuery, a statewide community-health data system that contains health information for millions of Arizonans in a manner that preserves privacy and is fully HIPAA compliant.</p>	<p>AZ HealthQuery possesses the capability to track patients across health-care systems and over time. It provides a valuable resource to the community, analyzing health-care utilization, quality of care, public-health policy, and community health needs. By expanding to include more genomic-based data and other key environmental-related factors for individuals, AZ HealthQuery can become a critical tool for advancing analysis in personalized medicine.</p>
<p><b>NORTHERN ARIZONA UNIVERSITY</b></p>	
<p>Complementing the Center for Microbial Genetics and Genomics led by Paul Keim lab is TGen North, which focuses on rapid disease diagnosis and pathogen detection and the development of advanced diagnostic devices. NAU is a member of the Partnership for Native American Cancer Prevention (with UA and members of the Hopi Tribe and Navajo and Tohono O’odham nations), which has received an NCI grant to confront cancer disparities among Native Americans.</p>	<p>This group is likely to become more important as personalized-medicine diagnostics research becomes more prevalent. The collaborative work with UA and tribal populations is a significant contribution to population-based health care.</p>
<p><b>ARIZONA BIOMEDICAL RESEARCH COMMISSION</b></p>	
<p><b>Research Infrastructure: Az TRANSNET</b></p>	
<p>AZTransNet is an ongoing initiative supported by the Arizona Biomedical Research Commission to provide Arizona with the capacity to facilitate collaborative translational and clinical-research activities in Arizona across the broad base of universities, non-profit research institutions, hospitals, medical centers, private-practice physicians, and industry. Initiatives include collaborative IRB approaches, the advancement of community-based participatory research, the Arizona Clinical Research Consortium, policy-development retreats, and the development of template forms and policy guidelines to facilitate Clinical and Translational Research.</p>	<p>The initiative has the infrastructure in place to facilitate development of policies and procedures that may be unique to research projects for personalized medicine.</p>
<p><b>Research Infrastructure: ARIZONA VIRTUAL TISSUE REPOSITORY</b></p>	
<p>ABRC is supporting the development of a virtual tissue repository linking the resources of multiple institutions and providing access to a variety of normal and disease specimens. The pilot project will focus on a few disease areas, with plans for expansion as processes and policies become standardized.</p>	<p>The Virtual Tissue Repository will provide enhanced access to tissue specimens for genetic analysis.</p>
<p><b>CARL T. HAYDEN VA HEALTH CARE SYSTEM CENTER (PHOENIX)</b></p>	
<p>The Carl T. Hayden VA Health Care System has a strong research program in diabetes and collaborates with other research programs in Arizona to translate research findings into therapeutic applications.</p>	<p>The Carl T. Hayden VA Medical Center offers access to a large patient population for clinical diabetes studies. Extensive electronic medical records could provide valuable information for clinical trials research.</p>
<p><b>SOUTHERN ARIZONA VA HEALTH CARE SYSTEM (TUCSON)</b></p>	
<p>The Southern Arizona VA Health Care System serves as a major source of health care for veterans in southern Arizona and also serves as a tissue repository for the VA system.</p>	<p>The VA system has extensive electronic medical records that are likely to provide valuable data for Tucson’s collaborations in diabetes clinical research. Access to the system’s tissue repository will also support genetic and phenotypic disease studies.</p>
<p><b>Statewide Research Consortia: ARIZONA PARKINSON’S DISEASE CONSORTIUM</b></p>	
<p>The Parkinson’s Consortium is a collaborative program involving ASU, Banner-Sun Health Research Institute, Banner Good Samaritan Hospital, Barrow Neurologic Institute, Mayo Clinic, and TGen.</p>	<p>The consortium provides communication and coordination of research activities.</p>
<p><b>Statewide Research Consortia: ARIZONA ALZHEIMER’S CONSORTIUM</b></p>	
<p>The Alzheimer’s Consortium is a collaborative program involving ASU, Banner Good Samaritan Hospital, Banner – Sun Health Research Institute, Barrow Neurologic Institute, Mayo Clinic, TGen, and UA.</p>	<p>The consortium provides communication and coordination of research activities.</p>

Statewide Research Consortia: PARTNERSHIP FOR PERSONALIZED MEDICINE	
<p>A multi-organization collaboration to develop new molecular diagnostics for the early detection and treatment of disease. The partnership includes “the discovery and development engine.”</p>	<p>The partnership serves as a driving force for the communication and coordination of research activities. In addition, the partnership is funding a key research center for biomarker discovery and validation, the Virginia G. Piper Center for Personalized Diagnostics at ASU.</p>
Statewide Research Consortia: ARIZONA PROTEOMICS ALLIANCE (AZPA)	
<p>A collaboration of nine institutions: ASU, Banner Health, Banner-Sun Health Research Institute, Barrow Neurological Institute, Carl T. Hayden Veterans Administration Medical Center, Intrinsic Bioprobes, Inc., Mayo Clinic, TGen, and UA. The alliance was formed to advance the field of proteomics in Arizona via “integrative proteomics” – developing proteomic-research capabilities to be complementary to fields such as genomics, bioinformatics and clinical research.</p>	<p>The Alliance will be valuable providers of communication and coordination to advance the field of proteomics and its possible utilization for projects in the area of personalized medicine in Arizona.</p>
<i>Outreach and Implementation Institutions and Programs –essential to the incorporation of personalized medicine into the health care system</i>	
Community Based Participatory Research: ITCA	
<p><b>The Inter Tribal Council of Arizona</b> provides member tribes with the means to coordinate and act on key issues including health care and research. Members of the ITCA are the highest elected tribal officials of 21 of the tribes of Arizona. Programs include the Southwest American Indian Collaborative Network and SAICN Cancer Grant in collaboration with the Arizona Cancer Center and the Phoenix Indian Medical Center; the American Indian Research Center for Health, and the Epidemiology Center.</p>	<p>An invaluable contact for research with the tribes of Arizona. Personalized medicine has potential to provide great value to underserved and minority populations, who often demonstrate distinct responses to common drugs and therapies.</p>
Community-Based Participatory Research: ARIZONA STATE UNIVERSITY	
<p>Center for the Advancement of Evidence-Based Practice  <b>Coalition For Evidence Based Medicine</b> – Statewide consortium of organizations dedicated to the advancement of evidence-based medicine and the improvement of health-care provision.</p>	<p>Source of data and feedback to researchers on patient response to therapies and treatments; could become providers of phenotypic data.</p>
Community Based Participatory Research: OTHER	
<p>Many universities and research hospitals have designated community liaisons for communications and interactions with underserved populations, including the elderly, children, Hispanic, and American Indian communities.</p>	

## APPENDIX B:

### Selected AZ BioIndustry Resources Relevant to Personalized Medicine

From late 2008 through the Spring of 2009, Flinn staff interviewed representatives of selected Arizona bioscience companies in order to profile their scientific and technical platforms and expertise. Specific goals of the interviews were to better understand companies' research capabilities and specific needs in order to identify ways Arizona's Bioscience Roadmap efforts might support bioscience industry development, as well as to identify opportunities for increased collaboration between companies, research institutions and researchers within Arizona.

Of particular relevance for personalized medicine is the development of a base of bioscience research-and-testing companies, which the Flinn interviews identified as actively involved in the development of biomarker-based diagnostic technologies.

#### Examples of Arizona Research and Testing Firms involved in Advancing Products and Services Related to Personalized Medicine

Roche	Development of tissue based diagnostics
High Throughput Genomics – Tucson	Biomarkers for diagnostics
Luceome Technologies – Tucson	Developing biomarkers (kinases) to support drug development
Genosensor - Phoenix	Measurement of gene expression (mRNA) for drug development
Provista Life Sciences – Phoenix	Biomarker panels for disease diagnosis
MDx - Tucson	Proteomics and bioinformatics for high-throughput analysis and detection of biomarkers
Intrinsic Bioprobes – Phoenix	Proteomics and bioinformatics for high-throughput analysis and detection of biomarkers
Caris/MPI – Phoenix	Service provider of microarray analyses to assist in the diagnosis and treatment of patients
Applied Microarrays – Phoenix	Manufacture of DNA/protein-based microarrays

## Appendix C: Interview Participants: Arizona Investigators

Investigator	Institution and Position
Michael J Demeure, MD	Translational Genomics Research Institute, Senior Investigator; Director, Rare Tumors Center, Scottsdale Healthcare; Director, Pancreatic Cancer Biospecimens Repository
Bernard W Futscher, PhD	University of Arizona, Department of Pharmacology and Toxicology, Professor
Jay A Gandolfi, PhD	University of Arizona, Department of Pharmacology and Toxicology, Associate Dean, Research and Graduate Studies; Professor
Christopher Hulme, PhD	University of Arizona, Department of Pharmacology and Toxicology, Associate Professor, co-PI, Medicinal Chemistry Center NIH award
Laurence Hurley, PhD	University of Arizona, Department of Pharmacology and Toxicology, Professor; Howard J. Schaeffer Endowed Chair in Pharmaceutical Sciences
Walter Klimecki, DVM, PhD	University of Arizona, Department of Pharmacology and Toxicology, Assistant Professor
Joshua LaBaer, MD, PhD	Arizona State University – Biodesign Institute, Virginia G. Piper Center for Personalized Diagnostics, Director
Serrine S Lau, PhD	University of Arizona, Department of Pharmacology and Toxicology, Professor; Director of Southwest Environmental Health Science Center; Director of Arizona Proteomics Alliance; Co-Director, UA Mass Spectrometry Consortium
Fernando D Martinez, MD	University of Arizona, Director, Arizona Respiratory Center; Director, BIO5 Institute; Swift-McNear Professor of Pediatrics
Lawrence Mandarino, PhD	Arizona State University, Department of Kinesiology, Professor and Chair; Center for Metabolic Biology, Director
Bernadette Melnyk, PhD, RN, CPNP/PMHNP, FNAP, FAAN	College of Nursing and Health Innovation, Dean and Distinguished Foundation Professor in Nursing
Deirdre Meldrum, PhD	Arizona State University, Fulton School of Engineering, Professor and Dean; Biodesign Institute, Ecogenomics Research Center,

	Director
Nathalie Meurice, PhD	Translational Genomics Research Institute, Associate Investigator, Pharmaceutical Genomics Division, co-PI – Medicinal Chemistry Center NIH award
Terrence J Monks, PhD	University of Arizona, Department of Pharmacology and Toxicology, Chair and Professor
John E Murphy, PharmD	University of Arizona, Depart. of Pharmacology and Toxicology, Associate Dean, Pharmacy Practice and Science; Professor
Konstantinos Petritis, PhD	Translational Genomics Research Institute, Center for Proteomics, Head
Phillip Schneider, MS	University of Arizona, Department of Pharmacology and Toxicology, Associate Dean for Academic and Professional Affairs – College of Pharmacy at the Phoenix Biomedical Campus
Cheryl Selinsky	Translational Genomics Research Institute, Center for Proteomics, Director of Technical Operations
Jeffrey Trent, PhD	Translational Genomics Research Institute, President and Research Director
Raymond Woosley, MD, PhD	Critical Path Institute, President and CEO