

**Knowledge Mining & Bioinformatics
Techniques to Advance Personalized
Diagnostics & Therapeutics:
The Case for White Space R&D**

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33 multi-disciplinary organizations including healthcare services, universities, public sector R&D, and private sector information technology companies from **11** countries and **8** US states

1 consensus:

New directions needed for knowledge mining and bioinformatics tools to impact patient care

2 imperatives:

- ① Compress translational timeframe
- ① Crack the economic code of Personalized Medicine

3 calls to action:

- ▶ FILL the translational white-spaces
- ▶ INNOVATE business models
- ▶ FACILITATE both

Acknowledgement

The impetus for writing this book was inspired by a two-day NSF international Workshop on Knowledge Mining and Bioinformatics Techniques to Advance Personalized Diagnostics and Therapeutics that was moderated by Dr. Ron Ribitzky in Florence, Italy in 2012 (<http://hit.fiu.edu/W/> and <http://HIT.FIU.edu/W/pre-report.pdf>). It is founded on the workshop deliberations and subsequent work of the moderator, members of the workshop's scientific steering committee, and participants including chapter submissions on selected topics.

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¹ Adapted from <http://www.va.gov/disclaim.htm>

A note from the Principal Author and Chief Editor Dr. Ron Ribitzky, M.D.



Contemplating and exploring the next wave of compelling problems that are worth pursuing on a global-scale is exciting indeed. Yet this book takes it further.

The thoughts expressed in this book were inspired by an international multi-disciplinary workshop that was funded by the US National Science Foundation (NSF), and the US Israel Science and Technology Foundation (USISTF).

This book is intended for worldwide audience of policy makers, program leaders, investors, and scientists from the public and the private sectors.

The public at large is kindly encouraged to explore certain fundamental sections that are not 'rocket science'. By this we mean that they do not require medical, scientific, or technical knowledge to understand, deliberate on, and take action.

And so this book informs the U.S. and other governments seeking to fund high impact research: whether in the form of an exclusive national pursuit, collaborative multinational endeavor, or global partnership among the public sector, private sector, and academia.

The workshop included four scientific sessions focusing on the policy implications of implementing personalized diagnostics and therapeutics based on big data analytics, the technological challenges facing computer scientists and physicians in creating useable systems, the challenges in utilizing big data analytics to predict future health outcomes, and the needs of clinicians in utilizing in their practices decision support systems based on big data analytics.

I greatly enjoyed facilitating this workshop using a technique based on Dr. Edward de Bono's theory 'Six Thinking Hats'². My first encounter with this technique was at Intel Innovation Lab in Ireland a few years ago. It has proven useful and exciting again to elicit insightful thoughts and perspectives from this multi-disciplinary international forum. Examples are 'Personalized medicine is ready for prime time. Why?..', 'Big Data is...!', 'Predictive analytics projects will fail because...!', etc. At times through deep-thoughts, and at other by witty remarks, the use of this technique led to rich conversations and valuable debate that inspired, and served the foundation for this book.

The workshop reached a broad-based consensus on new directions for knowledge mining and bioinformatics tools to impact patient care; as well as strategic, proactive, and preventive health and wellness decisions here and now.

A multi-faceted, grand-challenge undertaking, the highlights included a call-to-action for technological breakthroughs to fill the growing 'translational white spaces' among the many scientific and clinical disciplines throughout the personalized medicine cycle up to end-user clinicians, patients, and consumers; innovative business models to accelerate the reduction of new discoveries along that cycle to practice; and policies that facilitate both.

Following the workshop we expanded the scope of the report out and supplemented it with chapters written by participants following the workshop. These chapters provide deep insights and specific real world key learnings from a range of personalized medicine initiatives already underway.

This effort was made possible by the personal dedication of over three dozen passionate practitioners, scientists and their respective organizations representing the many disciplines that converge on the single, globally shared mission: accelerate the translation of scientific discovery to making actionable clinical decisions.

I want to take this opportunity to extend my appreciation and gratitude to the members of the Scientific Steering Committee for the opportunity to take part in this important and fascinating event. A special 'thank you' to Ann Liebschutz and her team at USISTF which included Eve Copeland, Charlie Swartz, and Robert Brunson for their outstanding support and assistance in making this book happen; and to Karell Müller, U.S. National Science Foundation's Industry/University Cooperative Research Center for Advanced Knowledge Enablement at Florida International University for working with me on the graphic design for the cover of this book.

To my wife Dafna and my children Romy, Laura, Tom, and Roy – thank you for being so supportive from inception to completion.

We call it 'A-to-Z'.

Ron Ribitzky, M.D.

CEO, R&D Ribitzky

R&DRibitzky
informatics • for life

² <http://edwdebono.com>

A note from the Scientific Steering Committee

The world has seen the human genome fully decoded by an international team of scientists after more than a decade of work to being available to scientists within days or hours. The question now is how will we use the wealth of information available to us through our newly understood genomic data and, further, given our massive computing power, can we merge this information with all patient's health data, compared with like patients and exponentially growing medical knowledge in order to better diagnose and offer therapeutics?

With the generous support of the U.S. National Science Foundation and our respective organizations we convened top scientists, practitioners, and industry leaders from multiple disciplines to take a hard look at what needs to be developed to help the industry grow; and chart a path to compress the cycle time and economics from emerging technologies and methodologies to deployable high-impact, scientifically-sound industrial-grade solutions.

We tasked this distinguished forum to factor-in regulatory, legal, technology infrastructure and other drivers and barriers to developing practical and achievable personalized medicine solutions that can be deployed around the world. This includes the developed and emerging economy countries alike.

We have requested Dr. Ron Ribitzky, an independent subject matter expert to facilitate this two-day workshop: from framing and focusing the questions to driving an open and lively debate, and wrapping it all up with scholarly peer-reviewed publication. The Committee would like to extend a very sincere Thank You to Dr. Ribitzky for his amazing work. We hold skills in the highest regards, as his extremely competent facilitation skills were instrumental in producing the high caliber output.

We need more scientific and outcome oriented workshops of this kind in an ongoing effort to bring again computer scientists and clinicians together and lay the groundwork for the future of medicine and translating this foundation into provisioning of the relevant information to the general practitioner treating the patient.



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1 Executive summary

1.1 Key take-aways and call to action

Key takeaways	Call to Action
<ol style="list-style-type: none"> 1. The ultimate goal of Personalized Medicine is making actionable decisions that matter about one's health or wellness, here and now 2. We envision the emergence of new markets and new industries with high-value breakthrough innovation and cross disciplinary pollination 3. Look for key learnings from Intel's 'Copy Exactly' and 'Tick Tock' innovation and production model for next generation breakthroughs in personalized medicine 	<ol style="list-style-type: none"> 1. Fill high-value white-spaces in translational research and personalized medicine 2. Innovate business models aimed at making the practice of personalized medicine a commodity 3. Facilitate both through legal and regulatory frameworks, and public-private partnerships

Focus areas *technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation*

1.2 Level set

Making actionable decisions about one's health or wellness, here and now, is the ultimate purpose of personalized medicine.

It was the theme of the National Science Foundation's direction-setting International Workshop on Knowledge Mining and Bio-informatics Techniques to Advance Personalized Diagnostics and Therapeutics ³in Florence, Italy 2012 that inspired, and continues through this book.

And so we have set out to discover future directions for high-value breakthrough research in bio-informatics that would influence concrete actions that matter in making these decisions.

We call it filling the white space of translational research and personalized medicine.

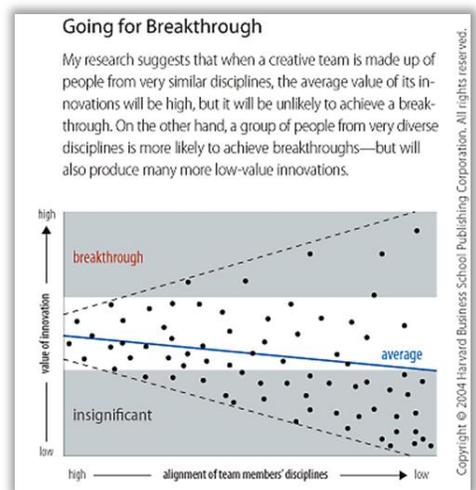
1.3 Breakthrough innovation

Contemplating and exploring the next wave of compelling problems that are worth pursuing on a global-scale is exciting indeed. Yet this book takes it further. We seek to accelerate emerging and ignite new technologies to match these problems.

*We envision the emergence of new markets and new industries that would thrive on filling the white space in personalized medicine and translational research with high-value breakthrough innovation and cross-disciplinary pollination.*⁴

This book aims to inform public and private sector organizations seeking to fund high impact research: whether in the form of an exclusive national pursuit, collaborative multinational endeavor, or global partnership among the public sector, private sector, and academia. And so, each chapter begins with a summary of key points (take-aways) and a call to action.

Where one begins? What's the roadmap?



³ <http://hit.fiu.edu/W/>

⁴ "Forethought Research: Perfecting Cross-Pollination" by Lee Fleming, Harvard Business Review, September 2004 <http://hbr.org/2004/09/perfecting-cross-pollination/ar/1>

1.4 Highlights

Personalized medicine is evolving through paths of micro tipping-points. Nevertheless, it takes too long and costs too much to transform scientific discovery to meaningful clinical actions. In the chapter on adoption, *we offer a dozen strategic approaches to accelerate application of discovery to practice aimed at cutting time lags 2-3X in 2 to 3 cycles.*

Consider this: we have massive computing power that continues to grow. Analytics and knowledge management paradigms continue to evolve rapidly. Social-media grows exponentially on a global-scale, threading through communities of scientists, practitioners, policy makers, investors, entrepreneurs, and - of course, the general public. The network effect of these multi-dimensional connections and diverse content is colossal.

What does it take to merge all these with one's illness, wellness, bio-markers, and environmental data in order to better predict, prevent, diagnose and treat his or her medical problem in a timely and economically affordable manner? Joshi, Joshi, Yesha, and Yesha offer an approach to construct a formidable policy based information technology infrastructure to do just that.⁵

“30 years ago we were trained on the premise that our primary role as specialists in Internal Medicine is to tailor our clinical practice personally to each patient. “

“So I guess this is the essence of what we now refer to as Personalized Medicine.”

“Then, we were doing it by common sense and professional judgment.”

“Today, we are trying to reach better outcomes for our patients by genetic testing, computerized analysis and new sciences that have meanwhile emerged.”

workshop participant, name on file

The world has seen the human genome fully decoded by an international team of scientists after more than a decade of work being available to scientists within days or hours.

The question now is *how will we use the wealth of information available to us* through our newly understood genomic data and, further, given our massive computing power, can we merge this information with all one's health data, compared with like patients and with exponentially growing medical knowledge in order to better diagnose and offer therapeutics?

Hsu, Tran, and Linninger inform us that we begin to master the capabilities to digitally reconstruct one's organs with such high degree of precision previously limited to manufacturing; and apply predictive analytics to that functional expression for personalized molecular therapy⁶.

Does it mean that informatics is no longer the best term to describe the use of information technology in translational research; and *would it make more sense to extend the use of 'Infomics'⁷, in line with genomics and proteomics?*

And because personalized medicine is entering the manufacturing space, albeit in the virtual digital form, *could or should we look for key learnings such as 'Copy Exactly'⁸ that is key to Intel's decades long technological and commercial success and 'Tick Tock'⁹ innovation and production model for next generation breakthroughs in our field?* In like manner, virtual organ reconstruction and disease modeling for personalized medicine would be

performed with 'Reconstruct Exactly' zeal and practice in mind.

How can that be achieved as information technology challenges grow consequent to the upward pace, volume, and diversity of scientific discovery in life sciences continue throughout the translational medicine stack¹⁰; episodic and longitudinal patient information accumulate in corporate information systems of healthcare providers and insurers; and individuals stream personal and wellness information up and down clouds and through social networks.

And so, Mennel proposes to form a “consortium of physicians, basic scientists, institutions, and companies to limit their investigation to the studies that will likely *answer the most important questions and not try to answer every question.*”¹¹

⁵ See chapter “Policy Driven Cloud based Services for Personalized Medicine” further in this book

⁶ See chapter “Disease Modeling for the Development of Personalized Molecular Therapies” by Hsu, Tran, and Linninger further in this book

⁷ <http://hemantvarma.wordpress.com/2010/07/26/welcome-to-infomics/>

⁸ The Evolution of Intel's Copy EXACTLY! Technology Transfer Method, McDonald, <http://download.intel.com/technology/iti/q41998/pdf/copyexactly.pdf>

⁹ <http://www.intel.com/content/www/us/en/silicon-innovations/intel-tick-tock-model-general.html>;
<http://web.mit.edu/nanosymposium/www/Presentations/GarginiPart1.pdf>

¹⁰ See 'Translational research framework' further in this book

¹¹ See chapter “Precision Medicine: Has Its Time Come?” further in this book

Yet many factors are at play in “What is the best question to pursue in a trial?” Campbell et. al. offer “Scalable methodologies for distributed development of logic-based convergent medical terminology”¹². Would such *consensus-building techniques help converge the widely diverse stakeholders of personalized medicine?*

How could that shift the balance where over 200 other doctors are involved in treating the Medicare patients of an average primary care physician; and one-third of health care expenditures does not improve health?¹³

What are the shortcomings of contemporary business model thinking? And what *business model innovation may emerge that would make personalized medicine a commodity?*

We offer a *domain model to help the different stakeholders frame and focus such questions*; and a *value model to facilitate making tough choices among promising personalized medicine projects in light of limited resources*¹⁴. Liebermann, Klang, Recanati, and Balicer share with us what may seem counter-intuitive case studies of national scale adoption of personalized medicine by a managed care organization.¹⁵

An insightful account of Mayo Clinic Vs. Prometheus wraps up this book. This landmark case of intellectual property pertaining to personalized medicine divided the industry. Avoiding being prescriptive, our hope is that it will *enrich our readers' positions and decisions as to whether or not to patent a new discovery* in this field.

¹² Methods Inf Med. 1998 Nov;37(4-5):426-39

¹³ What's possible for healthcare, IOM at <http://phlibraryres.wordpress.com/2012/09/06/whats-possible-for-health-care-infographic-from-the-iom/>

¹⁴ See chapter 'Value considerations' further in this book

¹⁵ See chapter "National-scale Adoption of Personalized Medicine in Socialized-Medicine Market" further in this book

2 Domain frameworks and key concepts

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2.1 Key take-aways and call to action

Key takeaways	Call to Action
<ol style="list-style-type: none">1. We describe the personalized medicine domain model to frame and focus the exchange of ideas among the multiple stakeholders aimed at accelerating the benefits of personalized medicine2. The personalized medicine domain model addresses disease lifecycle and translational research3. The personalized medicine domain model facilitates exploration of bench-to-bed and bed-to-bench program and project opportunities4. We offer a framework to explore the impact of strategy and action in the practice of personalized medicine5. Growing trustworthiness challenges make the pursuit of evidence in personalized medicine a monumental effort that amounts to a white space issue	<ol style="list-style-type: none">1. Model and measure value that is based on strength of evidence at each major aspect of the disease lifecycle and translational research leading to actionable personalized medicine decisions2. Fund white space R&D to tackle the growing trustworthiness problem in translational research and personalized medicine

Focus areas *technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation*

2.2 Level set: framing and focusing

Personalized medicine is a complicated high-stake field. Multiple disciplines are at play: from clinical to life sciences, information technology, business, legal, and regulatory, to name a few. Terms and concepts commonly used in one discipline may be vague or simply obscure to professionals in another. And the pace of discovery seems to accelerate exponentially while transforming it to clinical action may still take over a decade and cost over \$1B.

And so we propose a *value-based conceptual domain model to frame and focus the exchange of ideas among the multiple stakeholders aimed at accelerating the benefits of personalized medicine.*

2.3 Disease lifecycle framework



The disease lifecycle dimension of our framework seeks to *map out the key phases in the progression of diseases* (a.k.a. natural course of disease). Adapted from Prospective health care¹⁶, the following five phases offer useful context for

examining strategies and actions aimed at reducing the burden of diseases:

At Risk phase is when a person may have a tendency to be sick, yet no evidence is found that a disease process has begun.

The beginning of a disease process marks the transition from At-Risk to **Preclinical Progression** phase. The patient may not feel or otherwise realize that he or she is sick, and pathology may go undetected by means available to them.

¹⁶ Prospective health care: the second transformation of medicine, Ralph Snyderman and Jason Langheier, Genome Biology 2006, 7:104 (doi:10.1186/gb-2006-7-2-104) www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16522218

During the *Disease Initiation* phase, patients may begin feeling that something is wrong with them, or early signs of disease may be objectively detected.

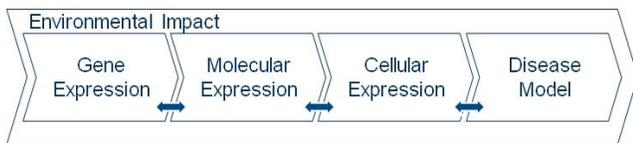
Disease Progression is when the symptoms and signs of illness are quite obvious. Certain diseases may progress to an early chronic phase. The duration of their illness is prolonged, and it may be more difficult to be cured.

Although not every illness ends up being chronic, some may deteriorate into an *Irreversible Damage* phase.

Chronic diseases at over 47% of the US population with projected steady growth ¹⁷drive over 75% of the cost of healthcare, and 4 of the 5 most expensive health conditions are chronic.¹⁸

The disease lifecycle can be illustrated in a process flow diagram:

2.4 Translational research framework



Like a cast, characters, and script make a play, the *Translational Dimension* of our framework seeks to *map out the structural elements, what they can do, and what is happening* in translational medicine.

For sake of simplicity, let's assume that *genes* constitute the foundation of personalized medicine; and that genotype and phenotype are the outermost edges of the personalized medicine domain. What is left for us to explore then are the transitional domains in between: the *molecular* and *cellular*.

Respectively, let's agree that the molecular domain is essentially the expression of one's genome in molecular terms; and that the cellular domain is essentially one's expression of the molecular play in terms of tissues and organs.

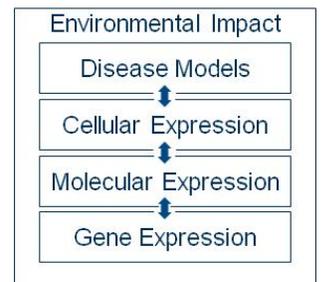
Because our concern is one's illness as well as wellness, we'd need to complement normal expressions with expressions of abnormality. What comes to mind is the use of *disease models* as a descriptive domain in our conceptual framework.

Because complex mechanisms of expression are at play (some are quite convoluted), let's refer to them as *pathways*.

Nevertheless, we know that environmental factors may influence the structural elements and their properties, eventually changing the original (or personalized) script quite substantially. So let's include *Environmental Impact* domain in our framework.

Seeking to *graphically illustrate the descriptive dimension of our framework to clinicians*, a time-based (temporal) model may be helpful. It aligns with the *natural course of disease*, a fundamental concept well known to clinical practitioners. The bidirectional arrows illustrate cyclical flow of information and knowledge required to continuously drive our understanding of translational medicine.

Yet *informatics professionals may more intuitively relate to a stack model* of the same - the equivalent of an architecture stack, a fundamental model widely used by information technologists. Similarly, the bidirectional arrows illustrate the equivalent of round-trip flow of information and knowledge required to continuously drive our understanding of translational medicine.



2.5 Putting it together: personalized medicine domain model

Let's begin constructing the domain model of personalized medicine by layering the *disease lifecycle dimension* on top. The equivalent of top-down approach, let's call it the *Bed-to-Bench methodology*. We are mindful that 'Bed' may suggest a progressive state of disease that bounds the patient to bed. However, for our purpose here, we borrow the widely known concept Bed-to-Bench to imply that clinical considerations drive scientific pursuit.

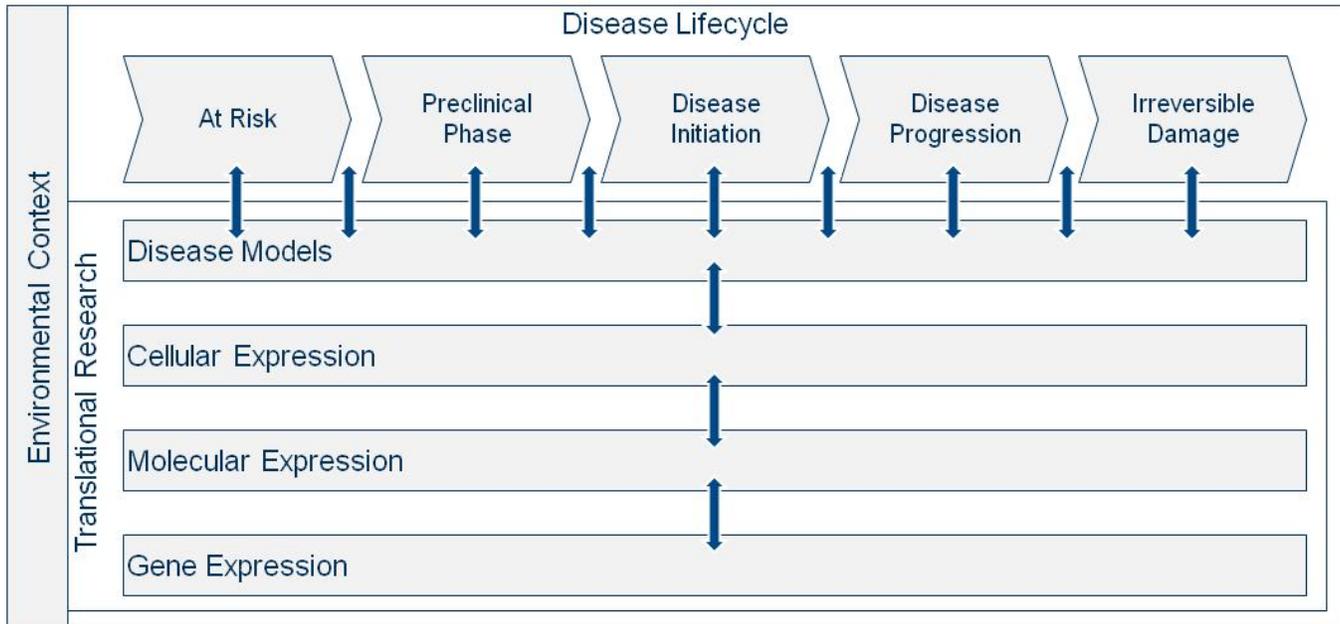
Inherent to this approach, of course, is the presumption that an individual may suffer from a single disease. It is often not the case. Nevertheless, at this stage of orienting ourselves to the conceptual framework, we will keep it simple, i.e. to a single disease. We address the impact of co-morbidity on personalized medicine elsewhere in this book.

¹⁷ Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionj.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf> citing Projection of Chronic Illness Prevalence and Cost Inflation. RAND Corporation

¹⁸ Source: National Health Council http://www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/AboutChronicDisease.pdf citing the Centers for Disease Control and Prevention at <http://www.cdc.gov/chronicdisease/resources/publications/AAG/chronic.htm>; and the Agency for Healthcare Research and Quality at <http://www.ahrq.gov/research/ria19/expendria.htm>

Let's now bring in the *translational research dimension* to inform us about the current state of the industry pertaining to the disease we are exploring. In this we mean the pipeline of scientific discovery, and opportunities that it may provide us. The equivalent of bottom-up approach, let's borrow the other widely known concept *Bench-to-Bed methodology* to describe it. In case you are not familiar with this term. Bench-to-Bed implies that scientific discovery may inform clinicians about new options available for their patients.

Putting the two together will look like this:

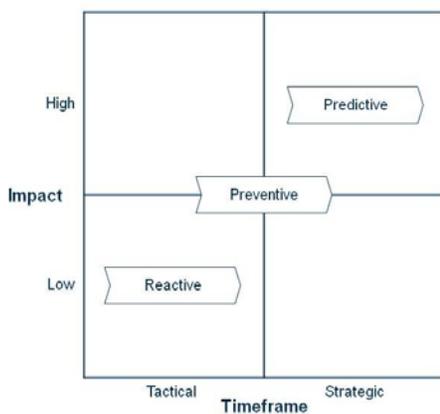


Combining disease lifecycle and translational research models provide us the equivalent of a map for treasure hunt as well as the beginning of a story board. Both are *useful for identifying high-value targets for white-space research and development and roadmaps*.

2.6 Strategy and action in the practice of personalized medicine

The actionable dimension of our framework seeks to *map out the key actionable themes in reference to the disease lifecycle*.

Arguably, *to do nothing is a course of action* that may and probably should be considered on a case by case basis by practitioners of personalized medicine – as well as by patients. Philosophically, one may associate a do-nothing option with the fundamental clinical premise of *first do no harm*.



Nevertheless, to keep our framework simple, we propose three actionable themes that – either practiced singularly or together, may have substantial impact on driving personalized medicine and translational research.

Reactive is taking action based on the recognition that illness is in process. For some, reactive medicine marks the legacy of clinical practice up until recently, and may continue to be commonplace so long as personalized medicine may not be widely adopted.

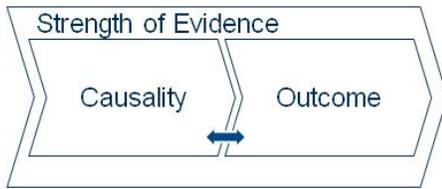
Preventive is the active pursuit aimed at avoiding the occurrence of undesirable condition.

Predictive is premised on one's ability to determine with reasonable evidence that certain condition may or may not occur, further driving reactive and/or preventive action.

Each of these themes may be further examined along a *Strategic* dimension which extends the timeframe of their respective impact.

2.7 Evidence in translational research and personalized medicine: sure about it?

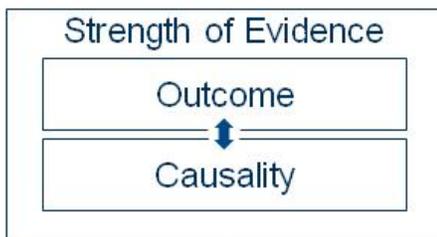
The evidence dimension seeks to *map out key elements that actions should rely on in personalized medicine*. Actions may range from setting direction for research, embarking on the development of next generation medical devices, implementing new clinical protocols, adapting policies, defining regulatory requirements, etc.



Causality expresses *cause and effect relationships throughout the descriptive dimension of our framework*. Let's agree that causality may be direct or indirect; and that causality may involve rather complex pathways – whether fully accounted for in the descriptive domain or not. Be it as it may, to understand and successfully act on causality in personalized medicine, we may need to factor cycle times (i.e., the timeframe in which the cause and effect of interest are at play)

Outcome expresses the *end-result of causality throughout the descriptive dimension of our framework*. Let's agree that outcomes may be expressed in qualitative and quantitative terms. Be they as they may, for outcomes to be considered they should be measurable.

Strength of Evidence indicates the *quantifiable measure of confidence that one may reasonable rely on considering causality and outcome that may or may not warrant action*. Ideally, the strength of evidence would be expressed in quantitative terms.



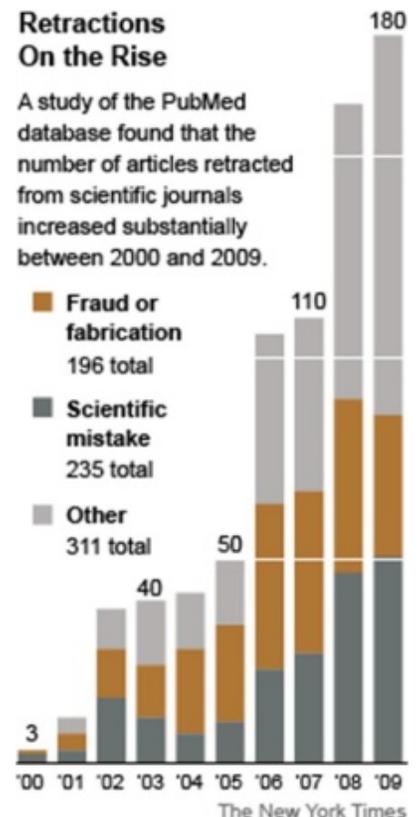
Nevertheless, white space in personalized medicine and translational research implies that still *there is much to be discovered*. Therefore, let's also agree that strength of evidence may be expressed in semi-quantitative terms (such as high, medium, low). The most extreme case would be 'none' (respectively, 'boundary condition' and 'null'). This is to say that an assumption of causality or outcome cannot be objectively substantiated.

We offer time-based model and stack model graphics of Strength of Evidence (SOE).

Applying the evidence framework requires such a monumental effort and caution that amounts to white space issue.

In "*Sloppy Science and Useless Information*", Burrill points out that the validity hence trust-worthiness of published scientific discovery has become a major concern:¹⁹

- 15X retraction rate growth on 44% increase in the number of publications in research journal since 2001 (Source: Wall Street Journal)
- 15.4X growth in retracted articles among 16,000 peer reviewed journals between 2001 and 2010 (Source: Thomson Reuters Web of Science)
- 7X growth of retractions related to fraud in medicine and biology studies published in the Journal of Medical Ethics during a 5-year period between 2004 and 2009
- 2X growth of retractions related to errors in medicine and biology studies published in the Journal of Medical Ethics during a 5-year period between 2004 and 2009



¹⁹ Biotech 2012: Innovating in the new austerity, Burrill & Company http://www.burrillandco.com/resources-66-0-0-503-Biotech_2012_Innovating_in_the_New_Austerity_PRINT.html

3 Towards a taxonomy of personalized medicine

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3.1 Key take-aways and call to action

Key takeaways	Call to Action
<ol style="list-style-type: none">1. An intuitively obvious concept, personalized medicine is inconsistently defined2. A person's biology is a system of expressions that derive from their individual information3. We offer taxonomy of concepts related to the term "Personalized Medicine", and a pragmatic framework to facilitate the application of these concepts for particular purposes and contexts	<ol style="list-style-type: none">1. Establish open-source semantic network of personalized medicine content in partnership between the public and private sector

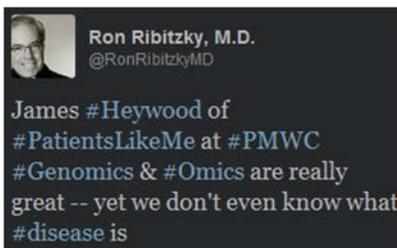
Focus areas *Definition of personalized medicine, taxonomy, framework, technology*

3.2 Perceptions, misunderstanding or plain controversy?

Reaching consensus over what is Personalized Medicine turned out to be a non-obvious undertaking. At the outset, a fundamental question dominated the effort of this multi-disciplinary, international forum to reach common grounds for the upcoming exploration:

What is medicine that is not personalized?

Except for population health, a nuance follow up question emerges: *Is there a line between personalized medicine and medicine that is not personalized?*



Personalized Medicine means different things to different people. Some may have vested interest forcing their own, exclusive definition. Other may define it from the narrow perspectives of the singular discipline they practice. Yet cross disciplinary practitioners such as systems biologists, translational medicine scientists, and policy makers seek broad, integrative definition of Personalized Medicine.

Clinicians wonder what the fuss is about, indicating that for them the practice of medicine was always personal – exclusively dedicating their passion, knowledge and skills to each patient individually, one person, one encounter at a time.

Yet certain scientists hold the opinion that Personalized Medicine is a relatively new, emerging field synonymous with nothing else but genomics. Some felt that proteomics might be considered too for this discipline-grounded definition of Personalized Medicine.

Some advocate a completely different approach to defining Personalized Medicine, recognizing that the subject matter is indeed very broad, very deep, and multi dimensional. Aside from academics, one may argue that it may be impractical to attempt reaching a singular definition. Instead, one may try sub-typing Personalized Medicine so that we can have Personalized Medicine of Type A, B, C, etc. The potential value of sub-typing Personalized Medicine lies in the ability to provide precise definitions of smaller scope which would drive clarity rather than ending up with a too high level, vague one.

Or is it?

3.3 Contemporary attempts to define personalized medicine

The US National Cancer Institute (NCI) of the National Institutes Health (NIH) defines it as “*a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.*”²⁰ The U.S.

²⁰ NCI Dictionary of Cancer Terms at <http://www.cancer.gov/dictionary?cdrid=561717>

National Library of Medicine® defines Personalized Medicine as “*an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease.*”²¹

Adopted by the personalized Medicine Coalition²², the US President's Council on Advisors on Science and Technology in 2008 refers to Personalized Medicine as the “*tailoring of medical treatment to the individual characteristics of each patient...to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.* Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.”²³

Eddie Blair of the UK-based Integrated Medicines suggested that Personalized Medicine means the right medicine for the right patient for the right disease at the right time and right dose for the right response and the right price.²⁴

Seeking to mediate the emerging spectrum of existing and potentially new definitions, experts in life sciences informatics offered the fluid approach: instead of trying to define Personalized Medicine in a binary, singular and exclusive fashion it may be useful to *characterize it by the type of data that may be involved in a particular real world situation – i.e. the qualitative dimension;* and by the *volume of data that may be required – i.e. the quantitative dimension,* pointing at the rising ‘Big Data’ field.

The notion of fluid approach stemmed from the forum's consensus that *fundamentally, a person's biology is a system of expressions that derive from their individual information;* and that *Personalized Medicine is the practice of actionable reasoning about it.* Pathways of translation and expression, external environmental factors, and homeostasis add up to fulfill the needs of contemporary discourse about Personalized Medicine.

The ever growing pace of new discovery and deeper sub-specialization make actionable reasoning exponentially daunting challenge for the entire ecosystem: from scientists to clinicians, policy makers and private sector, and the public at large – i.e. the ‘Person’ in ‘Personalized Medicine’ that is the grounding focus of this forum.

Osler's 100+ years old concept of medicine as the practice of comprehensive and careful observations is a useful baseline: “*the integration of scholarship with patient care, together with the science and art of medicine... concerned with the ideals of medicine as with its science and knowledge*”.²⁵

Citing John Keats's reflections in 1817, Dr. Nuland points out that medical education was short back then. “Although the examinations were difficult, there was little of real usefulness to learn... *patient care was conducted in a pervasive atmosphere of inexactness.*”

Providing pragmatic perspectives that are founded on philosophically insightful considerations, Dr. Nuland discusses the context for and role of *clinical judgment*: “*To become comfortable with uncertainty* is one of the primary goals in the training of a physician... *clinical decision making* is the realization that, perforce, it *must always be accomplished in the face of incomplete and largely ambiguous information.*”²⁶

Omics are commonly referred to as rapidly evolving fields of study that range from the structure and behavior of genes (*Genomics*), proteins (*Proteomics*), metabolites (*Metabolomics*) and other. These fields seek to develop *omics-based tests* and methods to accelerate progress of, widen access to, and reduce cost of *wellness programs, disease prevention, and patient care.*²⁷

And so, Burrill contemplates whether personalized medicine “[is] a surrogate for molecular diagnostics?”²⁸

²¹ NLM's Genetics Home Reference at <http://ghr.nlm.nih.gov/glossary=personalizedmedicine>

²² Personalized Medicine Coalition at <http://www.personalizedmedicinecoalition.org/about>

²³ Report of the President's Council of Advisors on Science and Technology September 2008 at http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf

²⁴ An Overview of Personalized Medicine by Eddie Blair, Integrated Medicines at http://www.admin.cam.ac.uk/offices/research/documents/local/events/downloads/pm/Eddie_Blair.pdf

²⁵ The Oslerian Tradition and Changing Medical Education: A Reappraisal by John P. Geyman, MD at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1010861/pdf/westimed00202-0102.pdf> West J Med. 1983 June; 138(6): 884–888 PMID: PMC1010861

²⁶ Dr. Sherwin B. Nuland, ‘The Uncertain Art’ Published: June 6, 2008 in the New York Times at http://www.nytimes.com/2008/06/06/books/chapter-uncertain-art.html?_r=2&

²⁷ Evolution of Translational Omics: Lessons Learned and the Path Forward, The Institute of Medicine of the National Academies, March 23, 2012 at <http://www.iom.edu/Reports/2012/Evolution-of-Translational-Omics.aspx>

²⁸ Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionj.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf>

4 Adoption of personalized medicine

4.1 Key take-aways and call to action

Key takeaways	Call to Action
<ol style="list-style-type: none"> 1. We describe strategic actions and roadmap to accelerate application of discovery to practice aimed at cutting time lags 2-3X in 2 to 3 cycles 2. Engaging patients in personalized medicine is essential for R&D and its adoption 3. Personalized medicine is evolutionary in certain aspects, and revolutionary in other 4. Personalized medicine is evolving through paths of micro tipping-points 5. Personalized medicine is a discipline of disciplines driving the creation of new ones along the way 6. Clinical informatics is a US board-certified subspecialty of primary care physicians 	<ol style="list-style-type: none"> 1. Investigate and develop strategies to engage patients, clinicians, and scientists in collaborative effort to influence research directions and adoption of personalized medicine 2. Fund white space R&D to accelerate knowledge and information transfer between one translational medicine domain to the other

Focus areas	<i>technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation</i>
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4.2 Level set

As scientifically fascinating a discussion may be about genomics and proteomics, pharma and biotech, big data and super computers, personalized medicine is essentially about patients: whether one knows that they are ill, or possess certain markers that are strongly suggestive of illness²⁹.

Personalized medicine is a global domain that traverses national and political boundaries – from formal collaborative research and development efforts to informal exchange of information, knowledge, and experience among professionals and consumers³⁰.

Clinicians need to understand what information they're getting, and they need to get it fast – typically within 10 minutes or less, because of the limited time they have for the encounter with the patient. *Usability of electronic health records and interoperability of health information systems are formidable barriers to achieve this goal.*

Ironically, *exponential growth of scientific and clinical discovery makes it no less exponentially difficult to put together with sufficient evidence to make it actionable for clinicians.*

Discovery runs faster around the world than improvements in electronic health records (EHRs), electronic medical records (EMRs), healthcare information systems (HIS), health information exchanges (HIEs), interoperability standards, and laws and regulations governing clinicians access to information about their patients and the conditions they suffer from.

4.3 Paths of micro tipping-points

Personalized medicine is evolutionary in certain aspects, and revolutionary in other.

²⁹ Dr. Hussein Hallak, Assistant Professor, Faculty Member, College of Pharmacy, Al-Quds University; Ron Ribitzky, M.D., CEO R&D Ribitzky and Visiting Professor, Kigali Institute of Science & Technology, Rwanda. Recommended reading: Personalized medicine: a windfall for science, but what about patients? Editorial, Canadian Medical Association Journal, December 13, 2011; Patients' and Consumers' Interests and Perspectives in Personalized Healthcare, Greg Simon, Margaret Anderson, Cecilia Arradaza, Kate Blenner, Kathi Hanna, and Kristin Schneeman, *FasterCures*, October 6, 2008; Pharmacogenetics - A Patient's Perspective, University of Liverpool, www.liv.ac.uk/pharmacogenetics/Pharmacogenetics.htm The Patient's View of Personalized Medicine, Neeli Bendapudi, Ph.D., Fisher College of Business, The Ohio State University www.slideshare.net/osumedicalcenter/the-patients-view-of-personalized-medicine-5443221

³⁰ Source: Dr. Hasan Salah Dweik Executive Vice President, Al-Quds University, Director of Science Discovery Center and Mathematics Museum

That *personalized medicine is an evolutionary phenomenon* founded on decades if not centuries of just fundamentally *right clinical practice* was strongly held position mostly by clinicians. It is reinforced in the chapters about precision medicine and adoption of personalized medicine by non-profit HMO further in this book.

Nevertheless, *personalized medicine is revolutionary as well, considering the exponential growth of highly specialized research projects by the many life sciences disciplines and sub-disciplines* that are driven by and further drive progress in personalized medicine; *exponential growth in volume and complexity* of data, information, and knowledge directly and indirectly impacting personalized medicine; and a *rapid stream of new information technology* components and capabilities that drive new usage models never before possible in science, business, and social life.

And *that revolution is disruptive*.

We can cure diseases we were unable to cure before; predict diseases we could not foresee before; prevent diseases we could not prevent before; be proactive like never before; and provide treatments not available before.

Conceivably, clinicians are able to practice in much higher specificity and efficacy more easily and faster, relying on complex and complicated information management and analytic processes and techniques. *While the practice of personalized medicine may or may not be revolutionary by itself, the outcomes and impact of personalized medicine on the individual and others is.* Certain chapters in this book describe specific real-world accomplishments along these lines.

The depth and breadth of understanding complex pathways and mechanisms of wellness and illness, as well as cure and prevention are by themselves revolutionary. From genomics up to translational omics, this disruption requires us to think and act differently about personalized medicine. It requires us to explore, develop, and evaluate new approaches to model and measure the multi-faceted value of new opportunities made available by personalized medicine to impact quality of life and economics.

Furthermore, the far-reaching innovative thinking and pace of innovative technologies that drive all this are fundamentally revolutionary. And so, there are the perpetual cycles of evolution and discovery, revolution and sharp turns in practice and outcomes.

This is why we call it the paths of micro tipping-points.

4.4 Is Personalized Medicine ready for prime time?

"I was doing research on complex genetics for behavioral phenotypes associated with autism..."

it takes about 17 years for something that gets discovered at bench research to ever make it into health care...

So something that I would discover today for a child that was born today would not be available as a therapy until they were heading to college... that's way too long, too late...

We need to speed this up!"

workshop participant, name on file

Insights and opinions on why personalize medicine as defined here is ready for prime time vary greatly. Nevertheless, it is badly needed, and in fact, it is already here.

Patients and the public at large play a key role in growing market demand for personalized medicine. There are clear or very obvious benefits to patients and other who may not become patients thanks to personalized medicine. Health 2.0 and social media are the driving forces in making the public increasingly educated, informed, and value-driven consumers.

Standardized one-size-fits-all protocol-guided medicine can be harmful to individuals who do not perfectly fit the persona of human subjects in controlled clinical trials.

Toxicity, side effects, comorbidity, further deterioration due to delayed diagnosis and treatment, and collateral adverse effects on social and economic well being of patients, their families, and their loved ones were cited as common undesired outcomes of population-based protocol guided care.

There's enough knowledge right now to support starting the practice of personalized medicine and professionals willing and able to practice it.

A growing body of evidence suggests that the *scientific foundation of certain discoveries pertaining to personalized medicine is sound and dependable to warrant action*. Nevertheless, we discuss the growing trustworthiness challenge of scientific publications in the section on evidence in this book.

Personalized options to prevent, decelerate progression, and treat diseases are already available. Full human genome sequencing is offered commercially and its cost is going down. Actionable biomedical markers and respective protocols

with great specificity and strong evidence of cause, effect, and outcome are commercially available, and new ones are in the pipeline.

Public and private sector collaboration around the world continues to drive wide accessibility to full human genome sequencing by making it less costly. With that, benefits to patients and those who may become ill, their families and loved ones, their medical providers, payers, governments, and society at large are obvious. The body of evidence of favorable, near and long-term clinical and economic outcomes of personalized medicine is growing.

The chapter about large scale adoption of personalized medicine by a non-profit HMO provides pragmatic real-world examples.

A growing number of personalized medicine elements such as diagnostic procedures for early detection and personalized best-fit therapeutic measures are commercially available, and more are in the pipeline, worldwide.

Enterprise-scale data warehouse and analytics that enabled the emergence and early adoption of personalized medicine are mature and main-stream. Big data analytics with broader reach and deeper capabilities enter the personalized medicine space in compelling fashion, driving innovation and providing opportunities for discovery like never before.

Disease-modeling complement the vast content in data warehouses and Big Data environments to provide near-real-world simulations and evaluation of actionable personalized medicine opportunities. Cloud-based computing and social media that connect professional and lay communities enable exponential growth in access to personalized medicine.

The chapters on information technology, cloud, and disease modeling further the discussion about these and related points.

4.5 Clinicians competency gap: informatics

Educating would-be physicians and nurses, and clinicians already in practice in the fundamentals of informatics is a significant factor determining wide spread adoption of personalized medicine. Understanding what are and what may be the questions in the practice of personalized medicine, and how information technology and informatics services can be used for that purpose: one encounter and one patient at a time are key to making personalized medicine the norm.

Generally speaking, primary care physicians and practitioners in the community are less ready to practice personalized medicine in real time than their fellow clinicians in academic medical centers and tertiary care organizations.

Seeking to address clinicians' competency in informatics, the American Board of Medical Specialties in 2011 approved *clinical informatics as a board-certified medical subspecialty of primary care physicians*³¹. AMA recognized that the practice of medicine is increasingly data-driven and dependent on information technology.

The role of Primary Care Physicians (PCPs) certified in clinical informatics includes:

- Assessing the knowledge-based needs of health care professionals and patients
- Characterizing, evaluating and refining clinical processes
- Developing, implementing and refining clinical decision support systems
- Leading or participating in the procurement, customization, development, implementation, management, evaluation and improvement of clinical information systems

This landmark move followed a six-year campaign led by the American Medical Informatics Association³² (AMIA). AMIA developed the core content of the clinical informatics subspecialty with support from a grant by the Robert Wood Johnson Foundation

The chapters on policy driven cloud based services for personalized medicine and patent considerations provide additional compelling insights on these topics.

4.6 Hurry-up-and-wait: the elusive whitespace of personalized medicine

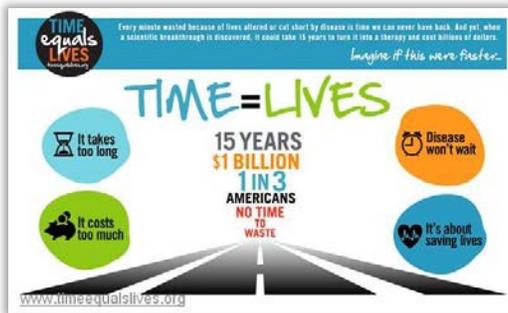
Notwithstanding the many paths of micro tipping-points, paved by exponential growth in pace and volume of new discovery, "*Patients suffering from debilitating and life threatening diseases do not have the luxury to wait the 13 years*

³¹ <http://www.ama-assn.org/amednews/2011/10/10/bisb1010.htm>

³² www.amia.org

it currently takes to translate new scientific discoveries into treatments that could save or improve the quality of their lives.” (Dr. Francis Collins, NIH Director).³³ Estimates of that wait-time range from 13 years to 15 and 17.

Or is this hurry-up-and-wait problem rooted in exactly that: many paths of micro-tipping points and exponential growth in pace and volume of new discovery?



In a massive, national-scale public-sector led effort to narrow that decade-plus gap from discovery to application, the US NIH National Center for Advancing Translational Sciences (NCATS) has set out to drive the development and implementation of technologies to accelerate discovery; enhance the evidence base for health care decisions; and encourage new investigators to come up with new ideas.³⁴

FasterCures, a private non-profit center for accelerating medical solutions attempts to speed up the time from discovery to patients by improving the medical research system.³⁵

Reducing the cycle time from discovery to practice can, and should be

exponential rather than linear.

Yet *exponential acceleration in personalized medicine requires addressing the whitespace that holds back progress from one domain of translational research to the other.*

4.7 Strategies to accelerate dissemination and adoption of personalized medicine

The NSF workshop forum reached consensus that the *time lag from discovery to practice can be cut 2-3X over 2 to 3 cycles*. It is achievable by executing on the following strategies and factoring synergy of programs, campaigns, and outcome measures.

Business strategy

- Establish value modeling programs for translational research and personalized medicine initiatives
- Develop and disseminate value models for personalized medicine that cater to the needs and concerns of consumers and patients, private sector investors, ecosystem players, and public sector funding
- Develop economic, scientific, and professional incentive campaigns that reward acceleration of personalized medicine solutions
- Use value models to focus the effort on value creation and set the stage to measure it...

Research and Development (R&D) strategy

- Set acceleration R&D agenda that is informed by input from key stakeholders on long term needs and trajectory of capabilities and assets across disciplines
- Set contests for achieving these goals based on the value models and incentives campaigns
- Measure success and elicit key feedback on what worked, what did not work, and how the next R&D cycle could be more productive (the equivalent of win/loss reviews in private sector marketing and sales)

“Disease research organizations focus on curing diseases, not fixing the research system.

But they are all delayed, and occasionally defeated, by the same systemic, cultural obstacles that slow medical progress.”

FasterCures <http://www.fastercures.org/Programs/train.php>

Technology strategy

- Adapt powerful horizontal technologies and explore the fit of special-purpose technologies from other industries to the acceleration R&D agenda

³³ NIH establishes National Center for Advancing Translational Sciences <http://www.nih.gov/news/health/dec2011/od-23.htm>

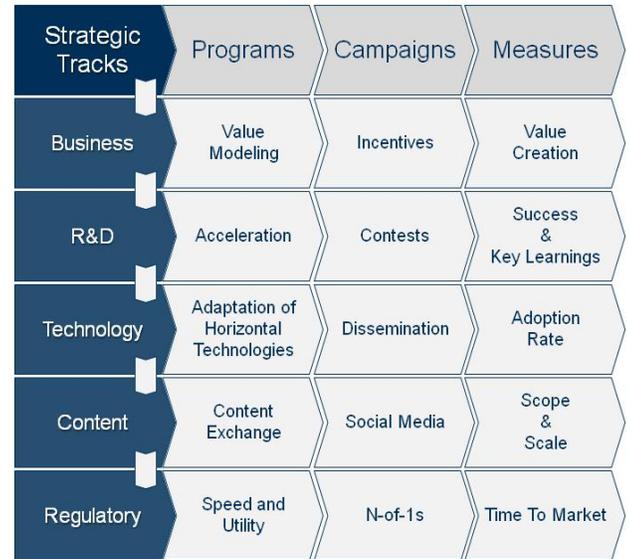
³⁴ US Dept of HHS NIH <http://officeofbudget.od.nih.gov/pdfs/FY12/Volume%201%20-%20Overview.pdf>

³⁵ <http://www.fastercures.org/About/what.php>

- Develop and pursue strategies to disseminate the acceleration-driven technologies and techniques across the disciplines involved from translational research (“bench”) to the clinical practice of personalized medicine (“bed”)
- Establish programs to measure the adoption rate of these new technologies and techniques

Content strategy

- Exploit accelerator technologies and techniques and breakthrough innovation to design content repositories as loosely federated collections of discrete, semantically-enabled fine-grain content components capable of expressing their attributes, general behaviors, and specific interactions throughout the translational research and personalized medicine domains
- Create and provide open access to massive repositories (physical and virtual clouds) of omics expressions with associated phenotypes and longitudinal clinical data



- Accelerate the development and adaptation of disease models that exploit these powerful information technologies, techniques, and content
- Leverage content exchanges to discover acceleration opportunities and assemble new tools, services, and solutions
- Develop and execute global social media campaign to foster multidimensional cross-disciplinary connections that leverage the network-effect from discovery and innovation to implementation aimed at achieving the research, development, and business goals
- Exploit the social media campaign to facilitate the equivalent of virtual personalized medicine teams
- Develop special-purpose personalized medicine education and training programs for consumers and professionals with major emphasis on contemporary informatics techniques
- Measure the success of the social media campaigns in terms of content scope and scale of engagement

Regulatory strategy

- Exploit global content exchange to adapt and optimize regulatory strategies to N-of-1 type studies in extraordinary situations of human suffering and consumers choice
- Leverage content strategy for the key components from multiple N-of-1s over time that may apply to larger populations
- Adapt regulatory oversight for speed and utility of applying new discovery in clinical practice by optimizing clearance for informed risk and benefit decisions of patients, consumers, and clinicians
- Measure the success of the regulatory strategy by Time To Market

5 The informatics gap of personalized medicine

5.1 Key take-aways and call to action

Key takeaways	Call to Action
<ol style="list-style-type: none">1. For personalized medicine to become widely adopted, information technology should be capable of elegantly displaying clinical roadmaps constructed from insights that are discovered within enormous amounts of massively disjointed data in clinical encounter timeframes at a price of single-digit pay-per-use2. Readiness of personalized medicine for prime time should be carefully evaluated based on venue, maturity of information systems available there, and practitioners' proficiency in informatics.3. Building and operating centralized Personalized Medicine Oriented Infrastructure is beyond the capability of any singular organization4. Bringing the information technology infrastructure is predicated on crafting a methodical multi-tier service-level interoperability framework and roadmap	<ol style="list-style-type: none">1. Fund R&D for search and discovery technologies that bridge across the white space in personalized medicine and translational research
Focus areas	<i>technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation</i>

5.2 Level set

Technological innovation and scientific discovery abound, yet ironically their confluence at the point of making actionable personalized clinical decisions is far from commonplace widespread reality.

The issues we're facing are not simply about tangible matters such as processing speeds, operating systems, applications, next generation wireless bandwidth, big data or clouds. Once these are accounted for, new challenges commonly referred to as soft issues are more difficult to overcome.

Tackling adoption as the product of usability, interoperability, and value of IT anywhere in the personalized medicine domain model we present at the beginning of this book is the equivalent of the perfect storm of personalized medicine informatics.

It is complicated indeed.

This chapter examines certain formidable challenges leading to the informatics gap of the kind of personalized medicine we discuss throughout this book, describes mega trends that should be factored in, and call to action to close that gap.

The chapters that follow expand on some of these topics through a combination of scientific projects underway, pragmatic real-world case studies, and key lessons.

5.3 Clinical-clock speed of informatics for personalized medicine

To enable the widespread practice of the kind of Personalized Medicine we discuss throughout this book, *technology should be capable of elegantly displaying medical roadmaps constructed from insights that are discovered within enormous amounts of massively disjointed data in clinical encounter timeframes at single-digit pay-per-use price.*

Whether it happens in a legacy brick-and-mortar environment or in the increasingly prevalent virtual encounter³⁶, it means the capability to *create compelling measurable value to the stakeholders that matter during the time that a person consults with someone or something* about their health, wellness, or illness.

We call it informatics for personalized medicine at clinical-clock speed.

Are we there yet?...

5.4 Information technology infrastructure for personalized medicine

US EMR Adoption Model™	
Stage	Cumulative Capabilities
Stage 7	Complete EMR; CCD transactions to share data; Data warehousing; Data continuity with ED, ambulatory, OP
Stage 6	Physician documentation (structured templates), full CDS (variance & compliance), full R-PACS
Stage 5	Closed loop medication administration
Stage 4	CPOE, Clinical Decision Support (clinical protocols)
Stage 3	Nursing/Clinical documentation (flow sheets), CDSS (error checking), PACS available outside Radiology
Stage 2	CDR, Controlled Medical Vocabulary, CDS, may have Document Imaging; HIE capable
Stage 1	Ancillaries - Lab, Rad, Pharmacy - All installed
Stage 0	All Three Ancillaries Not installed

Readiness of personalized medicine for prime time should be carefully evaluated based on the *maturity of information systems available at the venue under consideration*³⁷.

Clinicians' access to state of the art Electronic Medical Records³⁸ (EMR) and clinical decision support systems varies greatly. Access to personalized medicine support services capable of evaluating one's omics signature with correlative analytics at high strength of evidence is a formidable challenge to be reckoned with in figuring out whether personalized medicine is ready for prime time.

The Healthcare Information and Management Systems Society (HIMSS), publishes periodic updates of healthcare provider organizations' maturity of Electronic Medical Record systems that can be useful to determine their readiness for personalized medicine.

The scope of infrastructure required for personalized medicine that this book calls for is more complex than conventional healthcare IT, and its scale is vast. It amounts to a white space, grand-challenge as we discuss throughout this book.

We call it the *Personalized Medicine Oriented infrastructure* (PMO-I). Respectively, we call the architecture that drives it the *Personalized Medicine Oriented architecture* (PMO-A).

Monumental effort is required to achieve optimization for usage models, performance, information models, databases, configuration lifecycle management, and cost.

Thinking through the kind of architecture, infrastructure, implementation, and operations that are needed for personalized medicine takes an impressive assembly of senior level professionals. For a start, such will include Solution Architects, Chief Technology Officers (CTOs), Chief Information Officers (CIOs), Chief Medical Information Officers (CMIOs), and Chief Information Security Officers (CISOs).

This highly talented group will have to *factor in cross disciplinary collaboration frameworks and respective technologies* such as the US National Cancer Institute's caBIG® (cancer Biomedical Informatics Grid®)³⁹; i2b2 (Informatics for Integrating Biology and the Bedside)⁴⁰; the Total Cancer Care Consortium at Moffit⁴¹; Scripps Translational Science Institute⁴²; The European Commission 7th Framework Programme's CORDIS (Community Research and Development Information Service)⁴³; UK National Health Services National Translational Research Partnerships⁴⁴; etc.

Also at play are *rapid uptake and confluence of social media*⁴⁵ and *mobility* driving data, information, and communication to *cross traditional boundaries between private, corporate, and research environments*; exchanging and expressing *facts, opinions, thoughts, and sentiment*. This subject requires broad and deep discussion that are beyond the scope of this book.

³⁶ For example: www.americanwell.com; <http://2nd.md/>; <http://careclix.com/>; www.justanswer.com; www.fshealth.com; www.virtualmedicalgroup.com

³⁷ HIMSS Electronic Medical Record Adoption Model (EMRAM)SM http://www.himssanalytics.org/docs/HA_EMRAM_Overview_Eng%20011812.pdf

³⁸ For sake of simplicity, we use the term inclusively as proxy to Electronic Health Records (EHR) and Personal Health Records (PHR).

³⁹ <http://cabig.cancer.gov/about/>

⁴⁰ <https://www.i2b2.org/>

⁴¹ http://www.insidemoffitt.com/content.cfm?page_id=454

⁴² <http://www.stsiweb.org/index.php>

⁴³ http://cordis.europa.eu/home_en.html

⁴⁴ http://www.nih.ac.uk/industry/Pages/translational_research_partnerships.aspx

⁴⁵ Social media "likes" healthcare From marketing to social business, PwC <http://pwchealth.com/cgi-local/hregister.cgi/reg/health-care-social-media-report.pdf>

We anticipate that the pace of change of social media and mobility will far exceed the speed of publishing and readership outreach of this book. Therefore, media other than hard copy publishing would better serve this topic and our intended audience.

Bringing all this together is predicated on *crafting a methodical multi-tier interoperability framework and roadmap* that are founded on *achieving service-level semantic interoperability*.



**Blue Button
Download
My Data**

The consumer-centric BlueButton⁴⁶ method for health and wellness information exchange in the US is worth noting: from user's experience having real time control over granting access to their health and wellness information at a push of a button⁴⁷, to the vast scale of adoption that is within reach, and the formidable public-sector marketing campaign to make that happen which is

driven by the Office of the President of the United States⁴⁸.

The latter complements the US Government's financial and political drive to accelerate adoption of Electronic Medical Record systems in a multi-year effort that became known as 'Meaningful Use'⁴⁹; establish Health Information Exchanges⁵⁰(HIEs); and set up Health Insurance Exchanges⁵¹.

*Service-oriented approach*⁵² such as contemplated, for example, by the Object Management Group's Open Health Tools⁵³ is inevitable to achieving personalized medicine oriented infrastructure capable of the following *essentials*:

- Bringing in legacy environments
- Bridging across disciplines, organization boundaries, and national borders; and -
- Providing the kind of agility to address rapidly changing technological landscape

Semantic normalization is required to assure that terms, concepts, and contexts are *fully understood and applied consistently throughout our personalized medicine domain model*.

However, providing detailed strategy and technical information about the interoperability framework is beyond the scope of this book.

To illustrate how formidable PMO-I is, consider the reiterative ripple effect that a single new discovery may have on correlating cause and effect, contemplating the potential associations between and among markers and outcomes, and exploring the mechanisms that may explain them: from structural genomics to clinical outcomes.

Now repeat that with the next discovery and the one that follows. The challenges are exponentially compounding indeed.

Therefore, *building and operating a centralized PMO-I is beyond the capability of any one organization*, public or private – be it a national government or academic institution, global corporation or a start up. Extensive collaboration across diverse professional, scientific, and technological disciplines is therefore inevitable. The resulting *cross-pollination that PMO-i fosters is a potent generator of superior high-value breakthrough innovation⁵⁴*.

5.5 Cloud-enabled personalized medicine services

A computing model providing web-based software, middleware and computing resources on demand⁵⁵ for patients and medical practitioners alike is presently the ultimate PMO-i. From ubiquitous, always-on provisioning of executable

⁴⁶ <http://www.healthit.gov/bluebutton>, <http://www.va.gov/bluebutton/> <http://bluebuttondata.org/>, <http://www.healthit.gov/patients-families/blue-button/blue-button-image>

⁴⁷ For example, hUMETRIX iBlueButton usage model video at <http://www.ibluebutton.com/consumer-video/>

⁴⁸ <http://www.whitehouse.gov/blog/2010/10/07/blue-button-provides-access-downloadable-personal-health-data>

⁴⁹ <http://www.healthit.gov/policy-researchers-implementers/meaningful-use>, http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Meaningful_Use.html, <http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html?redirect=ehrincentiveprograms/>, <http://www.cdc.gov/ehrmmeaningfuluse/>, <http://www.himss.org/meaningfuluse/?navItemNumber=13303>

⁵⁰ <http://www.healthit.gov/providers-professionals/health-information-exchange>, <http://www.ahima.org/advocacy/healthinformationexchange.aspx?tab=3>

⁵¹ <http://cciio.cms.gov/programs/exchanges/index.html>, <http://www.pwc.com/us/en/health-industries/publications/health-insurance-exchanges-and-medicare-expansion.jhtml>

⁵² <http://www.soa-manifesto.org/>

⁵³ <http://www.openhealthtools.org/>

⁵⁴ Adapted from Perfecting Cross-Pollination, Lee Fleming, Forethought Research, Harvard Business Review, September 2004

⁵⁵ Source: Dr. Joanna Ng, Center for Advanced Studies, IBM Canada Software Laboratories; Dr. Anupam Joshi, University of Maryland, Baltimore County; Recommended reading: Cloud computing insights from 110 implementation projects, IBM Academy of Technology Survey, October 2010; Big data: The next frontier for innovation, competition, and productivity, McKinsey Global Institute, June 2011 ;Big Data, Personalized Medicine to Trend in Health Care in 2012, Brian Horowitz, EuroBioForum eWeek.com, December 28, 2011

content and collaboration environment to near real time and predictive analytics, and from semantic orchestration to global localization, cloud-enabled POM-i services eliminate the need to replicate complex and prohibitively costly infrastructure components.

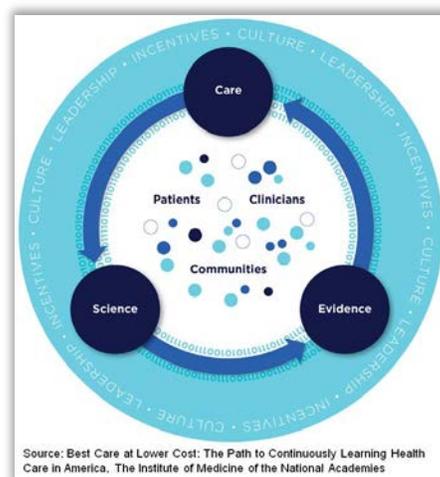
And so, cloud-enabled data services have the potential for making POM-i widely and easily accessible to the public at large, an everyday thing, for laymen and professionals alike. Commoditizing access to POM-i can drive return to adoption⁵⁶, *and business model innovation that can fuel the white space R&D.*

5.6 Personalized medicine as a learning system

Conceptualizing the practice of medicine as a learning system is an emerging approach that may help tackle this grand challenge towards making Personalized Medicine commonplace. The US Institute of Medicine (IOM) convened the *Committee on the Learning Health Care System in America* to explore these grand challenges. The committee's report *Best Care at Lower Cost* issued call-to-action that focuses on *"the rising complexity of modern health care, unsustainable cost increases, and outcomes below the system's potential."*

IOM proposes the following characteristics of a continuously learning health care system:⁵⁷

- Real-time access to best available evidence to guide and improve clinical decision-making, healthcare safety, and quality of care
- Digital capture of the care experience for real-time generation and application of knowledge
- Focus on patient needs and perspectives
- Promoting the inclusion of patients, families and other caregivers as vital members of the continuously learning care team
- Continuously aligning incentives for high-value care.
- Systematically monitoring the safety, quality, processes, prices, costs and outcomes of care
- Transparency of monitoring data to clinicians, patients and their families
- Leadership-instilled oversight of learning, teamwork, collaboration and adaptability in support of continuous learning
- Constantly refines complex care operations and processes through ongoing team training and skill building



Thought-leading stakeholders are already pursuing new strategies that leverage techniques and technologies not previously available to make that happen.⁵⁸

Seeking to *compress the average cycle time of 17 years from discovery in basic research to impact clinical care*, Deloitte offers a *four-phased perpetual model of learning health care system*. Running on data, this rolling-wheel model consists of Clinical Research, Clinical Care, Health Outcomes and Surveillance, and Basic Research.

Practice guidelines that are generated via large research studies and applied to diverse patient populations attempt to *standardize the clinical care process*. Yet new knowledge and *actionable reasoning* that follow new discoveries *do not always build up in a linear fashion*.

Dr. Nulan makes reference to Dr. Epstein's concern that notwithstanding ongoing progress with medical knowledge and

⁵⁶ Recommended reading: Competing technologies, increasing returns, and lock - in by historical events, W. Brian Arthur, The Economic Journal, 99 (March 1989), 116 – 131; Increasing returns to adoption: a multilevel approach, working paper 0804, Raúl Barroso Casado and Sabine Cacciatore, January 2008

⁵⁷ Adapted from IOM <http://www.iom.edu/Reports/2012/Best-Care-at-Lower-Cost-The-Path-to-Continuously-Learning-Health-Care-in-America/Table.aspx>

⁵⁸ Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, The Institute of Medicine of the National Academies, September 6, 2012 at <http://www.iom.edu/Reports/2012/Best-Care-at-Lower-Cost-The-Path-to-Continuously-Learning-Health-Care-in-America.aspx>

clinician's ability to apply it for patient care, "*too often the espoused remedies of one era [were proven] to be of limited value or frankly harmful in the next.*"⁵⁹

Data driven medicine is exemplified by Dr. Eugene Stead's effort to change medical practice of patients with heart diseases from relying on *anecdotal observations* to *evidence-based medicine*⁶⁰; and the practice-based National Cardiovascular Data Registry which supports the *outcomes-based quality improvement* program of the American College of Cardiology.⁶¹

Enabling technologies for medicine as a learning system offer evolving as well as *disruptive* capabilities. While a comprehensive account of these technologies is beyond the scope of this book, select topics are further discussed in the technology chapter. Examples of these technologies include *electronic medical record, electronic health record, hospital information system, computerized physician order entry, personal health record, health information exchange, gene sequencing, gene browser, ontology, semantic web, health 2.0, social media, machine learning, analytics, big data, cloud-based computing, parallel computing, high performance computing, human factor engineering, data visualization, image analysis, signal processing, data storage, search engines, natural language processing, learning systems, disease modeling, predictive analytics, security*, etc.

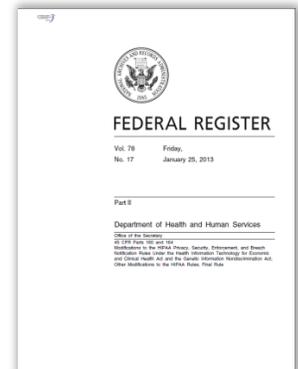
'The Future of Health Technology Over a 30 Year Span' offers a 360-style infographic that further illuminates the topic.⁶²

And so, an *open-source semantic network of personalized medicine content established in partnership between the public and private sector could help close the informatics gap in the field.*

5.7 Security and confidentiality references

Adoption of information technology in healthcare still lags behind other industries. Yet the *confluence of exponentially growing mobile technologies, consumerism of health and wellness, consumerism of IT, and outsourcing of technology enabled services* and infrastructure beyond national borders up-scales and complicates threats to the privacy and integrity of personal and health information.

Security and confidentiality of health information in general and recent *increase of regulatory burden on Protected Health Information (PHI)*⁶³ in particular require the kind of comprehensive discussion that is beyond the scope of this book. Instead, in addition to indicating the tremendous importance of this subject we offer a couple of recommended readings.



In an intriguing contrast, PricewaterhouseCoopers reports that *47% of surveyed individuals indicated that they are not concerned about sharing their Personal health information in public*; and over 50% are not concerned about having their health insurance coverage being impacted by that.⁶⁴

The International Standards Organization (ISO) identifies threats and specifies best practice guidelines for controlling and managing health information security.

*"By implementing this International Standard, healthcare organizations and other custodians of health information will be able to ensure a minimum requisite level of security that is appropriate to their organization's circumstances and that will maintain the confidentiality, integrity and availability of personal health information."*⁶⁵



⁵⁹ Dr. Sherwin B. Nuland, 'The Uncertain Art' Published: June 6, 2008 in the New York Times at http://www.nytimes.com/2008/06/06/books/chapter-uncertain-art.html?_r=2&

⁶⁰ "Eugene Stead, medical pioneer, dies" Duke Today, <http://today.duke.edu/2005/06/stead.html>

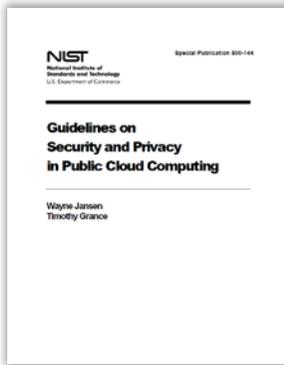
⁶¹ ACC-NCDR® at <http://www.ncdr.com/WebNCDR/COMMON/DEFAULT.ASPX>

⁶² The Future of Health Technology Over a 30 Year Span at <http://www.hitconsultant.net/2012/09/19/future-of-health-technology-infographic/>

⁶³ U.S. Department of Health & Human Services Health Information Privacy <http://www.hhs.gov/ocr/privacy/hipaa/understanding/index.html>, <http://www.gpo.gov/fdsys/pkg/FR-2013-01-25/pdf/2013-01073.pdf>

⁶⁴ Social media "likes" healthcare From marketing to social business <http://pwchealth.com/cgi-local/hregister.cgi/reg/health-care-social-media-report.pdf>

⁶⁵ Source: Health informatics -- Information security management in health using ISO/IEC 27002, ISO 27799:2008. Recommended reading: Health informatics -- Personal health records -- Definition, scope and context, ISO/TR 14292:2012; Health informatics -- Identification of subjects of health care, ISO/TR 22220:2011; Health Informatics - Classification of purposes for processing personal health information, ISO/TR 14265:2011; Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR, ISO/HL7 27953-2:2011.



The NIST provides guidelines on [security and privacy in public cloud computing](#)⁶⁶. Germany Federal Office for Information Security issued minimum information security requirements for cloud computing providers⁶⁷.

For a [comprehensive overview of recent and future trends in related challenges, frameworks, strategies, and solutions](#) please refer to "[The Road to Cloud Security](#)" by IBM⁶⁸.

[Emerging virtualized service models are driving innovation in policy-based cloud services](#)⁶⁹ designed to assure compliance with security and confidentiality of identifiable personal information.

Yesha et. al. at the University of Maryland Baltimore County (UMBC) propose [policy-based, integrated framework for automating discovery, negotiation, acquisition, and consumption of services from the cloud](#)⁷⁰.

This Smart Cloud Services tool applies service models that NIST defines: software-as-service (SaaS) platform-as-service (PaaS), and infrastructure service (IaaS); NIST's deployment models: private, public, community, and hybrid; and consumer types. Semantic Web technologies (SPARQL, RDF, OWL) represent and reason about services and service requirements.

[The UMBC team distinguishes between must-have hard requirements \(e.g. HIPAA\), and soft requirements that seek to optimize value, i.e. balance measurable service objectives with threats, risk mitigation, scope, control, usage model, usability, adoption, cost, etc.](#)

⁶⁶ Recommended reading:; Guidelines on Security and Privacy in Public Cloud Computing, Wayne Jansen and Timothy Grance, NIST Special Publication 800-144, December 2011

⁶⁷ Recommended reading: Security Recommendations for Cloud Computing Providers, Federal Office for Information Security, Germany

⁶⁸ Recommended reading: IBM Cloud Computing Technical Symposium, 28-30 November 2011, Darmstadt, Germany

⁶⁹ Source: Dr. Anupam Joshi, University of Maryland, Baltimore County; Recommended reading: A Policy-based approach to Smart Cloud Services, Karuna Pande Joshi, Tim Finin, Yelena Yesha, Anupam Joshi, Navid Golpayegani , and Nabil Adam, UMBC ebiquity: A Semantic Approach to Automate Service Management in the Cloud, Karuna Joshi, Tim Finin, Yelena Yesha, Technical Report TR-CS-11-02, University of Maryland Baltimore County, 1 June 2011

6 Analytics

6.1 Key take-aways and call to action

Key Take-aways	Call to Action
<ol style="list-style-type: none"> 1. Retrospective, concurrent, and predictive analytics are essential to any pursuit of translational research, disease modeling, and practicing anywhere along the disease life cycle 2. Too much information has its consequences, as does information that went undetected and presumed 'silent' by conventional methods 3. Going beyond "no signal", or even "weak signal" results of conventional data mining will have tremendous impact on health and wellness of millions of individuals and help secure multi-billion dollar investments 4. Emerging next-generation predictive analytics address conventional analytics with hypothesis-agnostic bottom-up search and machine learning techniques 5. We encourage questioning fundamental assumptions, doubting common wisdom, and deliberating on philosophical and conceptual themes in search for the kind of breakthrough innovation that is needed to accelerate adoption of personalized medicine 6. We describe a framework and roadmap to elicit and prioritize portfolios of predictive analytics projects that matter to them. 7. Payors are leading the market with implementing the essence of health care as a learning system founded on predictive analytics 8. Technology executives in the Payor segment are facing new and formidable challenges executing Payor analytics 	<ol style="list-style-type: none"> 1. Fund white space R&D of noise-cancelling informatics 2. Fund white space R&D of next generation database infrastructure expressing entities in life sciences and disease models as discrete service-level mashable micro applications the equivalent of Internet-of-Things 3. Fund white space R&D to accelerate the dissemination of next generation hypothesis agnostic analytics 4. Fund programs to address barriers to adoption of Big Data in personalized medicine
Focus areas	<i>technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation</i>

6.2 Level set

Analytics are at the core of the personalized medicine domain model. *Retrospective, concurrent, and predictive analytics are essential to any pursuit of translational research, disease modeling⁷¹, and practicing anywhere along the disease life cycle.* Pursued continuously it is the foundation of healthcare as a learning system.

Yet too much information has its consequences, as does information that went undetected and presumed 'silent' by conventional methods. And analytics is an ongoing pursuit.

⁷¹ The "Virtual Patient" system: modeling cancer using deep sequencing technologies for personalized cancer treatment, Kuhn, Lehrach 2012 <http://link.springer.com/article/10.1007%2Fs00003-011-0755-7#>

So we chose to focus on informatics that we need to cancel noise, explore the signals in silent information, examine the full life cycle of prediction, and discuss certain key aspects of Big Data. We rely on the discussion in previous chapters as foundation for these topics.

The chapter on precision medicine provides complementary theoretical insights on analytics. The chapter on national scale adoption of personalized medicine describes case studies and key learning on analytics in patient care and public health. The *disease modeling* chapter *takes analytics deep into basic science* and the construction of one's virtual organs. Finally, the chapter on policy driven cloud based services proposes pragmatic technology approaches to meet legal, regulatory, and policy requirements to enable analytics for personalized medicine.

6.3 Noise cancelling informatics: new IT category for personalized medicine

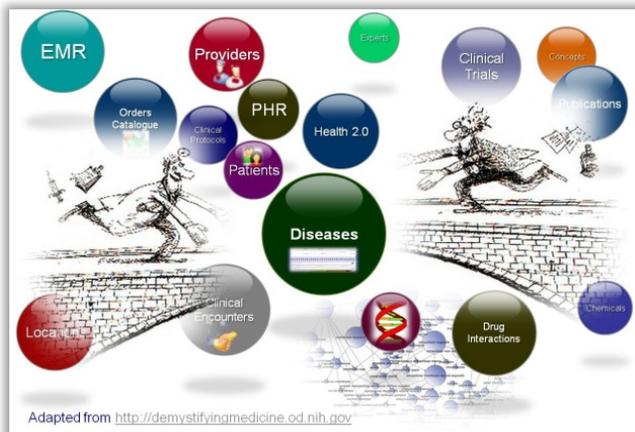
Extracting actionable insights for these medical roadmaps, whether instantaneously, in near-real time, or at any other time *is not trivial*.

Consider these public statements⁷² made by thought leaders in the field:

- "As patients and their doctors try to make critical decisions about serious illnesses, they *may be getting worthless information that is based on bad science*."⁷³
- "Genomics and Omics are really great yet *we don't even know what disease is*"⁷⁴
- "*geneticists are almost back to square one in knowing where to look for the roots of common disease*"⁷⁵
- "We have... learned nothing from the genome other than probabilities. *How does a 1 or 3 percent increased risk for something translate into the clinic? It is useless information*"⁷⁶
- "We have an abundance of scientific advances, but *we are using old tools*."⁷⁷
- "We are losing the war with complexity. *We need new navigation ways of seeing critical nodes in dynamic networks*."⁷⁸

Let's examine our personalized medicine domain model, and have outcome, causality, and strength of evidence ready to join the conversation.

Now let's try figuring out *what data, what information, and what knowledge really matter in making a personalized medicine decision – be it aimed at reactive, preventive, or predictive action*.



As we ponder that goal, let's assume the person we're doing it for has a couple of medical conditions at play in addition to her lung cancer. We know that "*comorbidity plays a significant factor in risk, survival, disease progression, and treatment of patients with cancer*..."⁷⁹ Because her medical insurance company knows that too, they placed certain restrictions on paying for diagnosis and treatment we might otherwise recommend.

The *volume and complexity of knowledge we need to evaluate for that purpose has grown exponentially beyond human capacity*⁸⁰. The healthcare system captures, analyzes, and executes on information of over 13,600 illnesses, 4,000 medical and surgical procedures, 6,000 drugs, and 1.5 million medical terms⁸¹.

⁷² Source of statements from the NY Times and Der Spiegel is Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionj.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf> citing Nicholas Wade The New York Times July 7, 2011

⁷³ How Bright Promise in Cancer Testing Fell Apart, The New York Times http://www.nytimes.com/2011/07/08/health/research/08genes.html?_r=0

⁷⁴ James Heywood, PatientsLikeMe at Personalized Medicine World Conference 2012 <http://www.pmwc2012.com/index.php>

⁷⁵ Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionj.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf> citing Nicholas Wade The New York Times July 7, 2011

⁷⁶ <http://www.spiegel.de/international/world/spiegel-interview-with-craig-venter-we-have-learned-nothing-from-the-genome-a-709174.html>

⁷⁷ Francis Collins, MD, NIH Director www.nih.gov/news/health/dec2011/od-23.htm

⁷⁸ Dr. Hellerstein of KineMed, at Personalized Medicine World Conference 2012

⁷⁹ Dr. Extermann, <http://www.moffitt.org/CCJRoot/v14n1/pdf/13.pdf>

⁸⁰ The Velluvial Matrix, Dr Gawande, The New Yorker <http://www.newyorker.com/online/blogs/newsdesk/2010/06/gawande-stanford-speech.html>

⁸¹ <http://public.dhe.ibm.com/common/ssi/ecm/en/ytw03166usen/YTW03166USEN.PDF>

Yet knowledge about illness and wellness keeps changing. And so, *from time to time we discover that treatments we counted on in the past are not as effective as we thought they would be, or worse: they may be harmful and have to be avoided*⁸².

Back to our task at hand: *what data, information, and knowledge are relevant?* Let's call it 'Signal'. All *the rest is distracting, or worse: it may be misleading*. Let's call it 'Noise'. That noise is growing at rapid pace too. So that leaves us with the next *call to action: use informatics to cancel noise*.

A new category of information technology, we call it *noise-canceling informatics*⁸³; founded on next generation database *infrastructure expressing entities in life sciences and disease models as discrete service-level mashable micro applications the equivalent of Internet-of-Things*.

6.4 The sound of silence in life-sciences informatics

The *capability to discover actionable information in what conventional analytics may conclude as "no-information", or something like "silent markers"* is not less important than noise canceling informatics. This is actually the far-end complement of techniques and methods aimed at separating signal from noise.

Being able to *go beyond "no signal", or even "weak signal" results of conventional data mining will have tremendous impact on health and wellness of millions of individuals; and help secure multi-billion dollar investments: from as early as identifying promising candidates for drug development to successfully expediting costly clinical trials, removing risk from unanticipated side effects of drugs already on the market, developing and optimizing clinical care protocols, and achieving desired outcomes*.

*Top-down analytics for clinical trials that are optimized for predicting medical responses or side effects may not properly detect and qualify sub-groups of optimal responders or non responders*⁸⁴. It may happen simply because they appear silent to that top-down hypothesis setting strategy. Removing incomplete records or replacing missing values in the data set may perpetuate that deficiency.

*Several kinds of emerging next-generation predictive analytics address this problem with hypothesis-agnostic bottom-up search and machine learning techniques that complement legacy statistical methods*⁸⁵. Outcomes to-date suggest a wide range of potential applications from translational research to the practice of personalized medicine.

At times, the impetus for reaching such far-end methods begins with *questioning fundamental assumptions, doubting common wisdom, and deliberating on philosophical and conceptual themes*.

The technology-enabled Personalized Medicine encounter requires the discovery and evaluation of actionable relationships and associations that may have not been previously identified. In this we mean detecting new markers as well as previously undetected silent markers, and the mechanisms that explain their action and outcome associations.

6.5 Predictive analytics: the round-trip

The field of predictive analytics draws growing attention from virtually all stakeholders. It is *fueled by the premise of exerting control not previously possible over process and resources to achieve desired outcomes*; enormous *financial incentives* to payers as well as developers of predictive analytics technologies and services; *political opportunities* for leaders; and *fascination about the science and technology* that make it possible.

Why Provider-segment Predictive Analytics projects for Personalized Medicine might fail

- Lack of clinical, scientific, and executive leadership
- Growing privacy restrictions on data access
- Lack of mechanism to understand what is achievable
- Moving targets over long range challenges
- Missing tools to address the evolving nature of human biology and the environment
- Each patient is the equivalent of a loosely or un-managed clinical trial of 1
- Cost of collecting and processing data
- Non use by practitioners
- Poor interaction between clinicians and IT
- Variability
- Data quality issues
- Making predictions based on false studies
- Improper use of prediction
- Complex system level interactions not fully understood
- Other unknown factors

⁸² The Uncertain Art, Dr. Nuland, New York Times http://www.nytimes.com/2008/06/06/books/chapter-uncertain-art.html?_r=2&

⁸³ Noise-Canceling Informatics: A New Framework for Personalized Medicine, Ribitzky, Value-Based Cancer Care, <http://www.valuebasedcancer.com/blog/noise-canceling-informatics-new-framework-personalized-medicine>

⁸⁴ Quinten's Savoir Faire Approach to Data Mining, Bio-IT World <http://www.bio-itworld.com/news/08/03/12/Quinten-savoir-faire-approach-data-mining.html>

⁸⁵ Quinten Q-Finder® <http://www.quinten-healthcare.com/en/our-technology/>

According to the Gartner Group, Predictive Analytics technology in general has reached the Plateau of Productivity, the ultimate phase in the technology hype cycle marked by high growth adoption.⁸⁶

Predictive analytics for personalized medicine encompass a full round-trip from lessons extracted by performing retrospective analysis of entities, relationships, and patterns either as static snap-shots, longitudinally, or both; to analysis of such entities, relationships, and patterns as they occur in real time; modeling and simulation; and evaluating predictive models going forward.

Furthermore, *new biomarkers* which can identify sub-populations of patients that may either have a positive response or adverse reaction *can turn failed clinical trials to successful breakthroughs*⁸⁷.

That means that *we ought to rethink, redesign, and execute predictive analytics re-runs*.

Objectively evaluating the strength of evidence about every material conclusion that is reached throughout the predictive analytic process is a make or break factor impacting the dependability and consequences of acting on it.

One's ability to reliably predict outcomes – clinical, economic, and otherwise, of interventions on wellness and illness conditions within measurable certainty is what makes personalized medicine revolutionary. It is a fundamental conceptual change of clinical practice.

Identifying and evaluating the myriad opportunities to exploit predictive analytics for personalized medicine is beyond the scope of this book. In lieu of it, the chapter “cracking the economic code” in *this book provides a framework and roadmap for individuals, teams, and organizations seeking to elicit and prioritize portfolios of predictive analytics projects that matter to them*.

Nevertheless, we offer insights on challenges likely to face any predictive analytics project for personalized medicine, as well as strategies to overcome them.

Strategies to overcome Provider-segment barriers to Predictive Analytics for Personalized Medicine

- Clinical, scientific, and business thought leadership
- Executive sponsorship
- Clarity of purpose and value
- Shared responsibility and rewards
- Setting realistic stakeholders expectations
- Program and project funding
- Provide clinicians with usable information systems
- Get clinicians to generate good data by demonstrating value
- Improve bio medical informatics techniques
- Investment in basic science
- General population education

6.6 Payor analytics: where have all the flowers gone?

The payer market in the US provides compelling insights to the *extraordinary course-changing impact of predictive analytics for personalized medicine*: from rethinking the business model to strategy, operations, technology, and ecosystem drive.

It appears that *payors are leading the market with implementing the essence of health care as a learning system*: “Health plans will need to expand analytics to incorporate clinical biomarker data to refine patient risk segmentation.”⁸⁸

Shifting focus from after-the-fact claims and fighting fraud to partners-in-care comes with new analytics paradigms driven by predictive analytics, personalized medicine, and translational research:

- Real-time right-action decision support models at the point-of-care
- Full round-trip benchmarking of predictive analytics against retrospective analysis, outcome measures, and best practices
- Vertical integration with disease models and translational research

Consequently, payor segment *technology executives are facing new and formidable challenges*:

- *Real-time bi-directional service-level interoperability with provider information systems* to enable rapid full-round-trip sense-and-respond analytic, action, and outcome measure cycles
- *Capability to execute on new data sets of finer granularity* such as results, orders, plan of care and clinical documentation

⁸⁶ Emerging Technologies Hype Cycle: what's hot for 2013, Gartner Group

⁸⁷ Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionj.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf> citing Margaret Hamburg FDA Commissioner AAAS – The Future of Personalized Medicine October 26, 2009

⁸⁸ The ROI for Targeted Therapies: A Strategic Perspective, Deloitte Center for Health Solutions 2009

- *Generate intrusive yet elegant, usable, and trusted guidance* to the clinical care team at the point of care
- Making it happen *during an era of massive overhaul of provider segment information systems*⁸⁹
- Assuring *compliance with legal and regulatory requirements* to protect health information⁹⁰

A couple of examples illustrate this trend.

Preparing to benefit from this sea-change in payor analytics, *Deloitte acquired Recombinant's data warehouse*.⁹¹ Capabilities include *genomic and biological data analytics to support personalized and evidence-based medicine*; development of new care delivery models; and value-based payment and clinical quality measures.

Combining analytics, integration, and 'Embedded Nurses' to drive clinical transformation in real time at the point-of-care, *CIGNA has set out to grow its Collaborative Care Network* ⁹²(CAC) 2.5X to 100 networks serving 1M customers by 2014. "*We have a wealth of patient-specific data we share with physicians daily to trigger action at the practice...Integrating hospitals' data networks with the physicians' and Cigna's is the next horizon... we're not adversaries, this is a common problem. We're changing our stripes.*"

6.7 Big Data

Attempting to reach a consensus-based *definition of Big Data has proven to be non trivial*. Similarly to personalized medicine, different people perceive Big Data differently. Some define it by purpose, other by process, size, or technical attributes.

And so we concluded that *for the purpose of personalized medicine, there is no particular need to define Big Data in a singular, rigid manner*.

Workshop participants offered examples of Big Data definitions useful to them, such as *vast quantities* of data that challenge storage, infrastructure, and analytical capabilities; very large amounts of *mixed structured, semi-structured, and unstructured data* that is *optimized for various purposes*; large amounts of information *to be absorbed and analyzed to yield actionable outcome*; large amounts of data that *can only be analyzed by supercomputers*; data of *50 or more genes*.

Examples for Big Data usage in personalized medicine include:

- Predictive, concurrent (real-time and near-real-time), and retrospective analytics for encounter-based clinical decisions, patterns, correlations, causality, prevalence, co-morbidity, outcomes, interventions, benchmarks, modeling, simulations, self-service by patients and the public at large, etc
- Analyze bio-sequences: DNA, Proteins, epigenomes
- Data describing people, their omics expressions, and behaviors such as feeding habits
- Data that can be automatically collected by sensors over time

IBM offers a pragmatic '4Vs' approach to the dimensions of Big Data: ⁹³

- *Volume*, commonly measured by terabytes or more;
- *Variety*, whereby multiple types of structured data, semi-structured data, unstructured data, image, voice, location, etc. coexist;
- *Velocity*, to indicate challenges of dealing with data that moves rapidly; and -
- *Veracity*, recognizing that in the real world data is imperfect.

⁸⁹ HHS announces next steps to promote use of electronic health records and health information exchange <http://www.hhs.gov/news/press/2012pres/08/20120823b.html>

⁹⁰ What Health Information Is Protected by the Privacy Rule? http://privacyruleandresearch.nih.gov/pr_07.asp

⁹¹ Deloitte Buys Data Warehouse with Focus on Payment Models <http://www.healthdatamanagement.com/news/acquisition-data-warehouse-analytics-recombinant-deloitte-45180-1.html?zkPrintable=true>

⁹² Cigna expands collaborative care network <http://healthcareinnovationhq.com/article/Cigna-Expands-Collaborative-Care-Network>; From Volume to Value: Cigna's collaborative accountable care programs <http://www.fiercehealthpayer.com/node/12763/print>

⁹³ Analytics: The real-world use of big data, IBM Institute for Business Value, 2012

Our consensus on Big Data is in line with key learnings from global survey released by IBM and Oxford University's on October 2012.⁹⁴

According to this IBM/Oxford survey, *Big Data means many things to many people, and is no longer just about technology.*

While the term is pervasive, Big Data has been used to express a variety of concepts, including: huge quantities of data, social media analytics, next generation data management capabilities, real-time data, etc.

A widely recognized business imperative, Big Data provides opportunities to address long standing business challenges as well as inspire new ways to transform processes, organizations, entire industries, and society at large. Most organizations use Big Data for customer-centric purposes and establishing higher-value information ecosystems.

According to the Gartner Group, Big Data in general is nearing the peak of inflated expectations; projecting high growth adoption phase as early as 2015.⁹⁵

Additional real-world perspectives on Big Data for personalized medicine are discussed in the chapter on policy driven, cloud based services for personalized medicine, and adoption of personalized medicine by a non-profit HMO in a national social-medicine market.

Barriers to exploiting Big Data for Personalized Medicine

- Modeling and measuring the business value
- "I don't know what I don't know so why do I need this?"
- "I believe I know everything there is for me to know, so why are we doing this?"
- High cost of acquisition, entry, deployment, and operations
- Funding
- Limited access to advanced software
- Concern about maturity of computer science to yield sought outcomes
- Lack of cross-disciplinary collaboration among clinicians, life-sciences researchers, biomedical informatics experts, and computer scientists
- Different terminologies, ontologies, and semantics
- Interoperability, primarily with Electronic Medical Records (EMR) and scientific databases
- Temporal changes
- Privacy, legal, and regulatory concerns
- Ecosystem fragmentation

⁹⁴ Analytics: The real-world use of big data, IBM Institute for Business Value, 2012

⁹⁵ Emerging Technologies Hype Cycle: what's hot for 2013, Gartner Group

7 Cracking the economic code: Value Model for Personalized Medicine

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7.1 Key take-aways and call to action

Key Take-aways

1. We describe value modeling framework to facilitate making tough choices among promising personalized medicine projects in light of limited resources
2. Value zones throughout the disease lifecycle model inform choices concerning personalized medicine and translational research projects

Call to Action

1. Fund white space R&D to periodically define the Top-10 worth pursuing personalized medicine Value Zones
2. Fund white space research and adoption of value modeling and measurement of personalized medicine and translational research projects
3. Mandate value modeling and measurement in public-funded personalized medicine and translational research projects

Focus areas

technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation

7.2 Level set: The changing landscape of stakeholders value



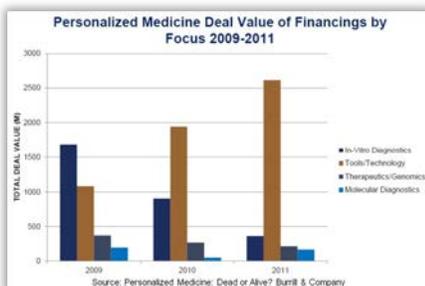
Ron Ribitzky, M.D. @RonRibitzkyMD
Call to action: manage your #Health as a resource and #value -- #Personal Health Net Worth -- #Snyderman of #Duke at closing #PMWC day 1

With an 11% projected growth of personalized medicine market year on year to over \$450 billion in 2015⁹⁶ arguably, patients suffering from or have tendency to develop devastating medical conditions are the primary winners.

Yet the cost of personalized medicine may be beyond reach for individuals.

On the other hand, costly personalized medicine practices can create value for managed care organizations venturing beyond short term calculations of return on investment, premiums, and unit cost. We provide a detailed case study on this subject in the chapter entitled National-scale Adoption of Personalized Medicine in Socialized-Medicine Market.

Pharmaceutical manufacturers face challenges with product performance as worldwide spending on ineffective drugs in 2010 may have exceeded \$350 billion and governments are exerting legal and other pressures on pricing⁹⁷.

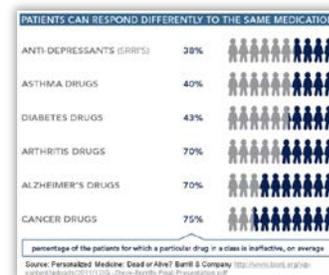


Developments in translational research continue to change value considerations for the different stakeholders.

A data, information, and analytics intensive field, *translational research and personalized medicine are a blessing to the information technology industry.*

This changing landscape requires comprehensive exploration of *how value is created* through the multiple stages of translational research, decade-long drug development cycles, evolving outcomes research, and formidable challenges of healthcare financing, to name a few.

A perceived game changer, for personalized medicine to be sustainable, *new business and economic models are yet to be discovered and tested.*



⁹⁶ \$232 Billion Personalized Medicine Market to Grow 11 Percent Annually, says PricewaterhouseCoopers <http://www.prnewswire.com/news-releases/232-billion-personalized-medicine-market-to-grow-11-percent-annually-says-pricewaterhousecoopers-78751072.html>

⁹⁷ Personalized Medicine: Dead or Alive? Burrill & Company <http://www.bionix.org/wp-content/uploads/2011/12/G.-Steve-Burrills-Final-Presentation.pdf>

7.3 Value modeling fundamentals

The value dimension of our framework seeks to *map out the key considerations for high-stakes resource-constrained actions in the science and practice of personalized medicine*. They serve to construct value models which guide data collection and analysis of whether certain actions are worth pursuing (a.k.a. return on investment; ROI).

Value can and should be measured at each major aspect of the disease lifecycle and translational research leading to actionable personalized medicine decisions.

Therefore, let's agree to use the term *Value Zone* to indicate *where in that process value may be created* and when should it be measured.

Yet *value may differ from one stakeholder to another*. For example, a high value action to a patient may cause economic loss to their insurer who stands to pay for it. So let's add *Stakeholder* consideration to our framework.

Value Drivers express *key reasons for actions*. Examples are quality of life, economics, disease burden, etc. (a.k.a. industry concerns).

Key Performance Indicators (KPIs) *define goals that matter in the context of the value drivers*. For example

- KPI for adoption of personalized medicine
 - Length of the translational cycle
 - Number of personalized medicine interventions adopted as standard of care practice
 - Number of new drugs/targets identified and brought to practice based on discoveries in personalized medicine
 - Number of FDA labels with pharmacogenomic information
 - Number of Personalized Medicine diagnostic interventions reimbursed by insurance
 - Number of Personalized Medicine treatments reimbursed by insurance
- KPI for quality of life is cure of breast cancer
- KPI for economics is reduction of cost to provide care to breast cancer patients
- KPI for disease burden is reduction of prevalence of chronic disease

Value Measures are *quantifiable properties of the KPIs*. They define what data one may need to collect and analyze for this purpose. For example:

- 50% of Family Physicians will use personalized medicine decision support for 50% of their patients in 5 years
- 100% of cancer therapies are based on 'omics analyses in 3 years
- 20% of patients with breast cancer are cured in 2 years
- 30% reduction of cost of care of breast cancer patients in 5 years
- Reduction of prevalence of chronic disease from 60% to 40% within 3 years
- Translational cycle under 2 years in 5 years
- 10% of FDA labels include pharmacogenomic information in 2 years
- Diagnostic test for personalized medicine is >90% reliable
- Anonymous comprehensive clinical data of 100 million people is available for authorized physicians over a secured web tool in 5 years; 10X growth of the number of patients in the following 5 years

The graphic illustrates the thematic relationships between a value driver, one or more key performance indicators, and one or more value measures for each KPI.

Value Zone: <i>Location on the personalized medicine domain model</i>		
Stakeholder: <i>The stakeholder you are evaluating this opportunity for</i>		
Value Driver	Key Performance Indicator (KPI)	Value Measure (VM)
<i>Key reason for action (a.k.a. industry concern)</i>	<i>Goal that matters in the context of the value driver</i>	<i>Quantifiable properties of the KPI</i>

7.4 Evidence-based strategic valuation model for personalized medicine

Determining the value of translational research and personalized medicine is a non-trivial undertaking. Yet the capability to measure near term and long term value is a compelling driver for the kind of breakthrough innovation that is required to accelerate the application of scientific discovery for clinical purposes and widespread adoption of personalized medicine.

Value models serve the foundation for exploring and developing innovative business models aimed at achieving strategic and sustainable high impact outcomes.

Combining value models with strength of evidence (as discussed in the first chapter) could inform our strategic choices and guide our actions. Specifically, the *quantifiable proof of a value measure* (Strength of Evidence; SOE) *could suggest what the actual impact of the action under consideration may have outside the controlled environment of the lab or clinical trial.*

Thinking in terms of project financing and venture capital considerations, *one may express projected (pro-forma) future impact of personalized medicine action as a discount of the value measure that was achieved under controlled conditions.*

To determine what that discount factor ought to be, let's agree to express Strength of Evidence as a number between 1% and 100% confidence. And so, the *Valuation Factor* (VF) will be equal to the Value Measure (VM) multiplied by the Strength of Evidence (SOE), or:

$$VF = VM \times SOE$$

Now we would have a common denominator to compare the potential value of acting on two or more opportunities in personalized medicine. The basic evidence-based valuation model would look like this:

Value Zone: <i>Location on the personalized medicine domain model</i>				
Stakeholder: <i>The stakeholder you are evaluating this opportunity for</i>				
Value Driver	Key Performance Indicator (KPI)	Value Measure (VM)	Strength of Evidence (SOE)	Valuation Factor (VF)
<i>Key reason for action (a.k.a. industry concern)</i>	<i>Goal that matters in the context of the value driver</i>	<i>Quantifiable properties of the KPI</i>	<i>Quantifiable proof of the value measure</i>	<i>VM x SOE</i>

However, basics are not good enough for this complicated, high-stakes field. *Our primary motivation is accelerating the transformation of scientific discovery in translational research to high-impact actionable personalized medicine decisions.* Therefore, to further inform these choices *we would target value zones in the disease lifecycle,* and *factor the strategic value of reactive, preventive, and predictive actions* that matter in personalized medicine.

The first step would be to use the strategic impact of the action under consideration as a multiplier. We call it *Strategic Rating*. And so, let's assign a *reactive* action the multiplier value of 1; *preventive* would be 2; and *predictive* would be 3.

Because we may end up with multiple options but have limited resources to pursue all of them, ranking would be helpful. So let's add *Ranking Factor* (RF) to our toolset that would be the product of *multiplying the Valuation Factor (VF) by the Strategic Rating (SR) value,* or:

$$RF = VF \times SR$$

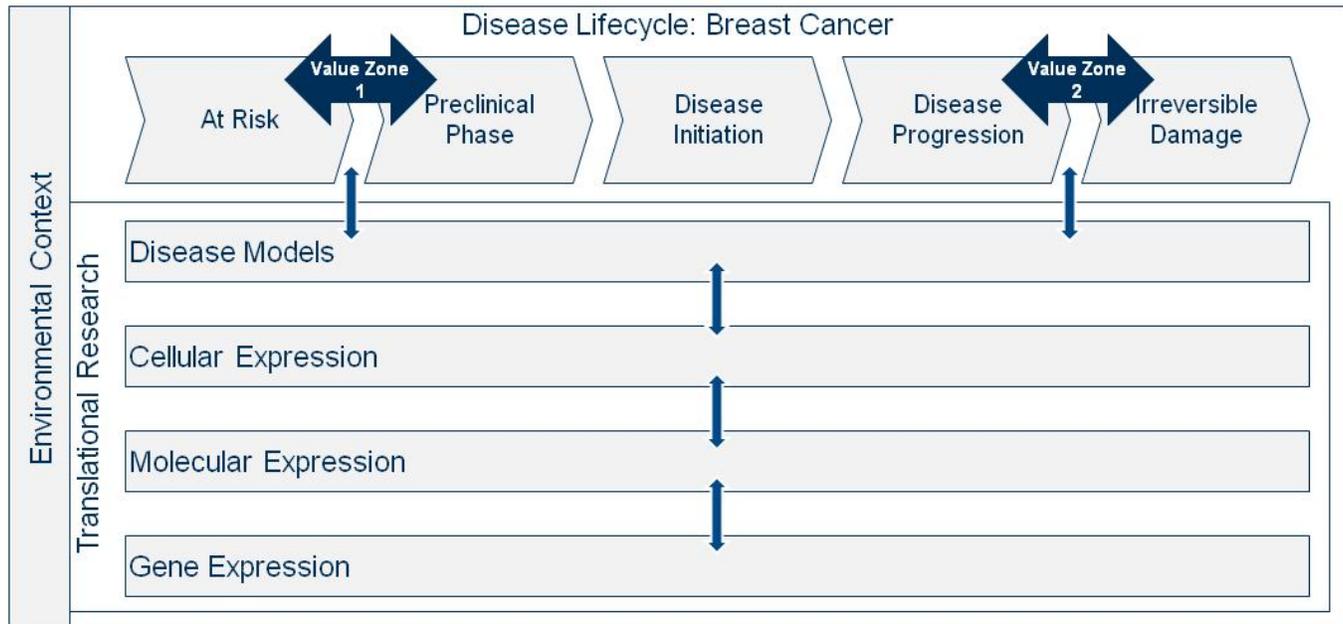
Now we would have a *stronger and more objective common denominator to compare the potential value of acting on multiple opportunities in personalized medicine.* The strategic evidence-based valuation model would look like this:

Value Zone: <i>Location on the personalized medicine domain model</i>						
Stakeholder: <i>The stakeholder you are evaluating this opportunity for</i>						
Value Driver	Key Performance Indicator (KPI)	Value Measure (VM)	Strength of Evidence (SOE)	Valuation Factor (VF)	Strategic Rating (SR)	Ranking Factor (RF)
<i>Key reason for action (a.k.a. industry concern)</i>	<i>Goal that matters in the context of the value driver</i>	<i>Quantifiable properties of the KPI</i>	<i>Quantifiable proof of the value measure</i>	<i>VM x SOE</i>	<i>Reactive = 1 Preventive = 2 Predictive = 3</i>	<i>VF x SR</i>

7.5 Case in point: Exploring Value Zones for Breast Cancer

To test it, let's assume we are asked to evaluate two highly promising personalized medicine projects that could help fight cancer. One project can predict the efficacy of a new drug that would prevent women at risk from developing the disease. The other can predict the efficacy of a new drug that would cure some patients suffering from stage 2 of the disease.

Using our framework we could illustrate our choices by identifying the competing value zones:



Because we can fund just one project, we will use the evidence-based strategic valuation model. And so, the valuation of Value Zone 1 would look like this:

Value Zone 1: Transition from At-Risk to Preclinical Phase						
Stakeholder: Patient						
Value Driver	Key Performance Indicator (KPI)	Value Measure (VM)	Strength of Evidence (SOE)	Valuation Factor (VF)	Strategic Rating (SR)	Ranking Factor (RF)
Fight cancer	Prevent breast cancer	Reduce the occurrence of breast cancer in women with positive gene signature by 50%	50%	25	3	75

The valuation of Value Zone 2 would look like this:

Value Zone 2: Progression to Irreversible Damage						
Stakeholder: Patient						
Value Driver	Key Performance Indicator (KPI)	Value Measure (VM)	Strength of Evidence (SOE)	Valuation Factor (VF)	Strategic Rating (SR)	Ranking Factor (RF)
Fight cancer	Cure breast cancer	Cure 50 % of stage 2 breast cancer patients	80%	40	1	40

Because Value Zone 1 ranks higher than Value Zone 2, the first option should be funded. We recognize that other considerations may change such choices; yet examining them is currently beyond our scope.

8 Precision Medicine: Has Its Time Come?

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8.1 Key take-aways and call to action

Key takeaways

1. Precision Medicine a useful framework to guiding discovery of Translational Research white space
2. We do not know what to do with approximately 97% of the information we discover
3. Unrealistic expectations and too long discovery-to-validation-and-application cycles are formidable barriers to practicing Personalized Medicine
4. The growing number of clinical trials nears overwhelming the number of available patients for study and other resources
5. Personalized Medicine may be negatively impacted by large scale randomized controlled studies
6. To advance Personalized Medicine we need to break down the walls of competition and build bridges of collaboration
7. How are we going to pay for Personalized Medicine - not paying just for direct patient care, but paying for everything that eventually leads to better care for our patients

Call to Action

1. Fund white space R&D to extract clinical meaning from exponentially growing discovery in Translational research
2. Fund white space R&D to compress the discovery-to-validation-and-application cycles in Personalized Medicine, e.g., investigate the strength of evidence that the predicted benefit of prescribing drugs based on pharmacogenetic information is achieved as measured by improved therapeutic effect, improved safety, and decreased cost for patients and their third party payers
3. Fund white space R&D for collaborative Personalized Medicine technologies
4. Fund white space R&D for techniques and tools to optimize planning for high impact, resource-constrained translational research
5. Develop value model for the full lifecycle of Personalized Medicine to inform and carry-out R&D agenda
6. Fund campaigns to influence adoption of evidence-based prescribing habits

Focus areas

medical, Precision Medicine, clinical trials, economic, value model, ethics, cultural change, validation, technological, commercialization, adoption, innovation

8.2 Level set

Some physicians object to the term Personalized Medicine because they have always delivered medicine in a personalized manner. Therefore, *the terms Precision Medicine and Personalized Medicine are used here interchangeably* to mean the application scientific mindset and methods to provide the optimal care for the patient (1).

Precision Medicine involve genomics, proteomics, metabolomics, as well as excellent histories and physical examination, and the accurate documentation, and integration of all of these data. Inherent in this definition is a robust informatics system that will allow the integration of the clinical and laboratory data and application of the data for the treatment of the patient.

Personalized Medicine involves prediction of the risk of developing disease, the selection of therapies based on individualized findings, leading to a much higher chance of success than population based selection of drugs. Also, Personalized Medicine leads to the development of more accurate diagnostics for a disease. Precision medicine will be influential in the care of the individual patient as well as to define the patho-biology of a particular disease. Personalized Medicine will lead to the discovery of abnormalities in the signature of a disease that will need to be validated as a true cause of the disease and a potential target for the treatment of the disease. Personalized Medicine involves basic research and clinical research before the standard application of these findings to the care of the patient.

8.3 Not a new concept

Although Personalized Medicine is a hot topic and an important buzzword in today's medicine, *the concept of Personalized Medicine is not new*. Personalized Medicine has always been the basis of any conscientious physician's modus operandi. For example, physicians have used bacterial susceptibility to a particular antibiotic to choose the proper antibiotic to treat an infection, or the glucose level and its response to therapy to determine the proper dose of insulin, or a Thyroid Stimulating Hormone level to determine the proper dose of thyroxine. However, *what has changed is the amount of scientific information and the sophistication and complexity of the scientific information that is now available to the practicing physician*. The advent of the polymerase chain reaction in 1983 has led to an exponential rise in the amount and complexity of scientific information available to the scientist for validation of its true importance, and to the clinician for its application to the care of the patient.

8.4 Patient expectations

The problems encountered in the practice of Personalized Medicine are going to center around the patients' and physicians' unrealistic expectations of what can be accomplished by Personalized Medicine at this point in history. This will especially be true when the cost of sequencing the human genome becomes affordable for the population as a whole.

Although we will be able to detect genomic variations from the normal, *we may not know the importance of that variation as a driver for future disease or the patient's present malady*. At this point in history *we may know the meaning of 3% of the abnormalities that we find during genomic, proteomic, or metabolomic exploration*. At the present time we do not know what to do with *more than 97% of the information that we discover*^(2,3). This underlines the importance of the repeating theme of discovery and validation.

8.5 Discovery and validation

The discovery of an abnormal mutation leading to increased or decreased protein and metabolite production does not mean that it has any impact on the patient's condition or is the target that we should direct therapy against. This will mean that we will have to think of a different way of approaching the scientific information that will be forth coming. This exponential growth in the scientific information that will be coming our way will be like taking a drink from a fire hose. We will need a structured way to determine what are the variants from normal that are the most likely to be the driver mutations, and are the ones that need to be studied in trials. This will involve the basic scientist to discover the mutations or abnormal metabolites.

The scientists will then need to search for the clues that will delineate the products that will turn out to be the real drivers and the really important targets to investigate. These clues may come from determining which abnormalities are recurring in the largest number of patients with the disease being investigated or which is the pathway that concentrates the largest number of abnormalities.

We will need a concerted effort and a dedication to work together as clinicians and scientists to determine which studies will be best for our patients. The good of the patient, either directly or indirectly, has to be the center of any trial. The number of patients will be limited relative to the number of targets and potential trials. *The number of clinical trials could easily overwhelm the number of available patients for study and give us many studies with no answers*. There will be many forces vying to enroll patients in the studies that they have a vested interest in. Investigators will have their particular interest that they will be pushing. Drug companies will have drugs that they will have large investments in and which they will want to get to market.

For this phase of Personalized Medicine research to be successful, *investigators will have to do something that may have never been accomplished* before. We will need to form a consortium of physicians and basic scientists representing every aspect of medicine to decide which are the most important questions to be answered for our patients. *We will need to put personal agendas aside to accomplish this*. This is truly a daunting task. We will have to become true partners with Pharma and companies that develop diagnostics and devices, and not just contributors to these company's trials.

The good of the patient and not the good of the company has to be the major goal. If we follow this mode of operating everyone will profit, the patients, the companies, the institutions and the physicians. If we can form true working relationships our patients will benefit. A true consortium of physicians interested in their patients' well being will be able to design any trial that is for the benefit their patients because they will control the most important element in completing any trial, the patient. As a group, physicians will need to realize there is true benefit in limiting the scale of trials. It has been said that "best is the enemy of good". If we subscribe to the unrealistic and unobtainable goal of trials designed to answer many questions our trials will not answer any question. This consortium of physicians, basic scientists,

institutions, and companies will need to limit their investigation to the studies that will likely answer the most important questions and not try to answer every question.

8.6 New concept of a clinical trial: N of 1, or something else?

What will be appropriate trials when we talk about investigating specific targets?(1).

If patients have a specific mutation will a randomized trial be necessary or more importantly ethical?

If our standard therapies for a particular disease are ineffective or marginally effective is it ethical to randomize a patient with the target to the arm of the trial that has the standard therapy and not the targeted therapy?

Most physicians have been schooled in the advantages of large randomized controlled studies. However, *Personalized Medicine* may not lend itself to these types of trials, and in fact *may be negatively impacted by trying to study it through large randomized controlled studies*. This offers physicians a problem, since we are creatures of habit, as most humans, who are slow to dispose of something that has worked in other situations and replace a tried and true method with something that is new and unproven. However, it seems obvious that *for many of the patients who have a specific marker, that randomized controlled studies will fail these patients* because it is likely that insufficient numbers of patients with the exact matching criteria will be found to give definite answers to the posed questions.

So what is the correct answer? *How are we to make sense out of the various markers that we think are drivers for a disease?*

At this time, I do not think that anyone knows the correct answer. If we look at a therapeutic trial, some groups have proposed that in a sense the patient should be his own control. For example, if there is a presumed target for the patient's disease and a drug against that target is available, the physician would treat the patient and look for regression or better control of the disease, or a decrease in the time to progression when compared to this patient's time to progression with his last therapy.

This is a trial with an N of 1. A trial with an N of 1 is against all statistical training and will be very difficult for physicians to accept. However, a trial with an N of 1 may be exactly the way that we need to study drugs directed against rare or uncommon targets.

However we need a consensus. We need to gather the best minds in the field together and to decide how to study these problems posed by precision medicine. No one knows the correct answer at this time. If nothing else a consensus on how to study the problem will facilitate the acceptance of the data generated by these studies. *And we need metrics* to prove whether this technique which is already being used adds value to the care of the patient, and whether it should be the new paradigm for medical care of other patients with similar Precision Medicine characteristics.

8.7 Informatics and the electronic health record

There is a common thought that if we can marry the Electronic Health Record with the Informatics System owned by the basic scientist, a reference lab, or a diagnostic or drug company that we will be able to decipher the meaning of the variations that we discover. At the present time, I think this is a misconception. Two definitions are needed. The Electronic Health Record is a device that a physician uses to record data about a particular patient and to transmit that data to other health care personnel for the care of that patient. The Informatics System is the system that stores all of the metabolomic, proteomic and genomic information on patients. It also will store all of the information on bio-bank samples.

Most Electronic Health Record systems are not designed as a research tool. They are designed primarily for the care of a particular patient. The Electronic Health Record is not designed to collect and aggregate data on many patients, However, some Electronic Health Record systems can analyze and report aggregate data. Much of the data entered by physicians into the Electronic Health Record is recorded as free text and not coded data points.

This method of recording data into the Electronic Health Record makes the recovery of the data on a group of patients difficult and incomplete. Also the data are only as good as the person entering data and that person's commitment to accuracy and completeness of the data entered. Also, *the type of data and the amount of data required for the care of the patient may be quite different from that required by the scientists looking for an association of a genomic variation for example with a group of diseases.*

Even if the data that is necessary for the scientist to make the association between the variation and a disease is present in the Electronic Health Record, this data may be very difficult to find if it is in free text. Some physicians construct their

notes with drop down menus that they click on to formulate their note. This method of constructing the physician's note would be easily searchable to find associations between a person's genotype and the resultant disease's phenotype. However, this is not the way that most physicians construct their clinical notes, radiology reports, and pathology notes. Most physicians dictate or type their notes. This is free text and would require someone to read the note and then to enter the desired data into a table that can be searched electronically to find the association between a genomic mutation, an abnormal protein or metabolite and the patient's phenotypic expression.

The other way of searching free text to find these discoverable events would be with an artificial intelligence program that could search free text looking for the elements that could be associated with the genomic, proteomic, and metabolic abnormalities; and *whether the gene and protein variations are true drivers, passengers, or artifacts of the particular method of measurement.*

Another possible problem with the Electronic Health Record that needs to be dealt with is the accuracy of the data. Information that is generated electronically, such as lab tests generally will be accurate. However, data derived from the patient's history and the physical exam is dependent on the expertise of the person performing the history and the physical exam. In a busy practice the entering of this data into the Electronic Health Record may occur hours after the history and physical were actually performed. This delay can lead to inaccuracies in the recorded findings from the history and physical exam. One area in clinical medicine where the data generally is more accurate is that recorded on patients that are on clinical protocols, where some data is prescribed to be looked for and recorded in an analyzable fashion.

After delineating *many of the problems with attempting to data mine from the Electronic Health Record, one statement needs to be made. We have no choice but to figure out a way to get the best information from the Electronic Health Record,* so we can discover the relationship between genotype and phenotype.

The data in the Informatics System by design is more oriented for research, although the information contained within it will also be used for the care of an individual patient. The way that the data is collected, namely electronically will make the data more accurate, more easily searchable, and easier to aggregate to find trends. Since much of the information in the basic scientist's Informatics System comes directly from instruments such as gene sequencers and mass spectrometers the data is electronically transferred to the Informatics System. As long as the instruments are properly calibrated, the data should be accurate. Since these data are digitally transmitted and are not in free text, they should be easily searchable, and deviations from the normal should be easily discoverable.

However, not all of the data in the informatics system is going to come from a strict transfer of electronically generated data points. Many of the discovered variations in genes, proteins, and metabolites must be analyzed by the scientists for their meaning and importance as a cause of a disease. These interpretations, which are very important, may be entered as free text, which brings up the same problems that exist in the Electronic Health Record when free text is employed.

8.8 Biobank: fundamental questions and value assurance

A Biobank is a topic that needs to be addressed under the topic of Personalized Medicine and especially within the subcategory of Informatics. Up to now the discussion has centered on taking a sample from an individual and finding an abnormality that predicts the individual's risk to develop a particular disease. The physician would then institute a therapy or a life modification or possibly in the future change the gene to prevent the development of the disease. In the case of the individual patient that has already developed a disease, the physician takes a sample, looking for a target that therapy can be directed against. The hope in this example would be that the therapy directed against this specific target would be curative. This method of practicing medicine is for the benefit of an individual, and exemplifies the basic premise on which the whole concept that Personalized Medicine is based, that is, individualized prediction or treatment.

The basic scientist and clinical investigator also have the obligation to improve the health of society by preventing them from developing a disease. The basic scientist and clinical investigator also are obliged to develop specific therapies

for the population that already has a particular disease. This now involves discovery and validation. This involves the discovery of variations from normal in genes, proteins, and metabolites and validation that these discoveries are actually causative of the disease. This discovery may start with an individual patient, but will require large populations with the specific variation to validate that this variation is the cause of the particular disease. This will require a Biobank.

The Biobank is simple in its basic concept but quickly becomes very complex in its application. In its simplest form a Biobank collects from a patient a biologic sample, blood, urine, tissue and stores them with samples from other patients for future investigation. This is done all of the time in protocols to investigate a question proposed in the design phase of the protocol.

The difference between collecting samples within the context of a protocol and the collection of samples for a Biobank is that the *Biobank collects and stores samples for questions yet to be asked.* Implicit in the charge *for a Biobank to be successful is linking the samples with reliable and complete clinical data in an informatics system for each person's sample that is in the Biobank.*

Who will pay for the storage of samples?

Who owns these samples?

Do patients own their own samples or does someone else own them?

Who will decide who may use the samples?

Who will decide what experiments these samples may be used for?

What criteria will guide these decisions?

Without this joining of clinical and basic science data for each sample, the Biobank would lose much of its value. Just as we have talked about the importance of the accuracy and reliability of the clinical information collected, the same stipulations for accuracy and reliability need to be applied to the collection of samples. For example, if you are collecting tumors for future study, are you sure that the sample contains the tissue that you are interested in, and is the tissue viable or are you saving necrotic and non viable tissue? Once the tissue is frozen, will the tumor be stored in a way that you will know whether it was thawed and for how long? There are systems that can automatically store tissue, obtain the samples that are necessary for study without thawing, and possibly ruining all of the other samples in proximity to the sample of interest. These instruments are effective but costly.

There is some precedent to say that the patient does not own their samples. Obviously the group that physically is housing the samples has the upper hand on ownership. In many institutions the task of verifying the accuracy of samples and storing the samples falls under the pathology department. However, many other departments, where samples have been collected on their patients and specifically on patients participating in studies that the departments are running may believe that they own the samples. This has been a real impediment to the development of tumor banks within an institution, and within disease categories between institutions. As much as we are reluctant to admit it, there is real competition within and between institutions. Sometimes this competition gets in the way of the care of the patient, and in the advancement and practice of Personalized Medicine at a particular institution. *In order to advance Personalized Medicine we need to break down the walls of competition and build bridges of collaboration,* collaboration within and between institutions. This will *require a change in our whole medical culture. This will be difficult but necessary.*

Biobank has real and significant value. Just as an institution that controls access to large numbers of patients has clinical importance and clinical capital, an institution that has a large Biobank of samples has translational science importance and research capital. Where Biobank samples and patients may be limited, an over site function must be employed.

Complementing the institutional IRB's role in protecting the safety for the patient in the conduct of a clinical trial, *and HIPAA's* protection of the patient's privacy in clinical trials, *a scientific oversight committee is needed to protect the value of the samples in the Biobank.*

This committee would make sure that the samples are being used to answer important questions and are being given to investigators that are capable of answering these questions. This oversight function should be exercised by a

research committee that ideally would be made up of representative members from each group that contributes samples to the Biobank and representatives of outside researchers.

The research oversight committee should clearly define its mission, and should review every request for its scientific/clinical merit and the ability of the group requesting samples to accomplish what they are proposing to do. Samples should be released only after this committee agrees that the proposed study has a high likelihood of producing interesting and important scientific answers.

These decisions need to be timely, so as not to delay the start and completion of important research. With the asymptotic growth of the biologic information being produced and the finite number of available samples with reliable clinical information such an oversight research committee becomes absolutely necessary to guarantee the conduct of high quality studies to answer important questions.

8.9 Advantages of personalized medicine

Presently, personalized medicine is expected to be the savior for medicine. This expectation is the greatest challenge for the implementation and eventual success of Personalized Medicine. What the public and many physicians expect that Personalized Medicine can deliver now may and probably will be available in the future, but is far from what it can deliver today. In order to implement Personalized Medicine the medical and scientific community must educate the public and much of the medical community of what Personalized Medicine can actually accomplish now and what is to be expected in the future.

The benefits of Personalized Medicine are potentially life changing for everyone. The advances and advantages of Personalized Medicine can be classified in the categories of risk prediction, more accurate diagnostics and more effective therapy.

If through the use of genomics, proteomics, and metabolomics, we could predict whether a group of people were at risk for developing a particular problem this would be an advance of unforeseen benefits. As long as we have the means to prevent the development of the disease, prediction of risk will be of great advantage for the individual. If we have no way of preventing the development of the disease then knowing about risk for developing the problem may be of no advantage. As a matter of fact, when you have no way of diminishing the risk of developing a disease, then knowing about the risk may actually be detrimental for the individual by causing him/her anxiety about something that he can do nothing about. However, if you have a therapy such as a colectomy in a patient with familial polyposis, you will almost assuredly prevent that individual from dying of colon cancer. We would however like to implement less drastic and less mutilating therapies.

The dream and hope would be that in the future you could engineer a change in the gene mutation so that you can eliminate the risk for the disease. However, until that day arrives, the physician will be left with life style modification and possibly drugs to decrease the risk or delay the development of a disease. If a patient had a genetic predisposition to develop obesity with all of obesity's attendant health risks (2,3), their physician could implement dietary and exercise, life style changes to delay if not prevent the development of obesity. The physician would prefer to have an active therapy, such as a drug, that would absolutely prevent the development of obesity.

This idea of having a drug to treat a disease or to decrease or eliminate the risk of developing a disease may be one area where Personalized Medicine can and will make the biggest difference in the practice of medicine. We have drugs for most diseases but in many instances they are not the correct drugs. The only way we have had in the past to determine whether a drug was the correct drug for a patient with a particular disease was trial and error, that is try the drug and see if it worked. A conservative estimate is that 40% of the time an ineffective drug is being used.

Not only can this have catastrophic health risks for the patient, but also the economic effects can be catastrophic for our health care system. *Many billions of dollars are spent on ineffective drugs each year* (4,5,6).

One example of the use of an ineffective drug is the use of clopidogrel (Plavix) to prevent clotting of coronary artery stents. If an anti platelet drug such, as clopidogrel is not used the incidence of clotting of the newly placed coronary

artery stent is very high. Clotting of this stent could result in the need to replace the stent. This is a risk to the patient and an added cost to our health care system. More importantly, the clotting of the stent can result in a myocardial infarction and possibly death of the patient.

CYP2C19 is the enzyme that activates the prodrug, clopidogrel, to the active form. Most of these patients for whom clopidogrel does not work have a mutation of the gene on chromosome 10 that produces the variant CYP2C19*2. The CYP2C19*2 mutation prevents the conversion of clopidogrel to the active form. Therefore in these patients clopidogrel does not inhibit platelet aggregation to the same degree as it does in patients without this mutation. It has been estimated that in 18% to 33% of the patients carry the CYP2C19*2 mutation which may make clopidogrel less effective in preventing clotting of the stent. (7) These patients have a risk of clotting their stent that is two and a half times greater than those patients without this mutation. (8) The CYP2C19*2 mutation can be tested for in minutes from a blood sample. However, this is not the practice in the cardiology community.

Why is this potentially life-saving and definitely cost saving test not in common use?

The reason is related to problems that we have already discussed. The first reason relates to the question of whether you should test for something that you do not have good therapy for. The second reason is related to the fact that most physicians are relatively conservative in their practice and *there needs to be a real culture change for physicians to accept this new finding*. Initially, when the CYP2C19*2 mutation was discovered there was not a good alternative. Now, there is the drug, prasugrel (Effient) that does not rely on the CYP2C19 enzyme for activation. However, testing for CYP2C19*2 and the use of prasugrel are not common practice.

8.10 Financial challenges for personalized medicine

How are we going to pay for Personalized Medicine? This is not just paying for direct patient care, but *paying for everything that eventually leads to better care for our patients*. This includes paying for the biobank, paying for discovery of the variations from normal in genomics, proteomics, and metabolomics, and then paying for the studies that validate that these variations are causative and predictive of the disease. There will be many sources that will need to be tapped to pay for Personalized Medicine. Payment for patient care should come from health insurance.

However, health insurance companies are not prone to pay for a new test until its validity has been proven, and even then these companies may need to be convinced that a particular test is not only valid but also is cost effective in the care of the patient. The cost effectiveness may actually be a strong selling point for Personalized Medicine. Theoretically, if you have markers that make the diagnosis of disease more certain, that make the prediction of disease development and the potential for preventing this disease possible, and that make the treatment of disease more successful by providing a target to treat, the insurance companies should embrace the concept of Personalized Medicine. The insurance companies should embrace these concepts of Personalized Medicine because these concepts should improve their patients' outcomes and should be more cost effective by eliminating ineffective therapies. The important term in this supposition is theoretically. All of these theories are probable but unproven and therefore theoretical advantages of Personalized Medicine.

To change these from theoretical to real advantages for Personalized Medicine we will need clinical trials to validate these predictions. These trials are unlikely to be paid for by health insurance companies. However, the argument can be made that these trials are to the advantage of these companies by defining the most effective and cost effective therapies for them. Perhaps these companies should be contributing financially to the completion of such trials. A strong and active lobby for these benefits of Personalized Medicine must be created. Most likely, funding for such trials will come from Pharma if they have a drug of potential application to a disease, or the funding will come from companies or academic institutions that have a test that is of potential value in diagnosing or treating a disease. Government funding is another obvious source for funding these trials. However, in these economically trying times, all of these avenues have become unreliable sources for funding these validation trials for Personalized Medicine.

Another outcome from this logic is that it makes sense to have a consortium that decides which trials are the most important to perform, and have all groups contribute patients to these select trials. Every group feels that they should develop trials and answer the question of particular interest to them.

However, this proliferation of many studies may actually prevent the important questions from being answered. There are a limited number of patients that can be entered into these trials. Therefore we should develop a collaborative effort to answer the most important questions rather than have everyone do their own thing. There are many deterrents to collaboration. Most of these center around personal agendas or institutional agendas. The focus of all clinical investigators has to be the individual patient, not our institution or company.

Collaboration is absolutely necessary for Personalized Medicine to be successful. *No institution is large enough to provide everything that is needed by every patient.* Therefore, we have to be willing to send samples or the patients, themselves to the investigators that are doing the most innovative work in that patient's problem. It is easy to suggest that we rate the most important studies and enroll patients in these studies, but the difficulty in getting agreement within the basic and clinical scientists on which studies to perform will not be an easy task.

Just as we stated earlier, that meeting of the top investigators is needed to decide the proper design of studies in this era of Personalized Medicine, a similar convocation of experts will be needed to define the most important studies that are needed and then to foster the collaboration to get these studies done. In this way, our patients will not be wasted by being in a study with an unimportant or unanswerable question.

8.11 Ethical challenges for personalized medicine

Personalized Medicine raises many ethical questions. These questions are not obstacles to the practice of Personalized Medicine. These questions should not be shunned but should be approached as any research question would be approached. Knowledge is good. However, when knowledge defines a problem that we have no answer for, it can be disconcerting and anxiety provoking for the person with the problem.

Do we tell a patient who feels well that he has a high risk to develop a disease, such as Alzheimer's, if we have no effective therapy for Alzheimer's? If we have no effective therapy now, how are we going to know whom to inform of new effective therapies when Personalized Medicine develops these therapies? Can we tell an adult daughter that her mother carries the BRCA1 mutation, which could be lethal for the daughter, if her mother does not want family members to know that she has this mutation? In countries where abortion is legal, for what conditions is it ethical to abort a fetus? Perhaps, many people would feel comfortable in aborting a fetus, known to have Down's syndrome.

However, as we understand the genome better and when prenatal genomic analysis becomes the norm rather than the exception, will it be ethical to abort a fetus that will have below average intelligence? These seem like unrealistic questions now, but I suspect these questions are right around the corner. Again these questions should not be looked upon as obstacles to the practice of Personalized Medicine, but as opportunities for ethical and social study.

8.12 Conclusion

I am not pessimistic when I ponder the title, PRECISION MEDICINE: HAS IT'S TIME COME? ARE WE READY FOR IT? *We are ready for Personalized Medicine, but with reservations.* We must be realistic about what Personalized Medicine will provide for our patients now. We must also be optimistic about the future of Personalized Medicine and we must approach it with the vigor of an explorer looking for the limitless future of new discovery. In order to keep the concept of Personalized Medicine alive and evolving we need to educate the public so they do not have unrealistic expectations for Personalized Medicine which when not delivered will lead to disillusionment with Personalized Medicine.

This possible disillusionment with Personalized Medicine could delay or prevent its full implementation. The public's and the medical community's expectations are all realistic, but Personalized Medicine may need time to bring these expectations to their full fruition.

In order to satisfy the public's expectations we need to:

1. Change the culture of medicine so that physicians approach the care of each patient by looking for predictors of disease and therapeutic success;
2. Discover variations from normal in genomics, proteomics, and metabolomics, and determine what these variations mean;
3. Validate that these variations are predictive and causative of disease;
4. Develop good informatics and clinical information systems and link them to give clues to the clinical meaning to the genomic, proteomic, and metabolomic abnormalities;
5. Determine what type of studies are going to replace the large randomized clinical studies;
6. Develop and follow metrics to prove the benefit and cost effectiveness of Personalized Medicine;
7. Create new ways and cultivate the old ways to pay for Personalized Medicine;
8. Convince everyone of the advantage of a biobank for the development of new and more effective diagnostics and therapeutics; and -
9. Involve other disciplines such as ethics, social science, and finance in the development of Personalized Medicine.

If we follow these tenants and set realistic timelines for the implementation of the present and future developments in the translational science of Personalized Medicine, then the principles of Personalized Medicine will become the foundation of medical practice.

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9 National-scale Adoption of Personalized Medicine in a Socialized-Medicine Market

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9.1 Key take-aways and call to action

Call to Action

1. Successful example of first mover adoption of innovative personalized medicine by a non-profit HMO operating under national-scale social medicine Health Law
2. Evaluating new and emerging means and technologies of personalized medicine is a non-trivial, multi-factorial undertaking
3. Evaluating personalized medicine requires thorough assessment of patients, providers, healthcare organizations, payers, and national perspectives
4. Assessment of risks and rewards of personalized medicine requires a balanced approach of quantitative and qualitative, near and long term considerations

Key takeaways

1. Develop and share value models for the next generation personalized medicine in order to accelerate its wide spread adoption system-wide at enterprises, and at national, regional, and global markets

Focus areas

Managed care, social medicine, adoption, innovation, personalized medicine, Oncotype DX, early detection, prevention, early interventions, outcomes, data mining, clinical decision support, electronic medical records, economics, value model

9.2 Level set

We describe key learning from national-scale adoption of personalized medicine by a non-profit HMO in socialized medicine market.

Tailoring diagnosis and treatment in a personalized manner to each patient is a decades-old edict of our medical education and everyday's practice. So essentially, there is nothing new in personalized medicine. In the distant past, common sense and clinical judgment guided our decisions in the face of fundamental uncertainty. In recent years we

Founded in 1911 by 150 immigrant workers as mutual aid health care association, Clalit Health Services ('Clalit') is Israel's largest HMO and one of the most progressive public health associations in the world. Through its network of 14 general, specialty, and rehabilitation hospitals and more than 1,200 primary and specialized clinics, Clalit provides comprehensive health insurance and highly advanced medical care to the majority of Israel's population. It is the only health fund with a countrywide network of more than 400 state-of-the-art pharmacies, dental clinics, laboratories, diagnostic-imaging and specialist centers.⁹⁸

Since the enactment of *National Health Law in 1995, every citizen and permanent resident is insured by the state and has to pay a fee for this insurance.* A national basket defines free preventive, ambulatory, inpatient, and rehabilitation health services for all.

⁹⁸ <http://www.clalit.co.il/HE-IL/english/about+clalit+health+services.htm#g1>

Driving *fierce competition on quality, access, consumer satisfaction, and complementary services, everyone has the right to change their HMOs every other month*. Three other HMOs operate in Israel. Clalit serves more than four million individuals.

Currently *we use personalized medicine in oncology, prevention intervention programs, computerized decision support systems (CDS), and electronic medical records (EMR)*.⁹⁹

This chapter discusses the experience of a non-profit HMO with personalized medicine operating in a government controlled, yet competitive social medicine market. We offer key learnings and call to action.

9.3 *Oncotype DX marks the beginning of personalized medicine in Clalit*

In early 2006 Clalit announced that it will fund Oncotype DX[®], the then most advanced test to determine whether a patient with breast cancer requires chemotherapy, or she can be spared the harsh treatment.¹⁰⁰ The world's first HMO to do so, the rationale to implement new technology was not consistent with the general perception of what non-profit HMOs do and don't.

The *controversy was rooted, in part, in the fundamentals of Evidence Based Medicine*: making decisions based on tried-and-proven guidelines which are founded on how "most of the patients" responded in controlled clinical trials involving hundreds and thousands of patients. In contrast, *personalized medicine is an emerging and rapidly evolving practice* of making decisions based on the unique personal characteristics of the patient. And adding Oncotype DX to Clalit's health basket was expensive.

Yet *Clalit is driven by commitment for quality, service excellence, and innovation as brand promise as well as competitive differentiation*.

OncotypeDX-Breast provided us the compelling opportunity to tell breast cancer patients after surgery that they are healthy with a sound level of certainty. For patients, the emotional difference between being a breast cancer patient and a cured breast cancer patient is tremendous. That difference has ripple effect on the entire family and their social network, with substantial spiritual and life style implications. Similar to other countries, Israeli women are the lead decision makers on health care matters for their families.

Ineffective or unfit chemotherapy can be harmful, and may be associated with short and long-term co-morbidity due to side effects. Collateral implications on the patient and her family include having to take time off from work which at times may result in job loss and loss of income; social isolation and declassification; adverse impact on family life when family members are away from home to support the patient, conscious and sub-conscious abuse, and deterioration of sex life; increased expenses, and other.

So *investing in OncotypeDX-Breast had much larger implications, making Clalit a preferred HMO for the entire family*.

Initially, we used the Oncotype DX to analyze 21 genetic and other biomarkers in the tumor. In 2007 we added node positive tumors achieving favorable medical and economic outcomes. Trailing Clalit by one year, the National Comprehensive Cancer Network (NCCN)¹⁰¹ incorporated Oncotype DX in its guidelines in 2007 for node negative cases, and in 2008 for node positive cases¹⁰².

9.4 *Personalized medicine in oncology*

Founded on decades of disciplined adherence to tried and proven, evidence-based protocols, *Oncologists are confronted with genetic tests and respective treatments which may not be part of a pre-existing protocol*.

⁹⁹ http://inteliprjects.com/wp-content/uploads/MEDICAL_INFORMATION_SHARING_IN_CLALIT_HEALTH_SERVICES_ISRAEL.pdf

¹⁰⁰ <http://www.oncotypedx.com/en-US/Breast/ManagedCare>

¹⁰¹ http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

¹⁰² <http://www.nccn.org/about/news/newsinfo.asp?NewsID=127>

Personalized Medicine in oncology is evolving. *Not all tests are sufficiently validated, and not all of them are accepted as standard of care.*

We divide personalized medicine in Oncology in three categories:

- *Special purpose diagnostic tests* that guide specific treatment decisions, usually associated with a specific drug for which the test was developed.
- *Tests that discover the tumor's genetic mutation* which may suggest the best treatment. Examples include Tumor Foundation Profile that are based on new generation sequencing, Target Now, and others.
- *Decision support tests* like Oncotype DX that direct treat or do-not-treat decisions.

New genetic driven therapy is usually costlier than standard protocols, and is determined on case by case basis. Biomarker based precision therapy may result in avoiding cost and suffering of otherwise inappropriate diagnostic procedures, treatments, and side effects. And *we have witnessed situations whereby personalized medicine approach led to inexpensive, non-protocol yet successful treatments.* Nevertheless, the blessing of prolonging life with partial cure is mixed with economic and other burden of the chronic disease on patients, their families and loved ones, and society at large.

Therefore, *forecasting organizational and national expenditures, and evaluating cost Vs quality are non-trivial undertaking.*

At Clalit we take all of this under consideration when making a system-wide decision on adopting new technology. We have done so prior to adopting Oncotype DX-Breast; Oncotype DX-Colon; miRview mets for identifying the origin of metastases of an unknown primary tumor; Target Now – use of tumor biomarkers to identify the next step treatment; next generation sequencing Tumor Foundation Profile for more than 180 tumor mutation biomarkers that guide the best treatment; KRAS, EGFR tests for fitting treatment with different oncologic drugs.

9.5 Personalized medicine in prevention and computerized decision support

Experiencing low attrition rate, disease prevention became a long term imperative for Clalit.

We began by instructing primary care physicians to aggressively treat hyperlipidemia, particularly in the presence of other risk factors; and equipped them with guidelines, decision support system, and EMR to treat patients with complex diabetes and other risk factors. *The outcomes were compelling:* 18% lower PCA's and 22% lower CABG's system wide.

We embarked on data mining to identify other populations at risk for severe or chronic diseases and start preventive measures in these populations. Currently underway are primary and secondary preventive programs in nephrology, and adult chronic NCD patients in primary medicine settings; predicting and preventing deterioration of elderly patients; lower antibiotic resistance by controlling regional use of correct antibiotics; and a national program for changing the paradigm in the prediction and prevention of high risk pregnancy, including Gestational Diabetes.

9.6 Personalized prevention and early detection and treatment of renal insufficiency

The number of dialysis patients grows at a rate of 7-8% per year nationwide. Complex disease prevention programs are needed to address it.

We developed data mining algorithms to identify patients at high risk for renal function deterioration, and protocols to guide their physicians through prevention, early detection, intervention, and monitoring.

Similarly, *we instructed primary care physicians to detect mild deterioration in renal function of patients not at risk for renal failure even when lab tests are still within normal range;* and follow diagnostic protocols to identify the reason for the renal deterioration and treat it accordingly. We implemented special computerized decision support protocol in the EMR to help the physicians do that.

9.7 Personalized intensive guided care of the complex chronically ill patients

Complex chronic patients pose formidable challenges to primary care physicians.

They usually don't have the time to fully attend to these complex patients during typical encounters. Multiple drug-drug interactions and differences in the opinions of the multiple physicians that are involved in their care are leading compounding problems. Consequently, the rate of readmission of these patients is high and their conditions worsen quickly, leading to high cost of care.

We developed and implemented early detection of patients prone to complex chronic diseases and intensive targeted care programs for them. Special nurses were trained to manage these complex patients. We are monitoring the performance of these programs for quality outcomes and cost.

9.8 Personalized geriatric medicine in primary care settings

For years 11% of Clalit's total medical expenses were due to interventions in the last year of the lives of 0.3% of our patients.

Implementing data mining techniques we began to identify preventable deteriorations of elderly patients, and alert their Primary Care Physicians to take proactive measures. Although the program is at early stage there are early indicators that it is successful, as measured by *lower re-admission rates and cost.*

9.9 Regional antibiotic resistance control

Antibiotic resistance is a notorious, worldwide problem. It is caused by unwise and uneducated usage of antibiotics in community medicine and hospitals. Resistant strains develop and we are in a continuous search for new antibiotics at ever increasing cost.

We recently published the results of analyzing over 6 million community-based encounters in which antibiotics were prescribed. Since Clalit is a fully computerized organization with EMR and CDS, we will analyze resistant strains on regional basis and publish algorithms for treatment in different community-based clinical situations according to resistance.

9.10 Prediction and prevention of high risk pregnancy

50-80% of Gestational Diabetes (GDM) mothers develop Type-2 Diabetes (T2DM) that can be prevented or its onset postponed. We seek to prevent next generation metabolic syndrome of the Big Babies, and detect genetic problems that may be missed in traditional follow ups.

We developed and implemented a program for predicting and preventing the development of high risk pregnancies, including more aggressive diagnosis of GDM according to the new Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study¹⁰³ criteria.

Nurses in Clalit's Women Health Centers will search for biochemical, genetic, and personal risks of the mother and her pregnancy in the 12th-14th weeks. At risk patients will be referred to the Ob/Gyn physicians with a complete laboratory and medical history survey.

New radiologic (Ultra Sound) and laboratory markers for identifying high risk states are used in the 24th to 26th weeks of pregnancy.

The Ob/Gy physicians use new protocols for prevention, early detection, early intervention, and follow up of the at risk patients. All pregnancies will be controlled at any stage through a special pregnancy follow-up protocol for physicians.

¹⁰³ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2897007/>

and their clinical care teams. Pregnant women will be able to use an internet pregnancy file to provide their pertinent medical information to all her care providers, and get help 24x7.

9.11 Conclusions and call for action

HMO's face the challenge of providing medical care according to modern concepts of prediction, early identification of risks, prevention and if everything fails – personally directed therapy according to genetic, biochemical and biologic markers.

Doing it seems excessively expensive. Yet Clalit's experience is different.

Performing thorough multi-factorial technology assessment and economical analysis, we were successful saving money while increasing the quality of medical care and achieving better outcomes.

It is imperative to use all data available in order to predict the course of disease – from the national, regional and personal points of view, and use these predictions in order to drive disease management protocols intended to early identification of risks, prevention and aggressive personally directed treatment.

Specifically, we call for the development and sharing of value models for the next generation personalized medicine in order to accelerate its wide spread adoption.

10 Disease Modeling for Personalized Molecular Therapies

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10.1 Key take-aways and call to action

Key takeaways

1. Many therapies fail to reach therapeutic endpoints due to the poor delivery of therapeutics to the target region
2. Outcomes of molecular therapies are difficult to predict without considering the anatomy of an organ, drug diffusion, and cellular events at the target site
3. Traditional trial and error animal infusion experiments do not provide quantitative answers for treating a human subject
4. Medical diagnostic imaging gives anatomical and quantitative information about a patient that can be used for predicting drug distribution a priori
5. This chapter describes a reproducible and adaptable disease modeling methodology capable of integrating the quantitative knowledge on signaling and gene regulation in systems biology with patient-specific diagnostic imaging at engineering precision
6. Macroscopic organ-wide model which predicts biodistribution is integrated with microscopic cellular model that describes transcriptional and translational events

Call to Action

1. Accelerate the development of more effective, predictive-based personalized therapies by funding white-space R&D that brings together clinical medicine, patient-specific diagnostic imaging, disease modeling, systems biology, and chip design and manufacturing best practices
2. Analyze temporal evolution of gene expression in an organ-wide model framework
3. Integrate medical imaging with systems engineering principles
4. Translate single cell signaling dynamics to an organ-wide analysis platform to understand disease progression and evaluate molecular treatment options
5. Predict how gene expression levels in an entire organ will be altered by an infusion therapy using quantitative systems engineering models that compute transcriptional and translational regulation events along with drug biotransport and drug-tissue interaction

Focus areas

patient-specific modeling, molecular therapy, gene regulation, intracellular signaling pathways, short-interfering RNAs (siRNAs), predictive modeling, chronic pain, central nervous system, disease modeling, systems biology, 3-D medical image reconstruction, medical imaging

10.2 Level set

We examine the role of disease modeling in the development of personalized molecular therapies through our experience with translating single-cell gene expression models to generate an organ-wide response prediction.

We propose to *build an informatics platform for designing molecular therapies* for tomorrow's medicine. *This chapter describes a reproducible and adaptable disease modeling methodology capable of integrating the quantitative knowledge about cellular signaling, gene regulation and drug delivery models in systems biology with patient-specific medical imaging.*

Many disorders of the central nervous system are caused by abnormal target gene expression levels. The over- or under-expression of the gene is often due to altered intracellular signaling pathways. Many studies have investigated intracellular signaling and regulatory events in a single cell in normal and pathological states with computational models.¹⁻⁸ Furthermore, some studies explored target gene expression levels in response to treatment.⁹⁻¹⁰

These models quantitatively describe the response of a cell to extracellular stimuli and the induced changes in gene expression levels. By studying these signaling events, *we can understand how abnormal gene expression levels are induced and how we can restore the cell to a normal state by pharmacological interventions. These cellular models*

that describe signaling, transcriptional and translational regulation events *serve as road maps for designing molecular infusion therapies*. However, there is a wide gap between quantifying the relationship between stress and induced gene expression in vitro and designing an infusion therapy which will cause a desired change in gene expression in an organism. We propose the systems integration of the microscopic model describing cellular events *with a model of the entire brain reconstructed from magnetic resonance images* (MRI) of a patient to build an informatics platform with medical imaging information incorporated.

We demonstrate for the first time the potential of organ-wide prediction of gene expression and protein levels in normal and disease states.

These organ-wide models *accelerate our understanding of the molecular perspectives of disease progression and serve as an in silico platform for testing pharmacological infusion therapies*.

We demonstrate in the first case study the construction of a cellular model describing translational regulation of the aquaporin-4 gene. This model predicts how the levels of aquaporin-4 protein and mRNA change in response to an extracellular osmotic stress. A simplified version of this cellular model will be incorporated within a brain geometry to demonstrate the brain-wide prediction of gene expression levels.

The influence of an infusion will be demonstrated in the second case study. In the second case study, we illustrate the design of *gene silencing therapies for the management of chronic pain* by downregulating pain-transmitting NMDA receptors in the spinal cord. Reducing the expression levels of NMDA receptors in a targeted region is expected to decrease pain sensitization in the spinal cords of chronic pain patients. With this informatics platform bridging cellular systems biology with medical imaging, we will predict the optimal infusion concentration for short interfering RNA molecules (siRNA) for targeting NMDA receptors in the spine. This adaptable and reproducible platform predicts the concentration of disease-related proteins in tissue based on cellular signaling events, transcriptional and translational regulation.

The *computation of drug-organ interaction within a framework* utilizing both physiological and biochemical information allows the determination of optimal dosage to successfully reach therapeutic endpoints. The integration of systems engineering, systems biology and medical diagnostic imaging will enhance our understanding of molecular perspectives of disease progression and accelerate the design of molecular therapies for tomorrow's medicine.

10.3 Case in point

Numerous disorders of the central nervous system (CNS) are tightly related to abnormal gene expression levels. Abnormal gene expression levels arise from altered intracellular signaling cascades in response to extracellular stresses¹¹⁻¹³ or intercellular cross-talk.¹⁴⁻¹⁸ Many pharmacological agents are currently being developed *to control the transcription and translation of a target gene*. These molecular therapies have great potential in treating disorders such as cancer and chronic pain by restoring normal gene expression in affected cells.

For the development of molecular therapies, many genes involved in pathogenesis have been studied using cell cultures. In these studies, the *relationship* between an external stimulus (such as signaling molecules or neurotoxic chemicals) and the resultant changes in transcript and protein levels in cells is quantified. In some instances, the possible signaling mechanisms are *postulated based on the application of an inhibitor and on measurements of key signaling molecules*.

For example, the anti-angiogenic signaling mechanisms in vascular endothelium in response to endostatin treatment has been proposed based on in vitro observations.¹⁹ The endostatin-induced anti-angiogenic signaling has potential for the clinical treatment of cancer to reduce unwanted vascularization. Moreover, the molecular circuitry of cancer centering around the tumor suppressor protein p53 has been established.²⁰

However, the *successful implementation of molecular therapies in humans requires* not only an understanding about gene expressions, but *also an effective drug delivery system to bring the active agents into desired cells in a specific target tissue*.

The effective *targeting of specific cell types and regions in an organ requires patient-specific information about anatomy and physiology*.

The *systematic design of organ-wide gene expression profiles rooted in systems biology knowledge would benefit from the integration of medical diagnostic imaging with cellular biochemistry*. Such a computer platform would predict *patient-specific gene expression changes* in normal and disease states. In addition, this integrative approach will *predict the dynamic changes in signaling, transcript levels and local protein concentrations in response to the injection of a therapeutic molecule*. In this chapter, we demonstrate the construction of such an informatics platform and its applications in designing novel molecular therapies.

Despite a rich knowledge base in cellular signaling networks, the organ-wide *prediction of gene expression and protein levels is still in the budding stage*. The *outcomes of molecular therapies will be difficult to predict basing solely on experimental observations in vitro, without considering the patient-specific anatomy, the heterogeneity in cell types, the effectiveness in drug biotransport and the dynamics of drug-cell interaction on an organ-wide level*.

Despite the advance of high resolution medical imaging techniques, the integration of the macroscopic anatomical data, patient physiology, and the microscopic cellular biochemistry has not been thoroughly investigated. There is a need to integrate clinically relevant physiological information with systems biology models for making organ-wide predictions of gene expression needed for the advancement of personalized medicine.

Whether or not an infusion therapy will cause the desired change in protein levels is *functions of the accessibility of the target tissue, drug biodistribution and metabolism, cellular uptake, as well as subsequent signaling and transcriptional events*.

We propose a novel computational approach for the design of more effective therapies by integrating systems biology models with patient-specific medical imaging technologies.

First, we will briefly outline the methodology to integrate medical imaging with cellular biochemistry. This methodology will be illustrated using two case studies. The first case study demonstrates the translational regulation of aquaporin-4 water channel (AQP4). The second case study focuses on the design of gene silencing therapies for the downregulation of pain-modulating NMDA receptors in the human spinal cord.

AQP4 is a water channel found predominantly in the central nervous system (CNS).²¹ This water channel has an important role in regulating water transport, cell volume and ionic environment inside the CNS.²²⁻²³ AQP4 channels are implicated in life-threatening disorders such as hydrocephalus²⁴ and edema.²⁵⁻²⁸ In hydrocephalus, cerebrospinal fluid (CSF) accumulates inside the ventricles; brain edema usually entails fluid accumulation inside the cells or within the extracellular space of the CNS. In both diseases, the crucial role of AQP4 in water management makes the *control of the transcriptional activation or translational regulation of aquaporin 4 gene* (aqp4) with pharmacological agents a promising target to restore water balance.

Quantitative analysis of the transcriptional and translational regulatory mechanisms of AQP4 throughout the entire brain would accelerate the introduction of pharmacological interventions to up- or downregulate AQP4 effectively. The first case study fuses new biochemical knowledge about *translational regulatory mechanisms of AQP4 with a patient-specific brain model*. This case study shows how a systems biology model describing translational regulatory mechanism of a target protein can be integrated with medical imaging to compute the organ-wide distribution of this protein in the entire brain in a specific patient.

The second case study will focus on a class of *novel molecular therapies* termed *gene silencing* therapies. *Gene silencing therapies are the next generation of treatments for CNS disorders*. In gene silencing therapies, *short-interfering RNAs (siRNAs) are injected near the target region to specifically downregulate a target protein*. siRNA molecules bind sequence-specifically to the targeted mRNAs in the cell, inhibiting their translation. Gene silencing therapies can temporarily change the expression of a gene and downregulate a disease-related protein without altering the genome.²⁹ In animal models, this promising technique induced downregulation of NMDA receptors in the spinal cord, temporarily inhibiting pain transmission.³⁰

The design of gene silencing therapies for treating chronic pain patients requires the quantification of NMDA receptor levels in the spinal cord and their dynamic changes after siRNA infusion. The inclusion of tissue properties and siRNA biochemical reactions into this adaptable platform gives it potential to design therapies for precisely controlling the expression of disease-related proteins in the human CNS.

The integration of medical reconstruction with mathematical models³¹⁻³⁹ may provide quantitative answers to issues that currently delay the clinical implementation of human siRNA therapies.

10.4 Construction of an anatomically consistent model of a target organ

For organ-wide gene expression analysis, the reconstruction of the organ anatomical geometry is a crucial first step. For gene expression analysis of the brain and spinal cord in the following case studies, the exact anatomy of the CNS is reconstructed from MRI of a subject using a procedure described elsewhere.^{33-34, 37, 39-40}

The anatomical geometry of the CNS in the *reconstructed models has subject-specific geometry*, and this accurate reconstruction of the anatomy is *important in the analysis of drug distribution patterns and the prediction of therapeutic effect for a specific subject* after an infusion therapy.

10.5 Three dimensional reconstruction of the human CNS

A patient-specific model was reconstructed from MRIs of the patient's CNS through a process termed image reconstruction (Figure 1).^{33-34, 37, 39-40} In an image reconstruction software - MIMICS innovation suite (Materialise, Leuven, Belgium), the anatomical geometry of the brain tissue, spinal cord tissue, and the surrounding CSF were captured by automatic and manual segmentation.

The brain was divided into the grey matter, white matter and different functional regions such as the pons. Different *drug transport properties, extracellular space fraction, cellular composition, anisotropic diffusion and endocytosis rates can be assigned to each region, reflecting physiological complexity of the brain.*⁴¹

This *subject-specific model was converted into an unstructured computational mesh* as described by Somayaji³³ for the organ-wide analysis of gene expression, protein levels, and predicted outcomes of molecular therapies.

10.6 Functional regions in the spinal cord

For developing novel treatment options for chronic pain patients, we quantify the levels of NMDA receptors inside the spinal cord after an infusion therapy.

Specific *downregulation of these receptors can cause desirable disruption in the pain signal transduction* and reduce the sensation of heightened pain.

The human spinal cord was reconstructed and divided into the grey matter and white matter. The NMDA receptors are mainly found in neurons of the grey matter, more specifically, in the second laminae within the dorsal horns⁴² as shown in the right panel of Figure 1.

Neurons within these target regions specialize in pain signal transduction.

Neurons outside of these regions have little or no NMDA receptors.

Therefore, siRNA molecules have no effect in neurons outside of the target regions due to the lack of NMDA receptor-encoding mRNA.

The bioreactivities of siRNA molecules differ in different functional regions in the spinal cord.

The *application of transport and reaction equations allows the computation of infusion, biodistribution, and reactions of siRNA within different cell types.*

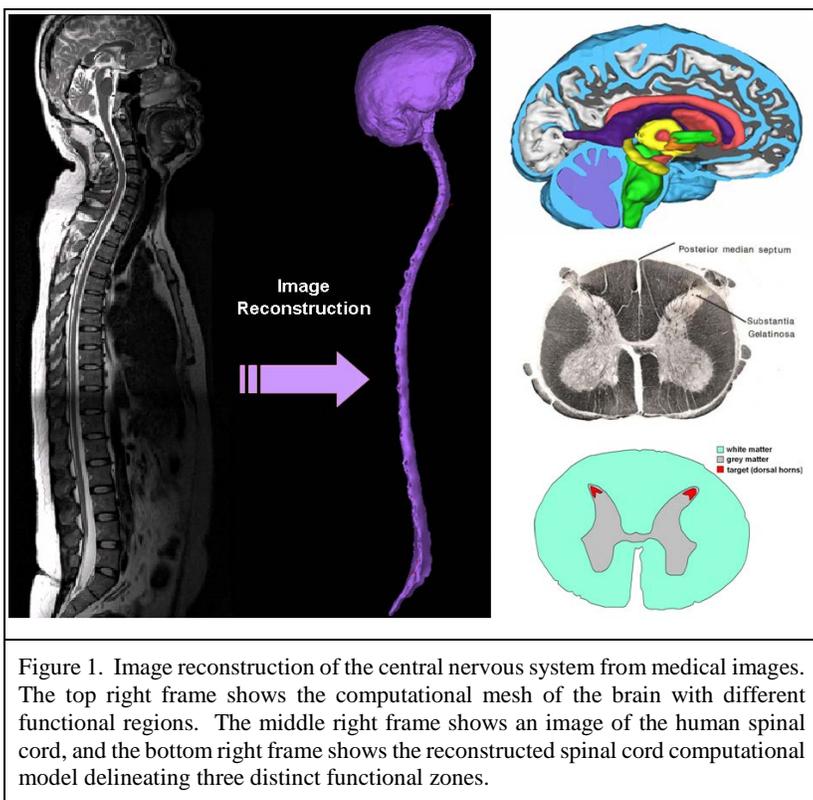


Figure 1. Image reconstruction of the central nervous system from medical images. The top right frame shows the computational mesh of the brain with different functional regions. The middle right frame shows an image of the human spinal cord, and the bottom right frame shows the reconstructed spinal cord computational model delineating three distinct functional zones.

10.7 Case study 1: translational regulation of aquaporin-4 in the entire brain

Aquaporin-4 (AQP4) is a water channel in the brain that is mainly expressed in cells around the blood brain barrier (BBB) or tissue-CSF boundaries.²¹ The conduction of water through AQP4 channels requires an osmotic gradient. The effective upregulation of AQP4 in the brain has been shown to aid in the restoration of water balance during vasogenic edema in animal models.²⁵

However, the design of new therapies for the upregulation of AQP4 presents two main challenges. First, *due to the complex architecture of the brain, the concentration of drugs reaching a target region depends on the delivery mode, infusion parameters, drug molecular properties, brain tissue anisotropy and heterogeneity, and anatomical brain geometry of a particular patient.*

Second, it is difficult to quantify the expected change in AQP4 transcript and protein levels after an infusion of a molecular agent. In targeted cells, the degree of AQP4 upregulation depends on how the drug interferes with the transcriptional and translational regulatory mechanism.

This novel approach uses state-of-the-art medical imaging to generate a patient-specific model of the brain, and this *macroscopic organ model is integrated with a microscopic cellular model that describes translational regulation events*. This integrated model can be used for testing specific molecular strategies to enhance transcription or translation based on aqp4 gene regulation and signaling.

Hydrocephalus and expression levels of aquaporin-4

Studies have shown that kaolin-induced hydrocephalic weanling rats show an initial decrease in AQP4 expression in both the periventricular and cortical regions of the brain. The AQP4 level returns to normal level after one week, and rises significantly above normal afterwards.⁴³

The causes for the dynamic response of the AQP4 expression levels remains to be explained.

In many CNS disorders, the osmotic environment changes in the brain due to the secretion of inflammatory cytokines, accumulation of ions, and extravasation of proteins from the cerebral vasculature. *We propose a possible mechanism of translational regulation of AQP4 mRNA transcript* that could be one of the contributing factors for the transient decrease in AQP4 water channels in the initial stages of hydrocephalus.

Proposed translational regulatory mechanism of aquaporin-4 in a single cell

When an osmotic stress is present, the cells exhibit an "osmoprotective response" to repair DNA damage and restore cell volume.⁴⁴

During this stage, the translation of the majority of mRNAs is halted, while the translation of some selected mRNAs is accelerated. The majority of the mRNAs enter storage temporarily until released to rejoin the translation process. A transient decrease in protein levels could be related to the temporary translational inhibition of these mRNAs. Based on the dynamics of mRNA translation and storage, we propose a translational regulatory mechanism of AQP4 mRNA.

In yeast, the *hog1 signaling pathway* is analogous to the p38 mitogen-activated protein kinase (MAPK) pathway. The hog1 pathway controls the production of yeast aquaporin (AQY), the equivalent water channel found in yeast cells. To study the response of the transcriptome to osmotic stress in yeast, the transcript and protein levels after exposure to osmotic stress were quantified in a study by Melamed.⁴⁵

The portion of actively translating AQY mRNAs found in polysomes (association of multiple ribosomes) is compared to the portion of those AQY mRNAs that were not being translated efficiently (with only one ribosome attached or without any ribosome).

After the induction of osmotic stress, the maximum inhibition of translation occurred after approximately one hour. The portion of the mRNAs in the polysomal pool drops from 75% at normal conditions to 10% under osmotic stress conditions.⁴⁵

The translational response to osmotic stress precedes the transcriptional response. The ratio of *translational efficiency* of AQY mRNA in normal and under osmotic stress conditions was evaluated by fractional comparison, see equation (1).

A number greater than 1 indicates the increased translational efficiency of that mRNA during osmotic stress.

A number between 0 and 1 indicates the inhibition of translation for that mRNA during osmotic stress.

The ratio of 0.146 indicates that the mRNA of AQY is translated about 8 times less efficiently during osmotic stress compared to during normal conditions.⁴⁵

$$\frac{\left(\frac{\text{polysome}}{\text{reference mRNA}}\right)_{\text{osmotic stress}}}{\left(\frac{\text{polysome}}{\text{reference mRNA}}\right)_{\text{normal conditions}}} = 0.146 \quad (1)$$

We propose a translational regulatory mechanism for AQP4 in mammalian cells based on the observations in yeast AQY.

Even though there are likely differences in the translational regulatory pathways of mammalian AQP4 and yeast AQY, it is reasonable to expect some similarity. The fate of AQP4 mRNA is described below. After exiting the nucleus, the mRNA is bound to ribosomes, creating a polysome.⁴⁶

The ratio of polysomes versus free mRNAs indicates the translation efficiency. The decapping promoter and enzyme complex (decapping complex) binds to the 5' end of the polysomal mRNA,⁴⁶ removes the poly(A) tail⁴⁷⁻⁴⁸ and recruits the degradation protein complex (Deg) to begin 5' to 3' degradation⁴⁹⁻⁵⁰ as the translational ribosomes fall off.

However, during osmotic stress,⁵¹ the poly(A) tail is instead decapped by the decapping complex.⁴⁷⁻⁴⁸

This complex recruits the binding proteins for the stabilization and storage of AQP4 mRNAs during osmotic stress. These binding proteins bind to the 5' end of the mRNA strand, and prevent the degradation enzymes from degrading the mRNA.

The decapped mRNA-binding protein complex will aggregate into processing bodies (P bodies) in the cytoplasm around the nucleus.^{47-48, 50, 52-54}

The stored mRNA can enter stress granules,⁵⁴⁻⁵⁵ which contains recapping factors like poly(A) protein, poly(A) tail, and translation initiation units (40s).^{48, 55}

The species involved in the proposed translational regulatory mechanisms are described in Table 1.

Based on the proposed mechanism, the dynamic changes in AQP4 transcript and protein levels in mammalian cell is predicted using a system of ordinary differential equations and a stochastic Gillespie algorithm.⁵⁶

Kinetic rates are assigned, and some kinetic rates vary as functions of the osmotic stress to reflect dynamic changes in biochemical reaction rates during the exposure of the cell to osmotic stress.

Figure 2 shows the dynamic evolution of key intracellular species in this proposed translational regulatory system.

In Figure 2 the translation process of AQP4 progressed at a steady rate for the first 1000 seconds (0.278 hour).

When an osmotic stress is introduced at 0.278 hour, the translational dynamics begin to change. First, we observe a rapid accumulation of stored AQP4 mRNA.

The number of AQP4 mRNA in actively translating polysomes decreased from 47 per cell to below 5 per cell, indicating a halt in the translation process, in agreement with observations in yeast cells during osmotic stress.

As a result of this translational inhibition, a decreased expression of AQP4 channels is observed.

Organ-wide expression of aquaporin-4 water channels

A simplified version of the single-cell model described above was integrated with a brain model to generate an organ-wide mapping of AQP4 transcript and protein levels.

Based on the observation that AQP4 expression levels are higher near brain-CSF boundaries, some kinetic rates are made functions of the distance from the location of the cell to nearest brain-CSF interface.

Table 1. Species for aquaporin 4 translatory mechanism

Species	Species Description
Decapped mRNA	Decapped mRNA
Stored mRNA	Stored mRNA
Stress Granules	Stress Granule, consisting of Poly(A) protein and 40s ribosomal proteins
Stress Granules + polyA	Stress Granule with Poly(A) tail
Decapping	Decapping promoter (Dhh1p) and enzymes complex which can recruit either Deg or Binding proteins
polyA	Poly(A) tail, is removed via Dhh1pdec
polyAprotein	Poly(A) tail binding protein, re-attaches Poly(A) tail to decapped mRNA
40s	Translation initiation ribosome, usually resides in Stress granules
Deg	Degradation proteins, degrade thedecapped mRNA from 5' to 3'
Binding proteins	Binding proteins, prevent Deg from binding and degrading mRNA
Polysome	mRNA bound to ribosomes, a translating mRNA complex
mRNA	AQP4 mRNA
Rib	Ribosomes for translation
AQP4	AQP4 water channel

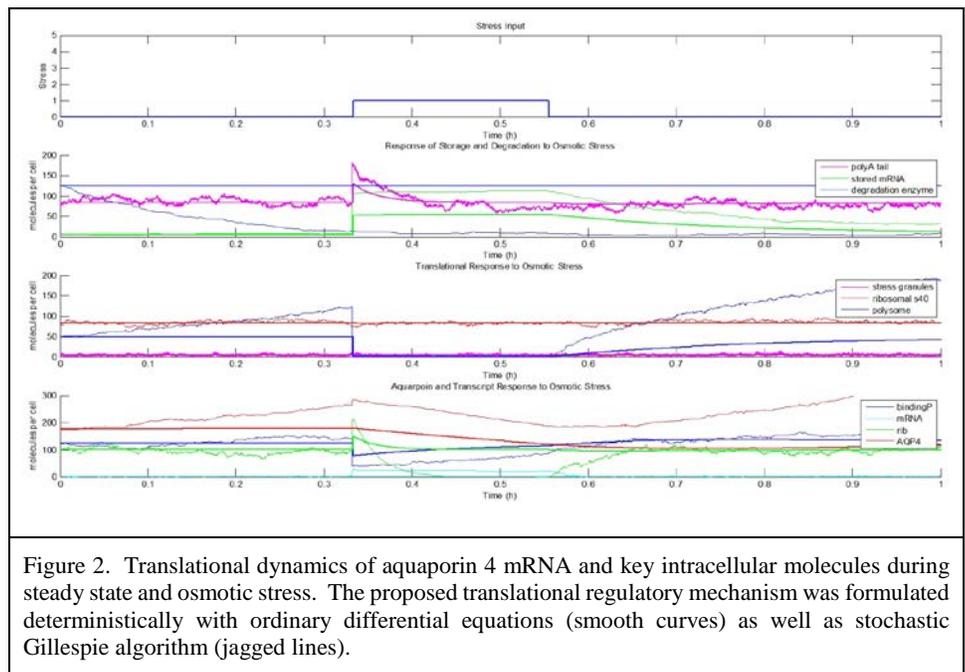


Figure 2. Translational dynamics of aquaporin 4 mRNA and key intracellular molecules during steady state and osmotic stress. The proposed translational regulatory mechanism was formulated deterministically with ordinary differential equations (smooth curves) as well as stochastic Gillespie algorithm (jagged lines).

The predicted levels of AQP4 mRNA transcripts per cell are shown in Figure 3. The computational results shown high density of AQP4 mRNAs around brain-CSF boundaries and periventricular regions as seen in the autoradiography image⁵⁷ in the left panel of Figure 3. The generation of brain-wide gene expression map of AQP4 will accelerate the design of molecular therapies.

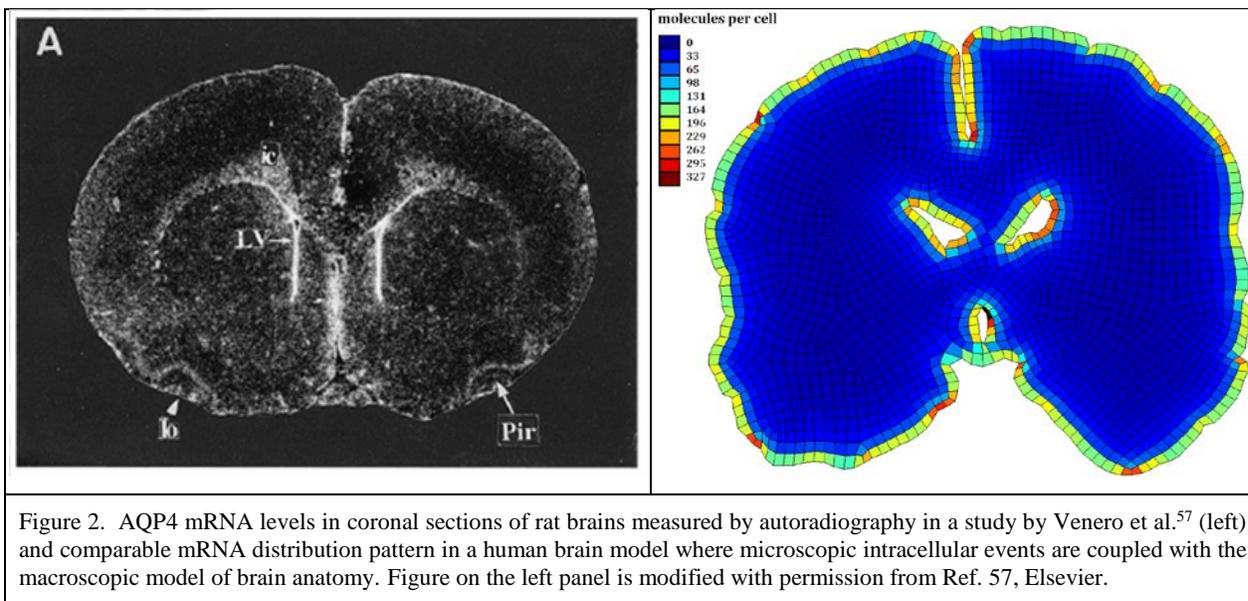


Figure 2. AQP4 mRNA levels in coronal sections of rat brains measured by autoradiography in a study by Venero et al.⁵⁷ (left) and comparable mRNA distribution pattern in a human brain model where microscopic intracellular events are coupled with the macroscopic model of brain anatomy. Figure on the left panel is modified with permission from Ref. 57, Elsevier.

10.8 Case study 2: novel gene silencing therapies for chronic pain

Gene silencing has successfully controlled the expression levels of a desired gene in animal models.

By infusing short-interfering RNA (siRNA), these molecules target a particular messenger RNA (mRNA) through sequence-specific binding, suppressing the final protein.

*The successful down-regulation of NMDA receptors in rats shows promise for treating chronic pain patients with little side effects.*³⁰

Chronic pain is traditionally treated with continuous infusion of morphine, but the severity of side-effects urges clinicians and biomedical engineers to seek novel therapies for pain management.

However, human therapy design often imposes complex *design considerations* such as a precise percent of protein downregulation, the targeting of a particular functional region, side effects in untargeted regions, and stringent requirements on the duration of gene silencing.

Despite the promising results obtained in animal studies, human gene silencing therapies still face major difficulties.

The trial and error approach in animal experiments cannot satisfy these stringent design requirements for clinical implementation of gene silencing therapies. *Incorporating the knowledge of systems biology and the advances in biomedical imaging, the organ-wide quantification of transcription, translation, and protein levels at steady state and after an infusion therapy may offer valuable insights.*

*To bypass the blood brain barrier and reach the brain or spinal cord tissue effectively, siRNAs can be infused into the cerebrospinal fluid (CSF), which surrounds the entire CNS.*³⁰ *After infusion, the biodistribution and reactions of these therapeutic molecules are unknown.* What is the distribution of these molecules along the spine? What percentage of the infused siRNA reached the target tissue? Can we quantify the biochemical interaction of siRNA with the tissue, such as binding, cellular uptake, or enzymatic activation of other intracellular proteins? We will provide quantitative answers to these open questions by incorporating cellular biochemistry with medical imaging of the spine.⁵⁸

Current challenges in designing gene silencing therapies.

The complex geometry of the CNS anatomy complicates drug targeting.

The *target region of gene silencing therapies is usually embedded within multiple tissue compartments*, cellular membranes, which is not easily accessible to siRNA molecules. For example, the NMDA receptors responsible for pain transmission in the spinal cord are mainly expressed in the dorsal horns of the grey matter, a few millimeters away from

the spinal cord surface. *Drugs infused into the spinal canal are rapidly diluted by the pulsating cerebrospinal fluid.*⁵⁹ Once the drugs reach the spinal cord, they are *degraded by enzymes* in the extracellular space or endocytosed by cells.

Achieving an effective concentration of siRNA inside the target cells of an organism poses a major challenge, despite considerable success in downregulating protein levels in cell cultures. Even though novel siRNA targets are being rapidly discovered, *many therapies fail to reach their therapeutic endpoints due to the poor delivery of siRNA to the target region.*

Diffusion barriers and biochemical uptake impede effective siRNA biotransport in vivo. The development of better siRNA vehicles is not sufficient to address all open issues including the scaling of siRNA infusion dose from animal experiments to human application.

The anatomical complexity of the CNS and siRNA bioavailability in target cells are important design considerations for an infusion therapy.

We propose to estimate the availability of siRNA within targeted dorsal horn neurons originally expressing high levels of NMDA receptors.

The *computation of the optimal dosage provides quantitative answers to the complex design considerations.* The knowledge gain from the systematic data driven approach is expected to meet therapeutic endpoints with fewer trial-and-error animal experiments as well as shorter durations and expenditures for clinical trails.

Computation of the intracellular kinetics of siRNA-induced gene silencing

The goal of this therapy is to silence 70% of the pain-transducing NMDA receptors in the target zones of the subject's spinal cord to suppress chronically heightened pain.

We estimate the siRNA infusion concentration that would achieve this precise demand. NMDA receptor down-regulation in the spinal cord is computed for four different siRNA concentrations in the CSF, simulating continuous spinal infusions of siRNA. The continuity (2) and species transport (3) equations compute the biotransport of siRNA.

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho v) = 0 \quad 2$$

$$\frac{\partial}{\partial t} (\rho Y_i) + \nabla \cdot (\rho v Y_i) = -\nabla \cdot J_i + S_i \quad 3$$

The cells in grey and white matter of the spinal cord actively uptake siRNA molecules diffusing in the extracellular space. In cells lacking NMDA receptors and their corresponding mRNA, which therefore are not targets, administered siRNA molecules accumulate without any therapeutic benefit and are merely degraded. Inside the target cells, siRNA initiates the activation of the gene silencing cascades by the binding to an intracellular protein termed RNA-induced-silencing-complex (RISC).

The activated siRNA binds to the NMDA receptor-encoding mRNA with high affinity and specificity. The RISC-siRNA cleaves the bound mRNA, and the translation of the receptor is suppressed for as long as an effective siRNA concentration is present in the cell. These biochemical reactions are computed for extracellular siRNA (4), intracellular siRNA (5), RISC (6), activated RISC-siRNA complex (7), bound RISC-siRNA-mRNA (8), target mRNA (9), and NMDA receptors (10).

$$\frac{\partial C_{\text{siRNAex}}}{\partial t} = -k_1 \cdot C_{\text{siRNAex}} - k_2 \cdot C_{\text{siRNAex}} \quad 4$$

$$\frac{\partial C_{\text{siRNAin}}}{\partial t} = +k_1 \cdot C_{\text{siRNAex}} - k_3 \cdot C_{\text{siRNAin}} \cdot C_{\text{RISC}} \quad 5$$

$$\frac{\partial C_{\text{RISC}}}{\partial t} = P_{\text{RISC}} - k_3 \cdot C_{\text{siRNAin}} \cdot C_{\text{RISC}} + k_6 \cdot C_{\text{RISC-siRNA}} - k_{10} \cdot C_{\text{RISC}} \quad 6$$

$$\frac{\partial C_{\text{RISC-siRNA}}}{\partial t} = k_3 \cdot C_{\text{siRNAin}} \cdot C_{\text{RISC}} - k_4 \cdot C_{\text{RISC-siRNA}} \cdot C_{\text{mRNA}} + k_5 \cdot C_{\text{RISC-siRNA-mRNA}} - k_6 \cdot C_{\text{RISC-siRNA}} \quad 7$$

$$\frac{\partial C_{\text{RISC-siRNA-mRNA}}}{\partial t} = k_4 \cdot C_{\text{RISC-siRNA}} \cdot C_{\text{mRNA}} - k_5 \cdot C_{\text{RISC-siRNA-mRNA}} \quad 8$$

$$\frac{\partial C_{mRNA}}{\partial t} = P_{mRNA} - k_4 \cdot C_{RISC-siRNA} \cdot C_{mRNA} - k_7 \cdot C_{mRNA} - k_8 \cdot C_{mRNA} \tag{9}$$

$$\frac{\partial C_{receptor}}{\partial t} = k_8 \cdot C_{mRNA} - k_9 \cdot C_{receptor} \tag{10}$$

In these equations, C is species concentration; $P_{RISC} = 5 \cdot 10^8$ is the RISC production rate, and $P_{mRNA} = 5 \cdot 10^9$ is the mRNA production rate. Reaction rate constants used (Table 2) were derived from experimental data by Bartlett and Davis.⁶⁰

Table 2. Reaction rate constants for gene silencing mechanisms

	Rate constant	Value and units	Source
k1	Endocytosis rate of siRNA	$1 \cdot 10^{-3} \text{ s}^{-1}$	Estimated
k2	Degradation rate of siRNA	$8.0556 \cdot 10^{-6} \text{ s}^{-1}$	Bartlett
k3	Binding rate of siRNA to RISC	$5.5556 \cdot 10^{-23} \text{ L s}^{-1} \text{ mole}^{-1}$	Bartlett
k4	Binding rate of RISC-siRNA to target mRNA	$3.056 \cdot 10^{10} \text{ L s}^{-1} \text{ mole}^{-1}$	Bartlett
k5	Destruction rate of mRNA by silencing complex	$2 \cdot 10^{-3} \text{ s}^{-1}$	Bartlett
k6	Dissociation rate of siRNA from the silencing complex	$2.7778 \cdot 10^{-13} \text{ s}^{-1}$	Bartlett
k7	Degradation rate of target mRNA	$5.5556 \cdot 10^{-4} \text{ s}^{-1}$	Bartlett
k8	Translation rate of mRNA to mature receptor	$6 \cdot 10^{-2} \text{ s}^{-1}$	Estimated
k9	Degradation rate of receptor	$9.7222 \cdot 10^{-4} \text{ s}^{-1}$	Estimated
k10	Degradation rate of RISC	$5 \cdot 10^{-5} \text{ s}^{-1}$	Estimated

Predicted gene silencing efficiency in the human spinal cord

Prior to siRNA treatment, the NMDA receptors and their encoding mRNAs in the target cells maintain constant levels due to steady synthesis and degradation rates. The number of "cells" per cm^3 is estimated based on the extracellular volume fraction and the average cell volume.

This allows us to *estimate the number of molecules per cell from computed concentrations.*

At steady state, there are 55,543 NMDA receptors and 900 receptor-encoding mRNA per cell.

The quantities of mRNA and protein are within reported range for mammalian genes.⁶¹

As expected, the amount of receptors per cell is much greater than its encoding mRNA,⁶¹ due to translational amplification. Each mRNA transcript is used for translation multiple times before its natural degradation.

After the start of a continuous siRNA infusion, the system in steady state experiences a dynamic transition. siRNA molecules diffuse into the tissue from the spinal cord surface.

Non-specific cellular uptake of siRNA molecules by targeted and untargeted cells occurs along with biotransport. A small amount of siRNA molecules reach the dorsal horns and initiate gene silencing. siRNA concentration inside dorsal horn cells is several orders of magnitude smaller than the infusion concentration due to the diffusion resistance and non-specific cellular uptake.

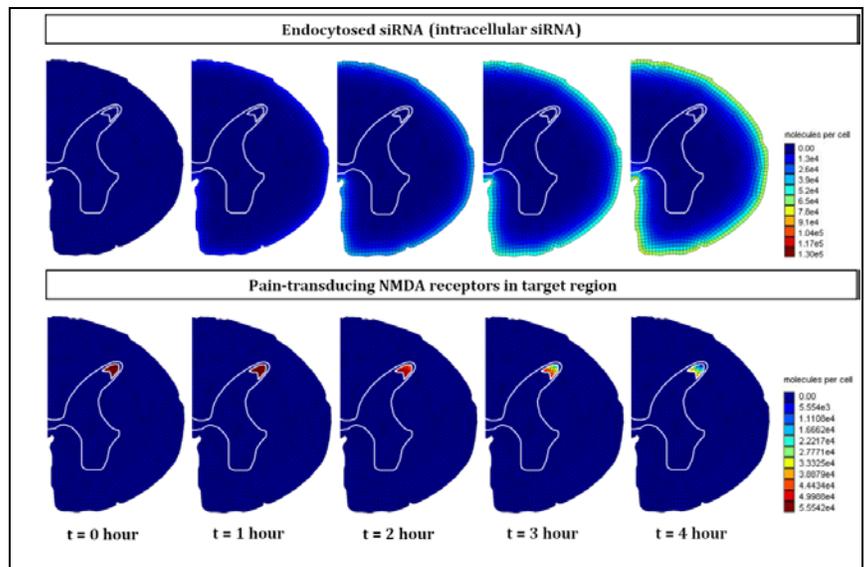


Figure 3. Intracellular siRNA (top) and NMDA receptors in the dorsal horns (bottom) in a cross section of the spinal cord over four hours of continuous siRNA infusion. During continuous infusion at 10^{-6} M , siRNA molecules diffuse and react in the subject's spinal cord. (Top panel) siRNA molecules are uptaken by cells during their diffusion. The final siRNA concentration in the dorsal horns is very small compared to the infusate concentration. This figure shows only the unbound intracellular siRNA, not those bound to RISC and mRNA. Slow diffusion and non-specific uptake of siRNA are principle barriers for effective delivery of siRNA into a targeted region in the CNS. (Bottom panel) gene silencing of pain-transducing NMDA receptors induced by intracellular siRNA molecules in the dorsal horns.

In silico infusion design can estimate the infusion concentration necessary for siRNAs to reach the target zone in sufficient concentration.

Intracellular siRNA in a cross section of the spinal cord is shown for four hours of continuous infusion at the concentration of 10^{-6} M (top panel of Figure 4). The receptor down-regulation in the dorsal horns is shown in the bottom panel (Figure 4).

Four different infusion concentrations were compared for gene silencing efficacy using this patient-specific model. NMDA receptor down-regulation for continuous siRNA infusions into the CSF over 9 hours is shown in Figure 5. After gene silencing, the target receptors were 92.9%, 85.9%, 57.6% and 29.4% of the steady state level for siRNA infusion concentrations of 10^{-7} M, $2 \cdot 10^{-7}$ M, $6 \cdot 10^{-7}$ M and 10^{-6} M, respectively.

The therapy goal of 70% NMDA receptor suppression was met using an injectate with 10^{-6} M siRNA concentration.

Translating single cell dynamics to an organ wide platform

Controlling the expression of disease-related genes in the CNS using gene silencing therapies is the next generation of CNS treatments.

However, *delivering an exact concentration of siRNA molecules to a targeted region in the CNS presents multiple challenges.*

CNS therapy design also poses stringent requirements. For example, a precise percent of protein downregulation may be desired in the target region, while maintaining unaltered protein levels elsewhere.

In many cases, it is not desirable to completely suppress the expression of a target gene, and flexible design platforms for making optimal dosing decisions are necessary.

The use of sub-optimal infusion parameters may cause either no effect on the gene expression or the complete suppression of a gene, leading to unwanted outcomes.

The traditional trial and error animal infusion experiments do not provide quantitative answers for the optimal dosing of a human subject.

This chapter *addresses the challenge of optimal human dosing by integrating medical imaging with systems engineering principles.* siRNA biochemical kinetics coupled with biotransport are fused with subject-specific anatomy to estimate drug action in vivo.

The systematic design of human gene silencing therapies can generate optimal infusion parameters to precisely suppress protein expression levels as desired. Future directions include the coupling of this patient-specific model with spatially distributed kinetic inversion technique for the determination of unknown siRNA reaction parameters.

10.9 Conclusion

The expression level of a gene is controlled by complex intracellular signalling networks, transcriptional and translational regulation mechanisms.

Many therapeutic compounds are being developed to restore the altered cellular signalling in a disease state. Numerous mathematical models in the field of systems biology have quantified cellular signalling and regulation events in normal, disease, and treatment phases.

These studies call attention to the promise of molecular therapies to control and reverse the state of pathological gene expression.

However, a platform for translating the rich knowledge base at the cellular level to organ-wide pharmacokinetics and pharmacodynamics does not exist yet.

How microscopic gene regulatory events acquired from cell culture studies could be incorporated to better molecular therapy design is still unclear.

We have developed and tested an adaptable bioinformatics platform that combines patient-specific anatomical information from medical imaging with microscopic events about gene regulation and control. With this platform,

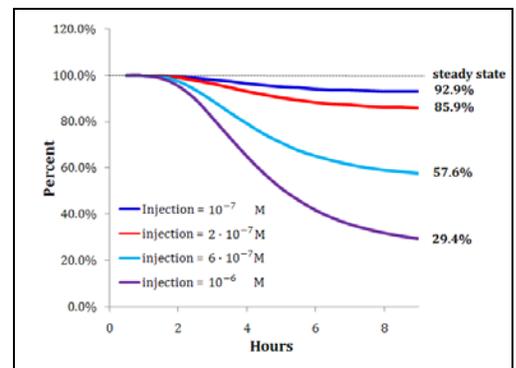


Figure 4. Pain-transducing NMDA receptor down-regulation for 9 hours of continuous siRNA infusion. The infusion concentration of 10^{-6} M induces 70.6% of receptor suppression, which meets the therapy goal.

predictions of gene expression changes using a single-cell model can be transformed into an organ-wide dose-response prediction.

Dynamic changes in protein and transcript levels can be computed in response to disease progression and molecular treatment. The integration of drug biotransport, tissue properties, fluid dynamics, and cellular biochemistry will enable researchers to conduct drug infusion experiments *in silico*, monitor the organ-wide response, and optimize infusion parameters.

Drug-tissue interaction, bioaccumulation, and induced changes of the target gene expression at the transcriptional and translational levels can be computed for the prediction of therapy efficacy *a priori*. With the current pace in quantitative knowledge gain derived from emerging tools in metabolomics, proteomics and genetics, *the predictive power of the proposed multi-scale platform for systematic therapy design is expected to advance personalized medicine at an ever accelerating pace.*

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11 Policy Driven Cloud based Services for Personalized Medicine

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11.1 Key take-aways and call to action

Call to Action

1. Electronic Health Records (EHRs) are nearing petabyte to exabyte size
2. Extracting actionable insights from petabyte to exabyte size EHRs for translational research and personalized health decisions at the point of care is beyond the capability of most healthcare enterprises in the foreseeable
3. Cloud-based healthcare can make meaningful and actionable petabyte to exabyte size EHRs achievable and economically sound
4. Special-purpose architectural design standards for trustworthiness, auditability, and interoperability of cloud-based healthcare is key translational white space
5. Closing the white space gap requires bold cross-disciplinary vertical and horizontal collaboration of public sector, industry and academia

Key takeaways

1. Fund white-space research to accelerate policy-driven development of and migration to cloud-based healthcare
2. Seed cross-disciplinary public-private-university accelerators for cloud-based healthcare innovation

Focus areas

technological, cloud, policy, legal, commercialization, economic value model, adoption, innovation

11.2 Level set

The potential for IT services to support healthcare providers at the point of delivery is tremendous and well established. This is leading to increasing adoption of technologies such as Electronic Health Records (EHR) to capture clinical data including doctors' notes. This migration to EHR is also mandated by the Health Information Technology for Economic and Clinical Health (HITECH'09) act. Data from Radiology and Labs is also increasingly captured in digital formats.

This data presents a trove of information, which when combined with genomic data about a patient can be analyzed and lead to significantly improved and personalized delivery of healthcare.

This data at present is very large in volume running to the order of terabytes. With the increasing adoption of *digitized patient records and physician's notes, it has the potential of reaching peta (10^{15}) or even exa (10^{18}) bytes* of data which in itself will be difficult to manage and analyze.

Further, much of this data is in separate silos, which prevents it from being correlated and analyzed. However, very few providers can afford the infrastructure, both hardware and software, needed to collect, clean, curate, and analyze this data. As such *cloud based healthcare services provide an important technique with which to make analytics driven personalized medicine services available to practitioners at the point of care.* This however raises *serious concerns around patient privacy, and also issues of regulatory compliance,* as the data would reside with the cloud provider and outside of the confines of the physician's control.

In this chapter, we identify the *two broad translational white spaces that exist in the industry today which are slowing down broader adoption of cloud based health care services.* There is *lack of industry-wide standards for healthcare systems stored on the cloud* and this poses the potential danger of organizations becoming dependent on a particular cloud platform and as a result unable to communicate efficiently with other healthcare providers.

Secondly, *significant research is still required to address some of the issues of security and privacy on the cloud platform*. In addition we need to address the data management issues arising from managing ‘big data’ healthcare services that *will require extensive resources not only from the cloud providers but also from network systems that will be transporting the data across stakeholders*. We recommend funding the projects that will address these two specific areas to accelerate the transformation of new discoveries in translational research to the practice of Personalized Medicine.

11.3 State of Art in Healthcare Systems

Majority of healthcare providers today maintain Electronic Medical Records (EMRs) detailing the medical history of their patients including visit information. While most providers purchase EMR systems as pre-packaged software applications, a significant number of them use proprietary or home grown systems to track their patients’ records. Electronic records shared between different EMR systems are called Electronic Health Records (EHRs). At present interoperability and sharing among different EMRs is very limited. Cost and poor usability are major obstacles to adoption of EHR. Personal Health Record (PHR) is the health record that is initiated and maintained by an individual. It includes summary of EMR and EHR.

Figure 1 illustrates the relation between the patient data stored by the three categories of health/medical records.

In addition to EHR systems, hospitals also use other information systems to efficiently manage their functions. Picture archiving and communication system (PACS) systems are used to manage the medical digital images. The universal format for PACS image storage and transfer is DICOM (Digital Imaging and Communications in Medicine). PACS primarily consist of Imaging modalities (such as X-ray, CT, MRI etc.), secured network for the transmission of patient information, workstations for interpreting and reviewing images and archives for the storage and retrieval of images and reports. Healthcare providers also use applications like Hospital information system (HIS) and Radiology Information System (RIS).

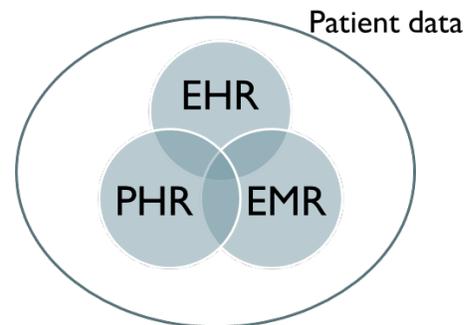


Figure 1: Relation between data stored in a EHR, EMR and PHR systems

Per *Certification Commission for Healthcare Information Technology (CCHIT)*, the following electronic medical IT systems are currently being offered in the market:

- Electronic Health Records (EHRs)
- Electronic Medical Records (EMRs)
- Personal Health Records (PHRs)
- Payer-based Health Records (PBHRs)
- Electronic Prescribing (E-prescribing)
- Medical Financial Billing/Administrative System
- Computerized Practitioner Order Entry (CPOE) Systems

The Health Information Technology for Economic and Clinical Health (HITECH) Act was enacted in 2009 to promote the adoption and meaningful use of health information technology 1. It authorized incentive payments through Medicare and Medicaid to clinicians and hospitals when they use Electronic Health Records (EHRs) privately and securely to achieve specified improvements in care delivery.

Equally important, HITECH's goal is not adoption alone but “meaningful use” of EHRs 2 - that is, their use by providers to achieve significant improvements in care. The legislation ties payments specifically to the achievement of advances in health care processes and outcomes.

11.4 Cloud based Healthcare systems

Cloud Computing is the latest paradigm for delivering IT resources or applications as ‘services’ to consumers. Cloud service/applications are stored and executed on remote provider-maintained platforms (called cloud) and accessed by

consumers via the Internet using computers or mobile devices. *Cloud based services can provide analytics driven personalized medicine services which will be available to practitioners at the point of care.*

Instances of Cloud based Healthcare Services include cloud based PACS, cloud based EHR systems (like CareCloud), cloud based Medical billing services, etc. According to industry experts, vendors will continue to develop cloud databases and supercomputers, such as *IBM Watson 9*, to store and process large volumes of "big data" and allow doctors to use this information to personalize medical treatments. In another instance of using Cloud for personalized medicine, Dell has recently donated its cloud infrastructure to Translational Genomics Research Institute (TGen) to store data for the world's first personalized medicine trial for pediatric cancer 9.

The *main advantages in using cloud based healthcare services* include

- Cloud services make *data and computing capabilities portable, sharable, and accessible* from any online device which meet the key objective of the HITECH Act.
- Cloud computing provides significant *cost savings and the option of avoiding capital investment* in IT Resources for organizations.
- *Elasticity enables cloud providers to easily scale up or scale down* their resources instantly and on-demand.
- Cloud services are *OS-neutral, and usually easy to use.*

Some of the open *challenges in using cloud computing for healthcare* systems include

- Concerns about service data security and patient privacy related to the issue of *trustworthiness* of the cloud provider, and also in case the cloud provider is attacked by hackers.
- *Auditing* cloud data is challenging since it resides on machines spanned across large geographical area.
- Compliance and *legal* issues: Issues of regulatory compliance.
- *Provider reliability* is a key concern for many cloud users, especially the risk that a provider can go out of business with very short notice.

11.5 Architecture of cloud Healthcare systems

Hospitals and healthcare providers currently manage patient information in various formats and by using various systems. They manage imaging data, Hospital Information Systems (HIS), Radiology Information Systems (RIS) and possibly a genomic database of their patients. In addition, real time sensors and data from collaborating medical teams can also provide critical information which when combined with a patient's genomic data can determine the best treatment option.

At present all this information is stored in separate silos and requires complex interaction between the different IT systems managing it. By using cloud based services and migrating this data to the cloud, hospitals and healthcare providers can more efficiently share patient data across their teams and with other hospitals and healthcare providers and other online medical communities. Organizations can also make data in the public domain more easily available via a cloud service. Figure 2 illustrates this architecture of a cloud based healthcare system.

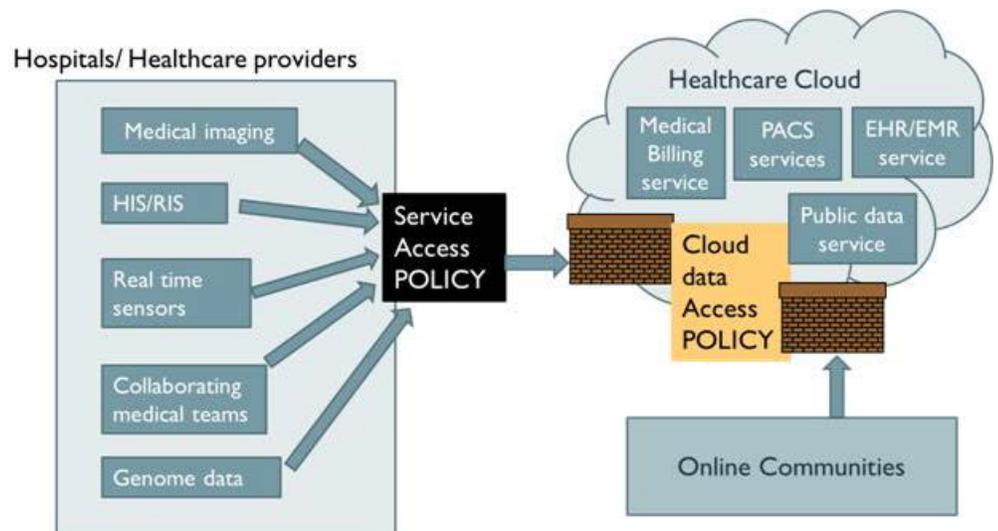


Figure 2: Healthcare Services on the Cloud

To successfully migrate IT systems to the cloud, healthcare organizations need to determine their enterprise policies regarding their data and systems. These policies fall in two broad areas – one is the *Service Access Policy* and the other is the *Cloud data Access policy*.

The former identifies who within their organization can access what systems and at what level, while the latter is the organization's policy regarding external individuals and organizations that can access their data. For instance, Service Access Policy may restrict real time sensor data only to hospital's emergency room (ER) staff or Cloud data access policy of a hospital may restrict access of patient data to the patient and his/her primary physician.

11.6 Policy driven cloud services

We believe that a semantically rich, policy-based framework can be used to automate acquisition of cloud based services. *We have developed a methodology which integrates all the processes and data flows that are needed to automatically procure, consume, and manage services on the cloud.* We divide this *IT service lifecycle on a cloud into five phases.* In sequential order of execution, they are requirements, discovery, negotiation, composition, and consumption. We have described these phases in detail in 3 .

When procuring healthcare services from a Cloud provider, consumers should clearly identify the key policies that the Cloud service should comply with. For instance, a mandatory policy requirement will be that the service should be HIPAA (Health Insurance Portability and Accountability Act) compliant. On the other hand, a flexible policy would be the service maintenance support needed which could be negotiable.

NIST 5 has identified three main Cloud Service Model - Software as a Service (SaaS), Platform as a Service (PaaS) and Infrastructure as a Service (IaaS). Most organizations acquiring cloud based EHR systems will go with the SaaS model. NIST has also identified four types of Cloud Deployment - Public, Private, Hybrid and Community – that determine who can access the cloud data. A community cloud or hybrid cloud deployment will best suit the HITECH act requirement of sharing of EHR across various hospitals and healthcare organizations.

Some other factors to consider for Service's security policy are listed below. Zhang and Liu 6 have described a security reference model specific to EHRs.

- [1] Control level needed over the cloud operating systems, hardware, and software.
- [2] User, resource, and data requests threshold policies
- [3] Whether cloud provider is internal within an organization-controlled data center or hosted externally.
- [4] Compliance requirement for healthcare domain – for instance mandatory HIPAA compliance.
- [5] Cloud Data Policies
 - a. Data/Cloud Location - US, Europe, Global
 - b. Data Deletion - archive / or secure wipe
 - c. Data Encryption
- [6] Cloud Privacy policy
 - a. Patient Data access across services, across consumers
 - b. Virtual Machine Separation
 - c. Controlled multi-tenancy

11.7 Research Issues

We list the major open issues that have to be addressed by the research community to encourage more healthcare providers to adopt EHR systems and use cloud based IT services.

Industry standards and Policies

There is a *lack of industry-wide standards for healthcare systems stored on the cloud* and this poses the potential danger of organizations becoming dependent on a particular cloud platform and as a result unable to communicate efficiently with other healthcare providers. National Institute of Standards and Technology (NIST) has released a special publication 800-145 7 defining cloud computing as a model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g., networks, servers, storage, applications, and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction. We recommend that the Health industry also adopt this standard for cloud solutions they adopt. The Healthcare industry has to also determine the standard security and compliances policies that cloud providers should adhere to.

Big Data Management

Medical data at present is very large in volume running to the order of terabytes (10^{12} bytes). *With the increasing adoption of digitized patient records and physician's notes, it has the potential of reaching peta (10¹⁵) or even exa (10¹⁸) bytes of data that in itself will be difficult to manage and analyze.*

Medical Data currently resides in separate silos, which prevents it from being correlated and analyzed. Few providers can afford the infrastructure, both hardware and software, needed to collect, clean, curate, and analyze this data.

Cloud Security and Privacy

Cloud computing allows multi-tenancy and multiple instantiations of the same service. While these enable cost savings for the consumers, *significant research is still required to address some of the issues of security and privacy that arise because of these features*. Auditing cloud data is a challenge since unlike traditional systems, cloud data resides on servers spanned across large geographical area. *Standards for auditing cloud providers and cloud data that will be acceptable to the Healthcare industry have to still be developed*.

11.8 Conclusion

With the mandate of HITECH'09 we anticipate a significant increase in adoption of cloud based IT services for Personalized Medicine. Apart from being more cost effective, this technology will make it easier for physicians and hospitals to collaborate and provide the best treatment to their patients. *To ensure rapid adoption of this new technology*, open issues like cloud data privacy and security, big data management will need to be addressed. Additionally, healthcare organizations will need to articulate and determine policies and standards for Health IT services hosted on cloud by varied service providers.

Additionally, we are nearing petabyte to exabyte EHRs and extracting value from such big data is and will be beyond the capability of most healthcare enterprises. Key translational white spaces will include trustworthiness, auditability, interoperability, architectural design standards of cloud-based healthcare. We need vertical and horizontal collaboration of public sector, industry and academia for making boldly meaningful and economically sound progress towards cloud-based healthcare.

We recommend two main calls for action firstly funding white-space research to accelerate policy-driven development of and migration to cloud-based healthcare and secondly seeding cross-disciplinary public-private-university accelerators for cloud-based healthcare innovation.

11.9 References

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12 To Patent or Not To Patent Personalized Medicine?

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12.1 Key take-aways and call to Action

Key take-aways

1. Patentability in the field of personalized medicine is controversial
2. Patent protection is key for personalized medicine to innovate Vs. allowing patent rights in these types of inventions will remove scientific information from the “storehouse of knowledge” and slow scientific discovery.
3. Physicians have ethical obligation to share medical knowledge with other physicians and their patients
4. Process that incorporates laws of nature – “truth about the physical world” - is not patentable Vs. all inventions can be reduced to a law of nature
5. The market was divided on this topic
6. Adjusting patent law to suit one particular field could have a huge unforeseen impact on another field

Call to Action

1. Fund interdisciplinary global R&D Center to conduct ongoing white-space R&D, provide education, and offer expert insights on emerging intellectual property issues pertaining to personalized medicine in partnership between academia, private sector, and governments.
2. Fund white-space R&D to develop personalized medicine value model to inform policy, research, and patient care decision

Focus areas

Intellectual Property, commercialization, managing innovation

12.2 Level set

The subject of *patent-eligible subject matter in the field of personalized medicine has become a hot button issue* in the last few years. This issue was recently thrust into the national spotlight when the U.S. Supreme Court took the Mayo Collaborative Services vs. Prometheus Laboratories, Inc. landmark case. The primary point of contention in this particular case was *the argument whether or not biological methods that measure metabolites in the blood after the administration of a drug to a patient’s body is patent-eligible.*¹⁰⁴

12.3 The landmark case of Mayo Clinic v. Prometheus

Prometheus requested and was granted a patent for a metabolite test called the Prometheus ProPredict test. The test measured the correlation between the metabolites in a patient’s body after the administration of a particular drug. Mayo purchased the test from Prometheus and used it for five years. Eventually, Mayo started to produce and market its own metabolite test which it considered to be a more accurate and cheaper alternative to the Prometheus test. Consequently, *Prometheus sued Mayo for patent infringement.*¹⁰⁵

Mayo and its proponents make the *argument that the metabolite test is, at its core, a natural phenomenon, therefore making it patent-ineligible.*

They claim that *making naturally occurring medical phenomenon patent-eligible could potentially stifle a doctor’s right to make appropriate healthcare decisions for their patients.* Mayo proponents include medical industry heavy weights such as the American Medical Association, medical technology companies, and other major health care associations.¹⁰⁶

¹⁰⁴ Coltart-Giordano, Jennifer. “Gene Patenting and Biological Methods in the Personalized Medicine Space.”

¹⁰⁵ Walsh, Mark. “Patents and Patients: Personalized Medicine is at the Heart of High Court Case.”

¹⁰⁶ Walsh, Mark. “Patents and Patients: Personalized Medicine is at the Heart of High Court Case.”

Prometheus supporters argue that *patent protection is necessary for the personalized medicine industry to continue to flourish*. They also claim that patent protection can *ultimately result in more innovation* and the commercialization of new pharmaceutical products and technologies *thus making personalized medicine accessible to everyone*.

On December 7, 2011 the Supreme Court heard oral arguments for the Mayo v. Prometheus case and on March 20, 2012 the Court issued its opinion on the case. In a unanimous vote the *Supreme Court made the following ruling*: “The *process* patent that Prometheus Laboratories had obtained *for correlations between blood test results and patient health is not eligible for a patent because it incorporates laws of nature*.”¹⁰⁷ This decision will have long term and far reaching effects on the healthcare industry as a whole as well as the personalized medicine field. For purposes of this *landmark case, we have provided a detailed legal analysis* for this publication.

12.4 Setting for the Prometheus decision

The *subject matter eligibility of a type of process patents lie at the heart of the conflict* in Mayo v. Prometheus. Prior to Mayo v. Prometheus, the Supreme Court addressed the subject matter eligibility of process patents in *Bilski v. Kappos*.¹⁰⁸ In *Bilski*, the Supreme Court upheld the subject matter eligibility of business method patents and found that the *machine-or-transformation test was not the exclusive test to determine the subject matter eligibility of process claims*.¹⁰⁹ This finding essentially destroyed the test used to determine the patent eligibility of process claims and left this area of patent law unclear.¹¹⁰ The patent community hoped that the Mayo v. Prometheus decision would shed light on the patent eligibility of process claims.

12.5 Stances taken prior to the Prometheus decision by different members of the industry

The patents at issue in *Prometheus v. Mayo* cover a method of treating gastrointestinal autoimmune diseases using thiopurines.¹¹¹ After the thiopurines are administered to a patient, *the thiopurine compounds are converted into biochemically active metabolites inside the patient's body*.¹¹² The thiopurine metabolites suppress the patient's immune system to alleviate symptoms.¹¹³ Autoimmune diseases that can be treated by thiopurine therapy include Crohn's disease, ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.¹¹⁴ *A method to determine the concentration of thiopurine metabolites in the patient's blood is necessary*; high levels of thiopurine metabolites are toxic, and low levels of the metabolites will not alleviate the patient's symptoms.¹¹⁵

Prometheus Laboratories is the sole licensee of patents 6,355,623 ('623) and 6,680,302 ('302).¹¹⁶ These patents cover a method of administering thiopurines to patients and determining the concentration of thiopurine metabolites in the patient's blood.¹¹⁷ *Using these patent rights, Prometheus developed the ProPredict test*.¹¹⁸ Mayo Clinic purchased the ProPredict test, and regularly used it between 1999 and 2007.¹¹⁹ During that time, *Mayo developed its own method of treating autoimmune diseases using a different effective range of metabolite concentrations* in the blood.¹²⁰ When Mayo announced that it was going to begin selling its own test to determine toxicity levels Prometheus sued Mayo for patent infringement.¹²¹

12.6 Prior history:

After Prometheus filed suit against Mayo for patent infringement, Mayo filed a motion for summary judgment, arguing that the Prometheus patents were invalid.¹²² The district court in the Southern District of California found in favor of

¹⁰⁷ <http://www.scotusblog.com/case-files/cases/mayo-collaborative-services-v-prometheus-laboratories-inc/>

¹⁰⁸ See *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

¹⁰⁹ *Id.*

¹¹⁰ Sue Ann Mota, *The Times They Are A' Changin': Bilski v. Kappos, Global Tech v. Seb, Standord V. Roche, and Microsoft V. I4I*, 16 J. Tech. L. & Pol'y 257, 261 (stating “[a]fter *Bilski*, abstract patent claims apparently remain non-patentable, but it is unclear where the line is drawn and which test is to be used.”).

¹¹¹ See U.S. Patent No. 6,355,623 (filed Apr. 8, 1999). See also U.S. patent No. 6,680,302 (filed Dec. 27, 2001).

¹¹² See U.S. Patent No. 6,355,623 (filed Apr. 8, 1999). See also U.S. patent No. 6,680,302 (filed Dec. 27, 2001).

¹¹³ See U.S. Patent No. 6,355,623 (filed Apr. 8, 1999).

¹¹⁴ *Id.*

¹¹⁵ *Id.* See also Brief for Respondent at 2 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S.Ct. 1289 (2012) (No. 10-1150).

¹¹⁶ See Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289, 1290 (2012).

¹¹⁷ See U.S. Patent No. 6,355,623 (filed Apr. 8, 1999). See also U.S. patent No. 6,680,302 (filed Dec. 27, 2001).

¹¹⁸ Brief for Respondent at 9 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S.Ct. 1289 (2012) (No. 10-1150).

¹¹⁹ Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289, 1295 (2012).

¹²⁰ *Id.* at 1296.

¹²¹ *Id.*

¹²² *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 2008 WL 878910 (S.D. Cal. 2008).

Mayo and invalidated the Prometheus patents.¹²³ On appeal, the Federal Circuit applied the machine-or-transformation test, reversed the decision of the lower court, and found in favor of Prometheus.¹²⁴ Mayo filed a petition for certiorari, the Supreme Court granted the petition, vacated the Federal Circuit's judgment, and remanded the case back to the Federal Circuit to be determined consistently with the Court's holding in *Bilski v. Kappos*.¹²⁵ Once again, the Federal Circuit upheld the validity of the Prometheus patent.¹²⁶ The Supreme Court granted certiorari again and held that both of Prometheus's patents were invalid.¹²⁷

12.7 Amicus Briefs

Twenty-eight groups submitted amicus briefs to the Supreme Court in an attempt to impact the decision of the Court. Seven groups filed amicus briefs on behalf of Mayo Laboratories, fifteen groups filed briefs on behalf of Prometheus, and six groups filed briefs on behalf of neither party. Some of the Amicus briefs were filed jointly.

Prometheus's position found much more support than Mayo's in the biotechnology and personalized medicine industry.

Amicus Brief: information offered to assist a court in deciding a matter before it by someone who is not a party to the case ("amicus curiae"; latin "friend of the court"). The decision on whether to admit the information is at the discretion of the court (adapted from Wikipedia)

Both sides of the debate as well as the independent group raise important policy considerations.

In support of Mayo's position:

- American College of Medical Genetics,
- American Medical Association
- American Hospital Association
- American Society of Human Genetics
- Association of American Medical Colleges
- Association for Molecular Pathology
- Association of Professors of Human and Medical Genetics
- College of American Pathologists
- Florida Hospital Association
- Minnesota Hospital Association
- Minnesota Medical Association
- Verizon Communications
- Hewlett Packard
- CATO Institute
- Arup Laboratories
- Laboratory Corporation of America,
- ACLU
- AARP
- Public Patent Foundation

In support of Prometheus's position:

- SAP America
- Pharmaceutical Research and Manufacturers of America
- Myriad Genetics, Biotechnology Organization
- Association of University Technology Managers
- American Intellectual Property Law Association
- Juhasz Law Firm
- National Venture Capital Association
- Intellectual Property Law Association of Chicago
- Intellectual Property Amicus Brief Clinic of the UNH School of Law
- Health Law
- Policy and Ethics Scholars
- Genomic Health Inc. et al.
- Brief for Connect
- San Diego Intellectual Property Law Association
- Novartis Corporation
- Intellectual Property Owners Association

¹²³ *Id.*

¹²⁴ *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 581 f.3d 1336 (Fed. Cir. 2009).

¹²⁵ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 130 S.Ct. 3543 (2010).

¹²⁶ *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 628 F.3d 1347 (Fed. Cir. 2010).

¹²⁷ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012).

The main arguments made by proponents of Mayo's position focus on the *negative impact that patents on treatment methods would have on the cost and quality of medical care*.¹²⁸ Mayo's allies also argue that allowing Prometheus's patents to stand would aid the growth of a patent thicket that stifles innovation.¹²⁹

Proponents of Prometheus's position *argue that not allowing patents similar to the Prometheus patents to stand would destroy the personalized medicine industry and slow innovation*.¹³⁰

12.8 The Cato Institute

The Cato Institute is one organization that has weighed in in favor of Mayo's position. Cato's brief argues against allowing abstract method patents to stand as patent eligible subject matter because strong patent protection may actually hinder innovation and *discourage investment in new technologies in most industries*.¹³¹ Cato's brief argues that allowing method patents to stand has negatively impacted the software industry and allowed for the development of a patent thicket.¹³²

This *patent thicket formed because it is impractical for companies to license all the patent rights necessary to create a non-infringing product*.¹³³

After a lengthy discussion of the impact of the patent thicket on the business habits of different software companies, Cato's brief discusses the problems that *process patents introduce into the medical and healthcare industries*.¹³⁴ Allowing patents to exist on abstract processes, Cato Argues, *constantly puts researchers and healthcare providers at risk for patent infringement lawsuits*.¹³⁵ To avoid such lawsuits, research and *healthcare institutions must constantly monitor the patent landscape to determine if the diagnostic method they are using violates any patents*.¹³⁶ Cato then makes the argument that a researcher's previously non-infringing activity could be transformed into patent infringement if the researcher later became acquainted with the method disclosed in Prometheus's patents.¹³⁷

Additionally Cato argues that the potential for a patent thicket to arise in the medical community similar to the patent thicket in the software community is high.¹³⁸

This is possible because *many small companies may discover diagnostic methods and obtain patents*.¹³⁹ Cato states that diversity of patent ownership combined with a high volume of patents in a particular field may result in *near-constant accidental infringement by parties that are unaware of existing patent rights*.¹⁴⁰

In addition to this concern, the patenting of medical diagnostic tools may prevent doctors from using their best judgment when treating patients and divert the doctor's resources to ensuring that they are not infringing any patents.¹⁴¹ Cato argues that the cost of this practice will lead to an increase in healthcare costs and *asks the court to consider the human cost of allowing such patents to exist*.¹⁴²

Independent position:

- International Association for the Protection of Intellectual Property
- United States of America
- Roche Molecular Systems
- New York Intellectual Property Law Association
- Microsoft
- EMC Corporation
- Intel Corporation
- Association Internationale Pour La Protection

¹²⁸ See generally *Id.*

¹²⁹ See generally Brief for Amici Curiae Cato Institute et al. in Support of Petitioners Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

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¹³¹ See Brief for Amici Curiae Cato Institute et al. in Support of Petitioners at 16 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹³² *Id.*

¹³³ *Id.* at 18-20.

¹³⁴ *Id.* at 24.

¹³⁵ *Id.*

¹³⁶ *Id.*

¹³⁷ *Id.* at 25.

¹³⁸ *Id.*

¹³⁹ *Id.*

¹⁴⁰ *Id.*

¹⁴¹ *Id.* at 26.

¹⁴² *Id.* at 32.

12.9 Arup Laboratories

Arup Laboratories also filed an amicus brief on behalf of Mayo.¹⁴³ Arup's brief focuses on the impact that method patents similar may have on biomedical research.¹⁴⁴ First, Arup takes the position that the Prometheus patents cover unpatentable subject matter because the *patents claim natural phenomena*.¹⁴⁵ Arup argues that research depends on the ability to build upon the research of others, and to allow ownership in the subject matter covered by Prometheus's patents would *negatively impact research by preventing others from using the patented information for further medical research*.¹⁴⁶

*Allowing patent rights in these types of inventions will slow scientific discovery because it will result in removing information from the "storehouse of knowledge."*¹⁴⁷

12.10 American College of Medical Genetics ("ACMG")

The brief filed by the American College of Medical Genetics ("ACMG") in conjunction with other medical organizations most clearly identifies the negative impact that method patents may have on medical treatment.¹⁴⁸ The main policy argument made by the ACMG focuses on the *impact that patents may have on health care policy*.¹⁴⁹

ACMG breaks its argument up into three different sub-arguments: 1) the concerns that these types of patents raise for physicians, 2) the impact that these patents may have on patient care and laboratory testing, and 3) the potential for these types of patents to stifle innovation.¹⁵⁰

ACMG characterizes the Prometheus patents as claiming a "scientific observation" stating, "[t]he patents at issue here give Prometheus exclusive private ownership not of a new drug, a new diagnostic test, or even a new method of diagnosing a particular disease. Rather, the patents at issue effectively award Prometheus *exclusive ownership of a pre-existing diagnostic test based on the mere observation of a naturally-occurring phenomenon*,".¹⁵¹ Allowing a patent of this nature to exist, the ACMG brief argues, will erode the quality of healthcare, stifle innovation, and place physicians in an ethically gray area.¹⁵²

The first argument that ACMG makes focuses on the ethical concerns that a physician may face because of the Prometheus patents.¹⁵³ *Physicians have an ethical obligation to share medical knowledge with other physicians and patients*.¹⁵⁴

Allowing patent laws to exist in scientific observations restricts information that physicians may use while treating patients and creating new treatments.¹⁵⁵ Because of this practice, allowing patent rights to exist in this type of information undermines the ethical practice of medicine.¹⁵⁶ Additionally, *Physicians are required to use the most recent information when treating patients*.¹⁵⁷ The treatment claimed by Prometheus is necessary for Physicians to provide satisfactory medical care for patients receiving thiopurine therapy.

Next, ACMG alleges that the quality of patient care will be eroded because of the threat of infringing the Prometheus patents.¹⁵⁸ ACMG argues "quality patient care demands that a physician consider test results in light of, among other things, current medical knowledge."¹⁵⁹ ACMG claims that the Prometheus *patents can be infringed by a doctor by just thinking about the correlation between thiopurine drugs and metabolite concentration*, and that this holds true even if the doctor ordered a metabolite test for reasons unrelated to the Prometheus test.¹⁶⁰

¹⁴³ See generally Brief for Arup Laboratories et al. as Amici Curiae in Support of Petitioners Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹⁴⁴ *Id.* at 11.

¹⁴⁵ *Id.*

¹⁴⁶ *Id.* at 12-13.

¹⁴⁷ *Id.* at 15-21.

¹⁴⁸ See generally Brief for American College of Medical Genetics, The American Medical Association, The Association of Professors of Human and Medical Genetics, The Association for Molecular Pathologists, and The Association of American Medical Colleges in Support of Petitioners at 8 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹⁴⁹ *Id.*

¹⁵⁰ *Id.*

¹⁵¹ *Id.*

¹⁵² *Id.*

¹⁵³ *Id.* at 9.

¹⁵⁴ *Id.*

¹⁵⁵ *Id.* at 10.

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

¹⁵⁸ *Id.* at 11.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.*

*A physician that learns of this correlation, must ignore the existence the correlation to treat patients in order to avoid patent infringement.*¹⁶¹ This may also lead laboratories to induce infringement by informing a physician of the correlation.¹⁶²

ACMG's third argument focuses on the potential for the Prometheus patents to stifle innovation.¹⁶³ Scientific facts, ACMG argues, free for all to use.¹⁶⁴ According to ACMG, easy access to basic facts, like relationship between thiopurine drugs and metabolite concentration, are essential for scientific progress.¹⁶⁵ Patents similar to the Prometheus patents, ACMG argues, threaten to slow innovation instead of aid it.¹⁶⁶ *Patents are not needed to incentivize the study of personalized medicine* because scientists and academic researchers in the field are motivated by their curiosity and ambition to engage in innovation.¹⁶⁷ Additionally, ACMG believes that patents are not necessary because the cost to develop this technology is low.¹⁶⁸

The proponents of Prometheus's patents have taken a different policy stance in the amicus briefs with the Court. Arguments in favor of Prometheus's patents focus on the necessity of patents for innovation, the impact that banning these types of patents would have on personalized medicine, the status of medical patents and the impact that not allowing patents in personalized medicine will have on patient care and public health.

12.11 Pharmaceutical Research and Manufacturers of America ("PhRMA")

The brief filed by Pharmaceutical Research and Manufacturers of America ("PhRMA") is primarily concerned with the importance of patent protection available to medical processes.¹⁶⁹

PhRMA's brief first emphasizes the *long history of medical patents and how patent protection has spurred innovation in medicine.*¹⁷⁰ PhRMA argues that *patent protection for medical inventions provides incentive for inventors to engage in expensive research and development.*¹⁷¹

The very practice of personalized medicine depends upon correlations similar to those found in the Prometheus patents, and invalidating the Prometheus patents would strip patent eligibility from many future breakthroughs in personalized medicine.¹⁷²

Without patent protection available as an incentive for innovation, PhRMA argues, it is likely that *innovation in personalized medicine will drastically slow.*¹⁷³

The process for *discovering new uses for existing drugs and for personalized medicine is expensive, and must pass many regulatory standards*, including obtaining FDA approval.¹⁷⁴ This is time consuming and expensive, and without the promise of patent protection companies may not choose to undergo the process of developing these breakthroughs.¹⁷⁵ PhRMA also attacks the assertion that academic research is harmed by patent protection on medical processes.¹⁷⁶ *According to PhRMA, patent protection does not slow academic research.*¹⁷⁷

In fact, PhRMA argues that *the disclosure required to obtain patent protection actually helps to encourage progress.*¹⁷⁸

¹⁶¹ *Id.*

¹⁶² *Id.*

¹⁶³ *Id.* at 13.

¹⁶⁴ *Id.*

¹⁶⁵ *Id.*

¹⁶⁶ *Id.* at 14.

¹⁶⁷ *Id.* at 14-15.

¹⁶⁸ *Id.* at 15.

¹⁶⁹ Brief of Pharmaceutical Research and Manufacturers of America as Amicus Curiae in Support of Respondent at 13 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹⁷⁰ *Id.*

¹⁷¹ *Id.* at 16.

¹⁷² *Id.*

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 22.

¹⁷⁵ *Id.* at 24.

¹⁷⁶ *Id.*

¹⁷⁷ *Id.* at 25.

¹⁷⁸ *Id.* at 26.

12.12 Myriad Genetics

Comparing and contrasting personalized medicine and the pharmaceutical industry, Myriad Genetics also rushed to the defense of Prometheus.¹⁷⁹ Myriad's main argument focuses on the dependence of the personalized medicine industry on the promise of strong patent protection.¹⁸⁰

Myriad compares the cost of research and development of personalized medicine to the cost of research and development in the pharmaceutical industry, saying “[m]uch like in the pharmaceutical industry, personalized medicine research and development are extremely costly and offer a very low rate of success.”¹⁸¹ Myriad especially emphasizes the *high cost barriers that exist when bringing a new product to market in personalized medicine*.¹⁸²

First, Myriad states, *clinical trials for hundreds or thousands of samples are necessary to gather data for thousands of molecular markers*.¹⁸³ Following that, scientists must analyze the data to determine whether a correlation exists between the molecular markers and a particular disease.¹⁸⁴ Usually, *more clinical trials are required to ensure that an actual correlation exists between the molecular marker and the disease*.¹⁸⁵ The cost to perform these trials is high, and more frequently these products fail than succeed.¹⁸⁶

In this way, Myriad argues, the personalized medicine industry is similar to the pharmaceutical industry.¹⁸⁷

The differences between the pharmaceutical industry and personalized medicine are also important points discussed in Myriad's brief.¹⁸⁸

The low ultimate payoff of investments in the personalized medicine industry is a major difference between the personalized medicine and pharmaceutical industries.¹⁸⁹ This is because patients only need to be tested a single time to determine if they possess certain biological markers.¹⁹⁰

Another difference between pharmaceuticals and personalized medicine lies in the broadness of the patent claims required to support the two industries.¹⁹¹

Myriad broad claims in patents for personalized medicine are required due to the lack of a regulatory agency that oversees genetic diagnostic tests.¹⁹² This broadness is necessary to prevent the easy circumvention of patents on personalized medicine inventions.¹⁹³

Myriad points to the huge cost that investors have to shoulder to perform this type of research, and that these investors have undertaken this burden with the intention of securing patent protection to recoup losses.¹⁹⁴ The patenting of correlations is the only protection that innovations in personalized medicine can receive, so it is essential to the future of the industry that these inventions remain eligible for patent protection.¹⁹⁵

12.13 The National Venture Capital Association (“NVCA”)

The National Venture Capital Association (“NVCA”) takes a different approach from Myriad.¹⁹⁶ The NVCA brief's main policy argument focuses on “realizing the promise of personalized medicine.”¹⁹⁷ First, the NVCA brief begins by identifying *the importance of venture capital to developments in personalized medicine*.

¹⁷⁹ See generally Brief for Myriad Genetics, Inc. As Amicus Curiae Supporting Respondent at 7 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹⁸⁰ *Id.*

¹⁸¹ *Id.*

¹⁸² *Id.* at 12-13.

¹⁸³ *Id.* at 13.

¹⁸⁴ *Id.*

¹⁸⁵ *Id.*

¹⁸⁶ *Id.* at 13-14 (citing the 100 million dollars that Genomic Health spent in 7 years to develop the OncoType DX®).

¹⁸⁷ *Id.* at 14.

¹⁸⁸ *Id.*

¹⁸⁹ *Id.*

¹⁹⁰ *Id.*

¹⁹¹ *Id.* at 14-15.

¹⁹² *Id.* at 15.

¹⁹³ *Id.*

¹⁹⁴ *Id.* at 15-16.

¹⁹⁵ *Id.* at 16-18.

¹⁹⁶ See generally Brief of Amicus Curiae National Venture Capital Association in support of Respondent at 4 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

¹⁹⁷ *Id.*

NVCA points to the significant obstacles that slow the progression of personalized medicine.¹⁹⁸ NVCA emphasizes that the huge cost that comes with researching and confirming the existence of correlations between genetic markers and various diseases.¹⁹⁹ T

he regulatory guidelines in the industry are also a significant burden because they are not meant to accommodate complex genome-based diagnostics.²⁰⁰ As a result, the regulatory framework for these diagnostics is vague, especially the standards for testing the risks associated with these diagnostic tests.²⁰¹

Additionally, *convincing insurance companies, Medicaid and Medicare to pay for diagnostic testing is also a significant barrier to success.*²⁰² Even after these challenges are met, the test developers must educate the public and market the new diagnostic test to physicians and patients to ensure its success.²⁰³

The NVCA brief moves on to the necessity of allowing patent protection for personalized medicine to thrive in the face of these obstacles.²⁰⁴ The NVCA argues that *because personalized medicine is a newly emerging industry, venture capital is the only true source of funding.*²⁰⁵

The NVCA brief then states that nearly \$25 billion dollars are invested by venture capitalists annually, and that one third of those investments fail.²⁰⁶ *In biotechnology the failure rate is especially high* due to developmental risks and regulatory barriers.²⁰⁷ *Investing in these industries is only feasible if the companies can generate significant capital to recoup financial losses.*²⁰⁸ The ability for biotechnology companies to obtain patent protection for new inventions allows companies to attract venture capital.²⁰⁹

According to the NVCA, there is a *correlation between strong patent protection and the amount of investments made in research and development.*²¹⁰ NVCA argues that not allowing for patent protection in personalized medicine “ will leave the promise of personalized medicine unrealized.”²¹¹

NVCA then walks the reader through three important innovations in personalized medicine, starting with the Corus® CAD test, then the Oncotype DX® test, and the PreDx DRS test.²¹² NVCA uses these *examples as incidents where venture capital contributed to the development of innovation in the personalized medicine industry.*²¹³

The NVCA brief also argues that much of the *fear over the growth of a patent thicket has been misguided.* NVCA also focuses on the non-patent impact of disallowing patent protection in personalized medicine. NVCA alleges that *invalidating patents in personalized medicine will “eliminate a sector of venture-backed biotechnology companies.”*²¹⁴ The elimination of these companies would lead to a decrease in jobs and revenue, and ultimately hurt the economy.²¹⁵

The *NVCA also adds that patents do not stifle innovation, and have a negligible effect on research.*²¹⁶

12.14 Genomic Health et. al.

The brief filed by Genomic Health, Veracyte, Biodesix, Target Discovery, The Coalition for 21st Medicine and BayBio (“GH”) also discusses the importance of patent protection to the personalized medicine industry.²¹⁷ The GH brief discusses ability of personalized medicine to revolutionize patient care and save huge amounts of money by catering treatment to a specific patient’s needs.²¹⁸

¹⁹⁸ *Id.*

¹⁹⁹ *Id.* at 6.

²⁰⁰ *Id.* at 6-7.

²⁰¹ *Id.*

²⁰² *Id.* at 7.

²⁰³ *Id.*

²⁰⁴ *Id.* at 7-8.

²⁰⁵ *Id.*

²⁰⁶ *Id.* at 8.

²⁰⁷ *Id.*

²⁰⁸ *Id.*

²⁰⁹ *Id.* at 8-9.

²¹⁰ *Id.* at 9.

²¹¹ *Id.* at 10.

²¹² *Id.* at 10-16.

²¹³ *Id.* at 16.

²¹⁴ *Id.* at 17.

²¹⁵ *Id.*

²¹⁶ *Id.* at 18.

²¹⁷ See generally Brief of Genomic Health, Inc., Veracyte, Inc., XDX, Inc., Biodesix, Inc., Target Discovery, Inc., The Coalition for 21st Medicine, and BayBio as Amici Curiae in support of Respondent, Prometheus Laboratories, Inc. at 8 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

²¹⁸ *Id.* at 12.

GH argues that *personalized medicine has grown as an industry based on the assumption that patent protection is available for inventions*.²¹⁹ The protection against copying offered by patents is essential to attract investments; this is especially true for inventions that are easy to imitate.²²⁰

Next, the GH brief discusses the huge cost of discovering and analyzing biomarkers.²²¹ Diagnostic companies, according to the GH brief, invested 35-200% of revenue in research and development, whereas pharmaceuticals and medical device companies only spent 11-16% of revenue in 2004.²²²

The GH brief also discusses the increase in cost due to regulatory requirements.²²³ After the cost of developing the test, additional cost to obtain approval from the FDA can range from \$31 million dollars to \$94 million dollars, according to a 2011 study cited in the GH brief.²²⁴

*The high cost of research and development, coupled with the expense required to gain approval from the FDA means that without the exclusivity provided by patent protection many investors are unlikely to invest in personalized medicine.*²²⁵ It is *unlikely that such funding can come from the public sector or academia.*²²⁶

The GH brief also argues that part of the *resistance to patents in personalized medicine come from within the medical field* itself.²²⁷

The *personalized medicine* industry has the *potential to change the status quo in current medical practices*, and because of this many entrenched companies with significant biotechnology interests are starkly opposed to allowing the personalized medicine industry to grow into a viable field.²²⁸ GH finishes the brief with the argument that any change in rules in current patent law would destabilize the system and make it less likely for investors to invest in diagnostic development.²²⁹

12.15 Health Law, Policy and Ethics Scholars (“HLPES”)

The brief filed by Health Law, Policy and Ethics Scholars (“HLPES”) focuses mostly on the *impact of personalized medicine patents on medical care*.²³⁰

HLPES starts by discussing how patentability of medical inventions encourages investment in medicine and spurs innovation, which ultimately saves lives.²³¹ The brief then goes into the history of patent eligibility for medical procedures and discusses the important role that patents play in advancing medical research by encouraging investment.²³² HLPES states “investors allocate resources based on whether the end result can be commercialized and patented, not whether medical technology will be advanced.”²³³

HLPES also discusses the *positive impact that medical patents have on public knowledge*.²³⁴ Patents *encourage the spread and discussion of medical knowledge*.²³⁵ The patent system offers a *better method of disclosing inventions than publication in a journal* because of the disclosure requirements that must be fulfilled to obtain a patent.²³⁶ *Unlike in medical journals, the applicant for a patent is required to explain the invention fully, in a manner that allows any person with ordinary skill in the art to recreate the patented invention.*²³⁷

Additionally, patents published by the USPTO can be *accessed for free on the USPTO website*.²³⁸

²¹⁹ *Id* at 15.

²²⁰ *Id*.

²²¹ *Id* at 16.

²²² *Id*.

²²³ *Id* at 16.

²²⁴ *Id*.

²²⁵ *Id* at 17.

²²⁶ *Id* at 18.

²²⁷ *Id* at 17.

²²⁸ *Id*.

²²⁹ *Id* at 18.

²³⁰ See generally Brief of Health Law, Policy and Ethics Scholars as Amici Curiae in Support of Respondents at 3 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

²³¹ *Id*.

²³² *Id* 4-8.

²³³ *Id* at 8-9.

²³⁴ *Id* at 11.

²³⁵ *Id*.

²³⁶ *Id* at 11-12.

²³⁷ *Id* at 12-13.

²³⁸ *Id*.

*Without the benefit of patent protection, some inventors may choose to keep their invention as a secret to prevent copying.*²³⁹

Secrecy slows the dissemination of medical knowledge and ultimately harms the patient.²⁴⁰

HLPES then goes on to directly contradict the arguments made in AMA's brief in favor of Mayo.²⁴¹ HLPES argues that the position taken by the AMA's brief is short sighted and considers the short-term well being of patients over what is best for society in the long term.²⁴²

HLPES argues that the focus of modern medical on the individual is, in part, a reaction to experimentation by Nazi scientists on humans.²⁴³

While this is positive, focusing solely on a patient's welfare skews the perspective of healthcare workers about what policy is best.²⁴⁴ HLPES argues that the AMA's focus on reduced patient access to a patented medical invention because of cost is misguided, because eventually public health will be improved by the patented invention regardless of the initial cost to patients.²⁴⁵ HLPES goes on to argue that the *AMA has not given any reason for medical process patents to be denied patent coverage*, and that this *decision should be left to Congress and not the Court*.²⁴⁶

12.16 American Intellectual Property Law Association ("AIPLA")

The brief filed by the American Intellectual Property Law Association ("AIPLA") focuses mainly on refuting the arguments made in amicus briefs on behalf of the petitioners.²⁴⁷

AIPLA's brief argues that the *patent statute specifically disallows infringement suits against doctors and medical institutions*, contrary to the arguments that patent protection would interfere with doctor's ability to provide competent medical care.²⁴⁸

AIPLA quotes 35 U.S.C. § 287(c)(1), stating "provisions of section § 281 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity."²⁴⁹ AIPLA states that the statute defines a "medical practitioner" as anyone licensed to provide medical activity, and "medical activity" as the performance of a medical procedure on the body.²⁵⁰ AIPLA emphasizes that Mayo's policy concerns related to medical practitioners is not grounded in the actual law.²⁵¹

There were also six amicus briefs filed on behalf of neither party. These briefs still discussed important policy considerations, but ultimately did not end up supporting the position of either party.

12.17 Association Internationale Pour La Protection De Le Propriete Intellectuelle

The brief filed by the Association Internationale Pour La Protection De Le Propriete Intellectuelle first discusses the organization's position on medical patents.²⁵²

The AIPPI is *against allowing patent rights to interfere with patient treatment*.²⁵³ *In most countries this is the case*.²⁵⁴

The AIPPI states that any situation where patents would prevent doctors from using their best judgment, force doctors to waste time entering licensing agreements, and divert resources to searching for patents will have a negative impact

²³⁹ *Id* at 14.

²⁴⁰ *Id*.

²⁴¹ *Id* at 16.

²⁴² *Id* at 16-17.

²⁴³ *Id* at 17.

²⁴⁴ *Id* at 18.

²⁴⁵ *Id* at 18-19.

²⁴⁶ *Id*.

²⁴⁷ See generally Brief Amicus Curiae American Intellectual Property Law Association in Support of Respondents at 4 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

²⁴⁸ *Id* at 4-5.

²⁴⁹ *Id* at 5-6.

²⁵⁰ *Id* at 6.

²⁵¹ *Id*.

²⁵² See generally Brief of Amici Curiae Association Internationale Pour La Protection De La Propriete Intellectuelle and International Association for the Protection of Intellectual Property (U.S.) in Support of Neither Party at 6 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

²⁵³ *Id*.

²⁵⁴ *Id*.

on medical care.²⁵⁵ The AIPPI then argues that this is precisely the impact that the patenting of medical correlations will have.²⁵⁶

*AIPPI fears that physicians will have to identify licenses that they need to obtain and then license patents before they can perform the method claimed in the Prometheus patents.*²⁵⁷

AIPPI argues that *there are no uses for Prometheus's invention is particularly dangerous because there are no uses for the patented invention other than patient treatment.*²⁵⁸

The AIPPI brief then discusses the limitations of 35 U.S.C. § 287(c)(1).²⁵⁹ Section 287 (c)(1) limits the federal court's ability to hear suits against healthcare entities for patent infringement.²⁶⁰ According to AIPPI, the parties involved in this suit satisfy the definition of "healthcare entities" used in the statute, and the case should be dismissed for lack of subject matter jurisdiction.²⁶¹

12.18 Roche Molecular Systems et. al. ("RMS")

Another brief in support of neither party was filed by Roche Molecular Systems, Ventana Medical Systems, Hoffmann-La Roche Inc. and Abbott Laboratories ("RMS").²⁶² The RMS brief primarily discusses the status of the personalized medicine industry, the importance of patent law in personalized medicine, and the impact of patents on patients and scientific progress.²⁶³

First, RMS brief discusses the traditional trial and error method of medicine, in which prescription medicine is only effective for a portion of the population, and toxic or ineffective for the other portion.²⁶⁴ The advantage of personalized medicine, RMS argues, is that it allows doctors to tailor treatment to each individual patient based on biomarkers.²⁶⁵ These biomarkers can be gene sequence variations, gene expression levels, protein expression levels, or metabolite levels.²⁶⁶ Diagnostic tests are necessary to determine what biomarkers the individual patient has.²⁶⁷ This information is then be used to determine if the patient is susceptible to a genetic disease, or if a treatment will be effective.²⁶⁸

Much like other amicus briefs, RMS then emphasizes the importance of patent rights to the economic health of the biotechnology industry because of the high cost of research and development and government regulation.²⁶⁹ RMS emphasizes how vital patent protection is to the survival of the personalized medicine industry.²⁷⁰

RMS also turns to the claims made by Mayo and other amici that diagnostic tests would stifle innovation.²⁷¹ These claims, RMS alleges, are largely based on speculation.²⁷² It is generally accepted that research is more likely to be slowed by lack publically accessible information because of a lack of patent protection.²⁷³

*The dreaded "anticommons," in which patent rights are not licensed and innovation is slowed, is not a reality in the modern patent landscape.*²⁷⁴ In fact, allowing for strong patent protection actually aids future innovation instead of slowing it.²⁷⁵

RMS also finds fault with the argument that patients would be unable to access diagnostic tests because of patent rights.²⁷⁶ The pricing of diagnostic tests, according to RMS, is not effected by the exclusivity of patent rights.²⁷⁷ Instead,

²⁵⁵ *Id* at 8.

²⁵⁶ *Id.*

²⁵⁷ *Id.*

²⁵⁸ *Id* at 10.

²⁵⁹ *Id.*

²⁶⁰ *Id.*

²⁶¹ *Id* at 12-13.

²⁶² See generally Brief for Amici Curiae Roche Molecular Systems, Inc., Ventana Medical Systems, Inc., Hoffmann-La Roche Inc., and Abbott Laboratories, Inc., in Support of Neither Party at 5 Mayo Collaborative Services v. Prometheus Laboratories, 132 S.Ct. 1289 (2012) (No. 10-1150).

²⁶³ *Id.*

²⁶⁴ *Id* at 5-6.

²⁶⁵ *Id* at 6.

²⁶⁶ *Id.*

²⁶⁷ *Id.*

²⁶⁸ *Id.*

²⁶⁹ *Id* at 7.

²⁷⁰ *Id.*

²⁷¹ *Id* at 19.

²⁷² *Id.*

²⁷³ *Id* at 20.

²⁷⁴ *Id.*

²⁷⁵ *Id.*

²⁷⁶ *Id* at 21.

²⁷⁷ *Id* at 22.

the incentive to advertise these tests to the public and increase awareness and public access is very high.²⁷⁸ The problems that can arise from a patent anticommons or lack of patient access, RMS argues, can be better addressed by patent clearing houses or patent pools instead of just declaring the subject matter patent ineligible.²⁷⁹

According to RMS, the concern that doctors would be subject to patent infringement lawsuits is also misplaced.²⁸⁰ Patent holders do not prefer to enforce their patents against non-commercial or non-competitive uses of their technology.²⁸¹

Attempting to sue researchers in academia or medicine would only harm the patent holder; these institutions would be unlikely to allow the patent holder to access their research and materials or collaborate with them if they were sued for patent infringement.²⁸²

Additionally, non-competitive infringement does not offer damages sufficient for a patent holder to shoulder the high cost of litigation.²⁸³ *The incentives for a private patent holder to allow research and medical use of diagnostic technologies is strong*, and concerns over patents on diagnostic methods chilling innovation is unfounded.²⁸⁴

12.19 Merit brief arguments - Mayo

Mayo's brief has two main arguments; 1) that Prometheus's patents claim patent ineligible subject matter, and 2) patents similar to the Prometheus patents will suppress innovation, increase healthcare cost, and erode patient care.

Mayo's first *argument can be broken down into six main parts*.

The first part states that the Prometheus patents are *unduly broad and preempt the use of a natural phenomenon*.

The second part emphasizes that *Supreme Court precedent bars the patenting of natural phenomenon*.

The third part argues that the *other steps in the Prometheus patent do not make the subject matter in the patents eligible* under § 101.

The fourth part disregards the Federal Circuit's reliance on the *machine-or-transformation test*.

The fifth part *compares the value* of Prometheus's *patents to the value* of Prometheus's *discovery to the public*.

The final part of the first argument asks the court to consider *whether the Prometheus patents claim an invention that Congress intended to be eligible for patent protection*.

Mayo's begins its first argument by stating that Prometheus's patents are *unpatentable because they claim the application of a law of nature, not a process*.²⁸⁵ Mayo argues the *correlation between metabolite levels and health occurs as an enzymatic activity inside the human body, and not as the result of Prometheus's invention*.²⁸⁶ Mayo supports this statement by quoting language taken directly from Prometheus, saying; "Prometheus concedes, as it must, that it *seeks to patent 'a truth' about 'the physical world'*," but asserts that its claims are nevertheless valid because they recite preliminary 'process steps that require concrete human actions.'²⁸⁷

Mayo focuses on the steps claimed in Prometheus's patent to prove that Prometheus has not satisfied the requirements for § 101.²⁸⁸ The "administering" and determining" steps tacked onto Prometheus's claims, Mayo argues, are part of the prior art and do not confine the scope of the claims or impose a limit on final step of the Prometheus patents.²⁸⁹ According to Mayo, this lack of limits on the claims means that the Prometheus patents preempt all uses of the correlations between the thiopurine drug and the metabolite levels.²⁹⁰

Mayo cites the suit filed by Prometheus against Mayo as an example of Prometheus attempting to enforce a broad interpretation of its patents.²⁹¹ Mayo alleges that Prometheus views the mere knowledge of the correlations in patents '623 and '302 while treating a patient with a thiopurine drug to be infringement, even if they do not use Prometheus's

²⁷⁸ *Id.*

²⁷⁹ *Id.* at 22-23.

²⁸⁰ *Id.* at 23.

²⁸¹ *Id.* at 23-24.

²⁸² *Id.*

²⁸³ *Id.* at 24-25.

²⁸⁴ *Id.*

²⁸⁵ Brief for Petitioner at 23 *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012) (No. 10-1150).

²⁸⁶ *Id.*

²⁸⁷ *Id.* at 23-24.

²⁸⁸ *Id.*

²⁸⁹ *Id.*

²⁹⁰ *Id.*

²⁹¹ *Id.* at 24-25.

correlations while treating patients.²⁹² The end result, Mayo argues, is that *Prometheus can prevent researchers and doctors from running routine laboratory tests that have been part of the physician's practice for years.*²⁹³

Mayo then makes the case that the broadness of the Prometheus patents are problematic for doctors and researchers by pointing to a lawsuit that Prometheus filed against a researcher, Dr. el-Azhary.²⁹⁴ Dr. el-Azhary was drawn into an infringement suit when Prometheus sued her employer.²⁹⁵ This example, Mayo argues, refutes the statement that Prometheus made that "it does not sue doctors".²⁹⁶ Mayo states that Prometheus has, and can in the case of Dr. El-Azhary, *interfere with essentially anything a physician can do with knowledge of the correlation between metabolite levels, including choosing not to use the levels.*²⁹⁷

The second point made by Mayo is that the Supreme Court's precedent bars the patenting of natural phenomenon.²⁹⁸ Mayo points out that the legislative history of the 1952 Patent Act does not allow for the patenting of all inventions.²⁹⁹ Instead, the legislative history specifies that certain conditions must be met to secure patent protection.³⁰⁰ Most importantly, *laws of nature, physical phenomena or abstract ideas have been explicitly excluded from patent eligible subject matter* under § 101.³⁰¹ Mayo supports this argument by quoting the Supreme Court in *Gottshalk v. Benson*, saying, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts' *cannot support a patent monopoly because they are the basic tools of scientific and technological work.*"³⁰² Mayo also quotes the Supreme Court in *Funk Brothers Seed v. Kalo*, stating that unpatentable subject matter are part of the public domain and must be free for all to use.³⁰³ Mayo adds that patents that have the "practical effect" of claiming natural phenomena may also preempt the use of the phenomena by others.³⁰⁴

Mayo then walks the reader through past Supreme Court precedent on the patentability of natural phenomena.³⁰⁵ Mayo uses past precedent to argue that the Court in *Diamond v. Diehr* affirmed three concepts: 1) that laws of nature cannot be abstractly claimed, 2) this limitation cannot be avoided by claiming the invention in "a particular technological environment," and 3) "insignificant post solution activity" cannot "transform an un-patentable principle into a patentable process."³⁰⁶ Mayo states that the court reaffirmed all this precedent in *Bilski v. Kappos*, and quotes *Bilski*, saying "it is essential to consider whether a claimed process, 'considered as a whole' is 'performing a function which patent laws were designed to protect.'"³⁰⁷

Mayo makes the argument that Prometheus's patents, like the patents that Mayo discussed, claim patent ineligible subject matter.³⁰⁸ Mayo states that the Prometheus patents claim a correlation between health and metabolite levels, and that this correlation is a natural phenomenon.³⁰⁹ Mayo also argues that *the "mental step" in the Prometheus patents makes the patent broad enough to preempt the use of the correlation for all autoimmune diseases.*³¹⁰

According to Mayo, the Prometheus patents claim subject matter cannot be claimed as a process for two reasons.³¹¹ The first reason is that the steps involving administering the drug and testing the blood for metabolites of the drug are conventional means of observing the correlation.³¹² Mayo calls these preliminary steps "data gathering steps" and states "Where 'qualities are the work of nature,' 'packaging' them with steps that make no difference to the way the natural phenomenon operates is "not enough" to satisfy Section 101."³¹³ Nor, according to Mayo, do the data gathering steps narrow the scope of the Prometheus patents.³¹⁴ Mayo argues that the broadness of Prometheus's claims allow Prometheus to preempt all practical uses of the claimed correlations; something that is specifically forbidden by past

²⁹² *Id.*

²⁹³ *Id.*

²⁹⁴ *Id.*

²⁹⁵ *Id.*

²⁹⁶ *Id.*

²⁹⁷ *Id.*

²⁹⁸ *Id.* at 26.

²⁹⁹ *Id.*

³⁰⁰ *Id.*

³⁰¹ *Id.*

³⁰² *Id.* at 27.

³⁰³ *Id.* at 27-28.

³⁰⁴ *Id.* at 29.

³⁰⁵ *Id.*

³⁰⁶ *Id.* at 30.

³⁰⁷ *Id.* at 31-32.

³⁰⁸ *Id.* at 33.

³⁰⁹ *Id.*

³¹⁰ *Id.*

³¹¹ *Id.* at 34.

³¹² *Id.*

³¹³ *Id.* at 34-35.

³¹⁴ *Id.* at 35.

Supreme Court precedent.³¹⁵ The second reason is because *the administration and testing steps are well-known and conventional methods used in the practice of medicine*.³¹⁶ The inclusion of well-known steps does not allow natural phenomenon to be patent eligible.³¹⁷

Next, Mayo argues against the holding of the Federal Circuit and the Federal Circuit's use of the machine-or-transformation test.³¹⁸ Mayo states that the Federal Circuit misinterpreted the Court's holding in *Bilski*, saying, "The Federal Circuit misunderstood *Bilski*, which held that a 'transformation' is a 'clue' to patent eligibility-not a talisman-and does not override the principle that 'laws of nature' must be free for all to use."³¹⁹ Then, Mayo argues that claims involving machines or transformations are relevant only if they show that the inventor intends to claim specific "real-world" applications of a natural phenomenon.³²⁰

Mayo emphasizes the *inconsistency between the Federal Circuit's holding in this case and the holding in Association for Molecular Pathology v. Myriad Genetics*.³²¹

In *Myriad*, Federal Circuit invalidated Myriad's method claims because they were directed to a method of comparing a patient's gene sequences with the gene sequences in the BRCA test.³²² These claims, the Federal Circuit held, were an abstract mental process and therefore were not patentable.³²³ Mayo characterizes the Prometheus patents as more abstract than the method claimed in the *Myriad* patents, and argues that the Federal Circuit's decision to uphold the Prometheus patents in light of the holding in *Myriad* is logically unsound.³²⁴ By comparing these two holdings, Mayo makes the argument that the machine-or-transformation test used by the Federal Circuit to determine if an invention satisfies § 101 is arbitrary, and ignores whether a natural law is actually claimed by the patent.³²⁵

Mayo's next argument focuses on the *value of Prometheus's discovery in comparison to the value of the monopoly that Prometheus is granted*.³²⁶

Mayo states that Prometheus's patents "leverage a minimal contribution to medicine ... into a patent that blocks a broad area of scientific inquiry into the best way to treat a wide variety of serious diseases."³²⁷ Mayo argues that the Supreme Court and the Patent Act both recognize that *existing patents cannot cover unknown inventions and block the development of future technology*.³²⁸

Mayo then discusses the necessary *balance between encouraging innovation and stifling innovation*.³²⁹

Mayo emphasizes the importance of considering whether granting patents on certain subject matter will promote progress.³³⁰ Vague patents, like Prometheus's, that do not limit the subject matter being claimed slow innovation by limiting the knowledge available to future inventors in the public domain.³³¹

Without the ability to build upon prior knowledge and create alternative technology, the cost of goods will rise, selection will shrink, and quality will suffer.³³² Mayo insists that this prediction holds true in the Prometheus case.³³³

Mayo alleges that Prometheus's patents claim the correlation between thiopurine metabolites and the health of the patient, thus giving Prometheus the power to bar the development of any competing technology that utilizes that correlation.³³⁴ *These patents will allow Prometheus to have a monopoly on "all thought about the health effects of the biologic fact, well known to physicians for many years, that thiopurine drugs product metabolites that relate to the health of patients with autoimmune diseases."*³³⁵

³¹⁵ *Id.*

³¹⁶ *Id.*

³¹⁷ *Id.* at 36.

³¹⁸ *Id.* at 38.

³¹⁹ *Id.*

³²⁰ *Id.*

³²¹ *Id.*

³²² *Id.*

³²³ *Id.*

³²⁴ *Id.*

³²⁵ *Id.* at 40.

³²⁶ *Id.*

³²⁷ *Id.*

³²⁸ *Id.* at 41.

³²⁹ *Id.* at 42.

³³⁰ *Id.* at 43.

³³¹ *Id.*

³³² *Id.* at 43-44.

³³³ *Id.* at 44-45.

³³⁴ *Id.* at 44.

³³⁵ *Id.*

The sixth part of Mayo's first argument declares that Prometheus has been unable to produce evidence that shows that Congress approves of patents similar to the Prometheus patents.³³⁶

Mayo alleges that *Congress never intended to allow patent rights to interfere with independent thought of a physician practicing medicine and performing research.*³³⁷

*Federal legislation must not be interpreted in a way that interferes with the First Amendment.*³³⁸ Mayo emphasizes the *importance of freedom of thought*, and that Prometheus's patent infringes upon this freedom.³³⁹

Mayo cites Prometheus's suit against Dr. el-Azhary for her research on metabolite ranges for dermatology patients as a negative result of Prometheus's patents.³⁴⁰ El-Azhary conducted independent research on the thiopurine metabolites without using Prometheus's correlations and concluded that the metabolite ranges disclosed in the Prometheus's patents were defective.³⁴¹ Mayo refers to this practice as "deferring to a physician's medical judgment, while demanding payment for exercising that judgment," and calls it ridiculous.³⁴² Mayo argues that Congress would never intent for a patent to limit thought and independent research on a natural phenomenon.³⁴³

Mayo's second argument focuses on the *impact that patents on medical correlations will have on research and innovation.* Mayo argues that patents similar to the Prometheus patents will "suppress both basic research and specific advances in medical treatment; interfere with patient care and the exercise of medical judgment by physicians; and raise consumer costs."³⁴⁴

Mayo's second argument can be broken up into three main sub-arguments:

- 1) a patent's validity rests on the *effect the patent will have on innovation*;
- 2) patent *protection is not necessary to promote innovation in personalized medicine* and
- 3) patents similar to the Prometheus patent *will inhibit innovation and degrade the quality of patient care.*

First, Mayo states that patents should only be awarded when necessary to ensure that the dual goals of the patent system are met.³⁴⁵ The patent system is meant to grant a monopoly in inventions that are worth exclusive protection.³⁴⁶ According to Mayo, the value of the patented invention to society must outweigh any negative effect of the patent monopoly.³⁴⁷ Ideally, Mayo argues, patents should only be granted when necessary to provide incentives for development of new inventions or encourage the disclosure of new inventions.³⁴⁸ *Patents that raise prices or slow innovation ultimately injure consumers and should not be granted*, according to Mayo.³⁴⁹ Mayo then places the burden on Prometheus to show that the invention claimed in its patents does not impede progress, and argues that Prometheus cannot show this.³⁵⁰

Next, Mayo argues that patent protection is unnecessary to spur innovation in personalized medicine.³⁵¹ Mayo states that the cost for developing tests similar to the invention in Prometheus's patents are low and involve low regulatory cost.³⁵² The risk involved, according to Mayo, is not as high as the risk involved in inventing traditional medical technology, such as pharmaceuticals or medical devices.³⁵³

Mayo then makes the claim that *patent protection does not play a role in motivating genetic researchers to innovate.*³⁵⁴

Instead, Mayo claims, Scientists are motivated by different factors, including "*the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement.*"³⁵⁵

³³⁶ *Id* at 45.

³³⁷ *Id* at 45-46.

³³⁸ *Id* at 46.

³³⁹ *Id* at 46-47.

³⁴⁰ *Id* page 47.

³⁴¹ *Id.*

³⁴² *Id.*

³⁴³ *Id* at 47.

³⁴⁴ *Id* at 48.

³⁴⁵ *Id.*

³⁴⁶ *Id* at 48-49.

³⁴⁷ *Id* at 49.

³⁴⁸ *Id.*

³⁴⁹ *Id.*

³⁵⁰ *Id.*

³⁵¹ *Id.*

³⁵² *Id* at 50.

³⁵³ *Id.*

³⁵⁴ *Id* at 51.

³⁵⁵ *Id.*

Mayo also argues that *patent protection is not necessary to secure funding because the federal government funds a large portion of research*.³⁵⁶ Nor, according to Mayo, is patent protection necessary to encourage the disclosure of new discoveries because of the norms of research; scientists involved in academia are likely to publish research, and have strong incentive to do so.³⁵⁷ Mayo quotes the Secretary Advisory Committee to give credibility to its claims, saying that exclusive patent protection was not necessary to develop test kits for genetic diseases.³⁵⁸ Mayo finishes this argument by emphasizing that these patents are unneeded by stating that the scientists that discovered the correlation licensed these rights at minimal cost to Prometheus.³⁵⁹

Mayo's final argument focuses on the potentially harmful impact of the Prometheus patents on innovation and cost.³⁶⁰ Mayo first argues that Prometheus's patents will preempt fields of research, resulting in slowed innovation and extra expense.³⁶¹ It is impossible to invent around a patent similar to the Prometheus patents because these patents are "[i]nventions that are nothing more than verbal assertions".³⁶² Mayo asserts that allowing a party to hold a patent on a natural phenomena or scientific principle gives that party the ability to threaten the competition with litigation.³⁶³ This threat may deter researchers from engaging in research areas that may be covered by a particular patent.³⁶⁴ This can deter entry into the market, and subsequent innovation by competitors.³⁶⁵ The end result, Mayo argues, is the ability for a patent holder to suppress competition.³⁶⁶

Mayo focuses next on the chilling effect the Prometheus patents can have on medical research.³⁶⁷ Mayo considers the correlations claimed by Prometheus's patents to be basic facts that are essential to medical research, and must be shared by the medical community.³⁶⁸ However, according to Mayo, if Prometheus's patents were allowed to stand, "a physician or researcher 'would become an infringer if he or she merely considered what to do about the results [of a test of metabolite levels] in light of relevant scientific information,'" while a laboratory would induce infringement simply 'by publishing articles or brochures discussing the correlation' between those levels and drug efficacy."³⁶⁹ Mayo also claims that allowing these patents to stand would slow follow-on research.³⁷⁰

Mayo buttresses this argument by quoting the Secretary's Advisory Committee's findings on gene patents.³⁷¹ These findings state that gene patents have already hindered the development of genetic tests, slowed or prevented the reporting of research findings and discouraged subsequent research.³⁷² Mayo argues that similar circumstances can be found as the result of Prometheus's patents, and cites the lawsuit with Dr. el-Azhary as an example.³⁷³

Mayo then focuses on the effect of the Prometheus patents on the quality of patient care. Mayo believes that the existence of the Prometheus patents will *increase the cost and reduce the availability of healthcare*.³⁷⁴ It is essential, Mayo argues, for physicians to monitor the metabolite levels of their patients to adjust the dose of various drugs.³⁷⁵ Mayo alleges that the existence of a patent on such a basic practice *will raise the cost of medical care without benefitting medical research*.³⁷⁶

Mayo cites the case at hand for an example of how the cost will be increased; Prometheus's patents will prevent Mayo from developing a better, cheaper alternative to Prometheus's test.³⁷⁷ The increase of costs prohibits some patients from purchasing the test or getting a second opinion.³⁷⁸ Secondly, allowing a single party to provide test results may lead to a lower quality test because of the inability to compare different results from more than one lab.³⁷⁹ Mayo quotes

³⁵⁶ *Id.*

³⁵⁷ *Id.*

³⁵⁸ *Id.*

³⁵⁹ *Id.* at 52.

³⁶⁰ *Id.*

³⁶¹ *Id.*

³⁶² *Id.* at 53.

³⁶³ *Id.*

³⁶⁴ *Id.*

³⁶⁵ *Id.*

³⁶⁶ *Id.*

³⁶⁷ *Id.* at 54.

³⁶⁸ *Id.*

³⁶⁹ *Id.*

³⁷⁰ *Id.* at 56.

³⁷¹ *Id.* at 55.

³⁷² *Id.*

³⁷³ *Id.*

³⁷⁴ *Id.*

³⁷⁵ *Id.*

³⁷⁶ *Id.* at 57.

³⁷⁷ *Id.*

³⁷⁸ *Id.*

³⁷⁹ *Id.*

the concerns of Justice Breyer in *Labcorp* to summarize the negative impact that patents may have on medical treatment.³⁸⁰

*These concerns include preventing doctors from using their best judgment, forcing doctors to waste time entering licensing agreements, diverting resources from healthcare to patent search, and raising the cost of healthcare.*³⁸¹

Mayo finishes the brief by making the argument that allowing patent protection to continue in correlations would force physicians to breach their ethical duty to patients.³⁸² Physicians, in this case, cannot avoid infringing Prometheus's patent during the course of practice.³⁸³ Prometheus's only solution to this problem is to require doctors to pay them.³⁸⁴ Mayo finishes by asking the court to disallow all patents on biological relationships.³⁸⁵

12.20 Merit brief arguments - Prometheus

Prometheus makes three main arguments in its merit brief. The first is that Prometheus's patents are patent eligible subject matter under § 101. The second, is that it is Congress's job, not the Court's to determine whether upholding patents similar to the Prometheus patents will encourage innovation. The third focuses on the impact that invalidating Prometheus's patents would have on the patent community.

Prometheus begins its first argument by discussing the history of 35 U.S.C. § 101.³⁸⁶ Prometheus quotes § 101, saying "*Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent* therefor, subject to the conditions and requirements of this title."³⁸⁷ Prometheus emphasizes that Congress's use of the word "any" in § 101 gives patent laws a broad scope to encompass unforeseen inventions.³⁸⁸

Next, Prometheus recognizes that laws of nature, natural phenomena and abstract ideas are not patent eligible, but argues that the Court must be careful when interpreting these limitations because *all inventions can be reduced to a law of nature.*³⁸⁹

Prometheus states that there are two main concerns discussed in the case law when determining if a process is patent eligible; 1) concern over whether a process patent claims an abstract principle or an application of that principle and 2) concern over whether a process patent preempts basic scientific tools.³⁹⁰ Prometheus then makes the argument that its patents do not raise either of these concerns because the patents claim specific applications scientific principles and do not preempt any scientific knowledge.³⁹¹

The first issue Prometheus addresses is the patent eligibility of the process claimed in patents '623 and '302 under § 101.³⁹² Prometheus quotes the Patent Act's definition of "process" as "'a mode of treatment of certain materials to produce a given result'; it 'requires that certain things should be done with certain substances, and in a certain order.'"³⁹³ According to this definition abstract ideas cannot be patented, but *specific applications of these abstract ideas are patentable.*³⁹⁴ Then, Prometheus begins to make the case that its patents claim the applications of scientific principles instead of the scientific principles themselves.³⁹⁵

First, Prometheus focuses on the concreteness of the application claimed in their '623 and '302 patents.³⁹⁶ Prometheus states that the machine-or-transformation test confirms that their patents do not claim abstract principles, but instead claim the application of those principles.³⁹⁷ The validity of the machine-or-transformation test remains intact after the holding in *Bilski*, according to Prometheus.³⁹⁸

³⁸⁰ *Id* at 58.

³⁸¹ *Id.*

³⁸² *Id.*

³⁸³ *Id.*

³⁸⁴ *Id.*

³⁸⁵ *Id.*

³⁸⁶ Brief for Respondent at 20 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S.Ct. 1289 (2012) (No. 10-1150).

³⁸⁷ *Id* at 21.

³⁸⁸ *Id.*

³⁸⁹ *Id* at 22.

³⁹⁰ *Id.*

³⁹¹ *Id* at 22-23.

³⁹² *Id* at 23.

³⁹³ *Id.*

³⁹⁴ *Id.*

³⁹⁵ *Id* at 24.

³⁹⁶ *Id.*

³⁹⁷ *Id* at 25.

³⁹⁸ *Id.*

Prometheus argues that its patents are valid because they satisfy the two prongs of the machine-or-transformation test.³⁹⁹ The first prong of the test, the transformation prong, is satisfied because patents '623 and '302 feature two transformative steps.⁴⁰⁰ The first is during the administering step, when the thiopurine drugs are transformed into metabolites in the human body.⁴⁰¹ The second is during the determining step, when the metabolites and blood are transformed to determine the level of metabolites in the blood.⁴⁰²

Additionally, Prometheus argues that the patents also satisfy the machine prong of the machine-or-transformation test because machines are necessary to determine the level of metabolites in the blood.⁴⁰³ According to Prometheus, both the determining and the administering steps independently constitute patent eligible processes under § 101.⁴⁰⁴

Prometheus then turns its attention to the arguments made by Mayo and Mayo's amici that the "administering" and "determining" steps are patent ineligible under § 101 because of lack of novelty.⁴⁰⁵ Prometheus frames Mayo's argument as stripping Prometheus's patents of the administering and determining steps and asking the court only to consider what Mayo calls the "warning" step.⁴⁰⁶ Prometheus argues that Mayo's view is "an improper conflation of patentable subject matter with novelty issues that are properly treated under § 102."⁴⁰⁷

To support this argument, Prometheus quotes the portion of *Diamond v. Diehr* that emphasizes the importance of considering the whole invention instead of separating the elements during a § 101 analysis.⁴⁰⁸ Prometheus emphasizes that new uses of old processes can obtain patent protection, and that the Court has considered and disregarded Mayo's novelty-based argument.⁴⁰⁹

*Prometheus quotes the definition of "process" listed in 100(b) to buttress its argument, stating "Section 100(b)'s definition of 'process' expressly includes 'a new use of a known process, machine, manufacture, composition of matter, or material.'"*⁴¹⁰ Prometheus also disregards the argument made in the Professor's amicus brief that "inventiveness" is a necessary requirement for patentability under § 101 by pointing out that this argument has no statutory basis.⁴¹¹ Prometheus refers to this argument as "dubious" and emphasizes that this type of change in patent law is an issue for Congress, not the Court.⁴¹²

Next, Prometheus attacks Mayo's assertion that the Prometheus patents enjoy an extremely broad monopoly, in which all activities relating to the correlations in Prometheus's patents can be considered infringement.⁴¹³ Prometheus cites two different holdings in which the Federal Circuit determined the meaning of the claims in Prometheus's patents to be limited to patient treatment.⁴¹⁴ However, Mayo may not raise the issue of claim meaning on the Supreme Court level because they did not challenge the Federal Circuit's construction of Prometheus's claims.⁴¹⁵

Because of this, Prometheus argues that the Federal Circuit's construction of the Prometheus patents are binding.⁴¹⁶

Prometheus also addresses the argument that doctors and researchers can be subject to patent infringement for thinking about the correlations in Prometheus's patents.⁴¹⁷ Prometheus argues that *no one can infringe a patent by thinking about the correlations in the patent or performing research outside of the scope of patient treatment.*⁴¹⁸ Infringement can only occur when the thiopurine drugs are administered to a patient, samples are taken from the patient, the metabolite levels are analyzed using special instruments, and a doctor determines whether a dosage needs to be adjusted according to the Prometheus correlation guidelines.⁴¹⁹ A physician that does not carry out the administering and determining steps in Prometheus's patents is not infringing, according to Prometheus.⁴²⁰

³⁹⁹ *Id* at 26.

⁴⁰⁰ *Id.*

⁴⁰¹ *Id.*

⁴⁰² *Id.*

⁴⁰³ *Id* at 27.

⁴⁰⁴ *Id* at 28.

⁴⁰⁵ *Id* at 29.

⁴⁰⁶ *Id.*

⁴⁰⁷ *Id.*

⁴⁰⁸ *Id* at 30.

⁴⁰⁹ *Id.*

⁴¹⁰ *Id.*

⁴¹¹ *Id* at 31.

⁴¹² *Id.*

⁴¹³ *Id* at 32.

⁴¹⁴ *Id.*

⁴¹⁵ *Id.*

⁴¹⁶ *Id.*

⁴¹⁷ *Id* at 33.

⁴¹⁸ *Id.*

⁴¹⁹ *Id.*

⁴²⁰ *Id* at 33-34.

Prometheus then focuses on Mayo's argument that Prometheus's claims are invalid because they end in a "mental step."⁴²¹ Prometheus quotes the Federal Circuit, saying: "the addition of the mental steps to the claimed methods ... does not remove the prior two steps from that realm."⁴²² This precedent has stood since *Diehr*, in which the court upheld the eligibility of a patent claiming a mathematical equation as a step.⁴²³

Emphasizing that it does not matter where the mental step lies in the claims, Prometheus asks the Court to uphold its patents.⁴²⁴ Prometheus points out that Mayo's argument that claims must end with an action step instead of a mental step would only further complicate drafting by requiring the patent drafter to determine each potential application of a method to end the patent with an action step.⁴²⁵

Patents may include steps that allow for the "the judgment of the operator," and Prometheus argues that the inclusion of such a step would not have the negative impact that Mayo suggests.⁴²⁶ Prometheus finishes by arguing that Mayo's approach would only inject uncertainty into the patent system.⁴²⁷

The next issue Prometheus addresses is whether the '623 and '302 patents preempt the use of a natural phenomenon.⁴²⁸ Prometheus begins with the argument that *all patents preempt uses of natural principle in specific ways*; this is the point of patent protection.⁴²⁹

According to Prometheus, the exclusion of natural phenomena from patent eligibility "has been applied only when patents would practically foreclose all uses of truly fundamental principles, in the abstract and across a broad range of potential endeavors and future applications, monopolizing future inventions the patentee may never have conceived."⁴³⁰

Prometheus discusses *Benson*, *Flook* and *Bilski* as examples where the court explicitly rejected patents that claimed broad natural laws that would preempt the use of the concept in other fields.⁴³¹ The Court, Prometheus is quick to point out, also has precedent that allows patents to claim narrowly defined scientific principles.⁴³² Prometheus cites the court's holding in *Tilghman*, where the court upheld a process patent for creating glycerin and fat acids from fatty bodies using highly pressurized, high temperature water.⁴³³ This patent was allowed because it did not preclude the use of other methods to obtain similar results or preempt the natural phenomena that temperature and pressure can break bonds.⁴³⁴

Prometheus also cites the Court's holding in *Neilson*, where the court upheld a patent that claimed a method of heating a blast to smelt iron in a furnace, and *Diehr*, where the court allowed the use of the Arrhenius equation to predict the proper time to open a rubber mold.⁴³⁵ Neither of these patents preempted the use of the natural phenomena or prevented other means of smelting iron or curing rubber to be developed.⁴³⁶ Prometheus argues that like *Diehr*, *Tilghman*, and *Neilson*, the claims of patents '623 and '302 do not preempt a natural phenomena, and that only the application of what Prometheus calls "non-natural phenomena" are claimed.⁴³⁷

Prometheus begins this portion of its brief by pointing out that the patents do not preempt a "natural phenomena."⁴³⁸ The Court's past precedent distinguishes between phenomena that exist unchanged in its natural state and phenomena that would not exist without human intervention.⁴³⁹ Prometheus argues that the Court should allow the Prometheus patents to stand because the processes require the administering of a synthetic thiopurine drug to a patient, the measuring of the levels of metabolites in the blood, and the choice, based on the metabolite levels, to adjust the next dose of the thiopurine drug.⁴⁴⁰

⁴²¹ *Id* at 34.

⁴²² *Id*.

⁴²³ *Id*.

⁴²⁴ *Id*.

⁴²⁵ *Id* at 35.

⁴²⁶ *Id*.

⁴²⁷ *Id* at 36.

⁴²⁸ *Id* at 36-37.

⁴²⁹ *Id* at 37.

⁴³⁰ *Id*.

⁴³¹ *Id* at 37-38.

⁴³² *Id* at 38-39.

⁴³³ *Id*.

⁴³⁴ *Id* at 39.

⁴³⁵ *Id*.

⁴³⁶ *Id*.

⁴³⁷ *Id* at 40.

⁴³⁸ *Id*.

⁴³⁹ *Id*.

⁴⁴⁰ *Id* at 41.

*Without the handwork of man, this method would not exist, and because of this, Prometheus makes the argument that the correlations claimed by these patents are “unnatural,” and exist as the result of human ingenuity.*⁴⁴¹

The next argument that Prometheus makes is against Mayo’s statement that the subject matter of Prometheus’s patents is not properly limited.⁴⁴² Prometheus states that the “transformations, ties to statutory subject matter, and limitation to patient treatment confine the scope of the claims sufficiently to ensure that no fundamental building blocks are removed from the public realm.”⁴⁴³

Prometheus argues that these patents would have no impact on other fields, nor do they preempt the measuring of a correlation of any other drug that is metabolized by the body, prevent the use of other drugs to treat the same disease, prevent the use of the correlations outside of patient treatment, or prevent other ways of calibrating thiopurines for the treatment of autoimmune diseases.⁴⁴⁴ Prometheus states, “Mayo has yet to identify any substantial [research] activity that is preempted by Prometheus’s patents, aside from Mayo’s desire to copy and market a competing commercial test for the exact same application.”⁴⁴⁵

Additionally, Prometheus alleges that Mayo’s references to Dr. el-Azhary are “red herrings;” el-Azhary is only involved in the case because Mayo asked its employees to use Mayo’s new test instead of Prometheus’s.⁴⁴⁶ There was no infringement if el-Azhary was not treating patients or did not consider the Prometheus correlations during patient treatment.⁴⁴⁷

Prometheus then asks the Court to remand the case to the lower court so that the patents can be analyzed under § 102 and § 103.⁴⁴⁸ These issues were not decided by the lower court, so the Supreme Court does not have the authority to determine if the Prometheus patents are novel or non-obvious.⁴⁴⁹ Prometheus also *addresses the argument that the Prometheus patents were inherently anticipated by the prior art.*⁴⁵⁰

However, because this issue was not raised at the trial court the Supreme Court must remand the case if wants this issue to be resolved.⁴⁵¹ Prometheus emphasizes that Mayo will not be able to demonstrate that the Prometheus patents are inherently anticipated.⁴⁵²

The second main argument that Prometheus makes is concerned with the Court’s role in promoting innovation.⁴⁵³ Prometheus states “Mayo insists that, to decide the Threshold question whether “‘certain subject matter’” falls within § 101, the federal courts ... should in each case “‘ask whether granting [the] patents ... in fact will promote [scientific] progress’ or instead “‘hinder competition that can effectively spur innovation.’”⁴⁵⁴ Prometheus argues that the court should reject Mayo’s argument because this power lies with Congress, not the Courts.⁴⁵⁵

Prometheus even quotes the Court, saying “[a]s the Court has recognized, ‘*the decision as to what will accomplish the greatest good for the inventor, the government and the public rests with the Congress,*’.”⁴⁵⁶

Prometheus also addresses the argument that subject matter eligibility should be limited to subject matter that patent laws were meant to protect.⁴⁵⁷ Prometheus dismisses this argument as allowing for judicial policymaking.⁴⁵⁸ Quoting Judge Rader, Prometheus argues that limiting § 101 in this way will introduce a new “‘substantive due process’” into patent law, creating a number of problems.⁴⁵⁹

Asking the court to change the § 101 analysis to consider whether a patent will slow innovation essentially de-regulates the practice of the USPTO, and asks patent examiners and courts to make policy considerations that they otherwise are not equipped for, Prometheus argues.⁴⁶⁰

⁴⁴¹ *Id.*

⁴⁴² *Id.*

⁴⁴³ *Id.*

⁴⁴⁴ *Id.* at 42-43.

⁴⁴⁵ *Id.* at 43-44.

⁴⁴⁶ *Id.* at 44.

⁴⁴⁷ *Id.*

⁴⁴⁸ *Id.* at 46.

⁴⁴⁹ *Id.* at 46.

⁴⁵⁰ *Id.* at 46-47.

⁴⁵¹ *Id.* at 47.

⁴⁵² *Id.* at 48.

⁴⁵³ *Id.* at 49.

⁴⁵⁴ *Id.*

⁴⁵⁵ *Id.*

⁴⁵⁶ *Id.* at 49 (*quoting* US v. Dubilier Condenser Corp. 289 U.S. 178, 198-99 (1933).).

⁴⁵⁷ *Id.*

⁴⁵⁸ *Id.* at 49-50.

⁴⁵⁹ *Id.*

⁴⁶⁰ *Id.* at 50.

*The end result is high cost, unpredictability, and less incentive to innovate.*⁴⁶¹

Prometheus finishes its second argument with a quote from Judge Learned Hand; “*It is not for [the courts] to decide what ‘discoveries’ shall ‘promote the progress of science and the useful arts’* sufficiently to grant any ‘exclusive right’ of inventors.”⁴⁶²

Prometheus’s final argument focuses on the disruption that would occur in the current patent system if the Court adopted Mayo’s arguments.⁴⁶³ Prometheus predicts that the impact will be especially felt in personalized medicine, because the use of correlations to determine information for clinical diagnosis lies at the core of personalized medicine.⁴⁶⁴ The result is that a ruling in favor of Mayo would invalidate thousands of personalized medicine patents.⁴⁶⁵ Even worse, without the right to obtain patent protection, the incentive to develop this technology is diminished.⁴⁶⁶ Prometheus argues that *the newest breakthroughs in medicine will arise in personalized medicine, and that this will reduce cost, lead to earlier and more accurate diagnosis, and more effective treatment.*⁴⁶⁷

The advantages of personalized medicine come with a large cost.⁴⁶⁸ Prometheus states that substantial investments are required to fund the discovery of biomarkers, complete the trials required by regulatory agencies, and commercialize the product.⁴⁶⁹ Patent protection is necessary to incentivize investment.⁴⁷⁰ Prometheus emphasizes this point, stating “*without the confidence that investment-backed expectations can be realized, innovation will be retarded.*”⁴⁷¹

Prometheus touches on Mayo’s argument that the federal government can fund the research necessary to provide incentive to innovate in personalized medicine.⁴⁷² Assuming that the federal government is an adequate substitute for private capital, simply funding research is not sufficient to complete “the full innovation life-cycle and ‘convert inventions that might otherwise exist only on paper into commercially viable products that improve the health and quality of life of the public,’” Prometheus argues.⁴⁷³ Prometheus also states “the suggestion that innovation will nonetheless continue apace because *doctors will perform the necessary research and development on their own, out of a sense of duty or professional curiosity ... is shockingly naïve.*”⁴⁷⁴

Prometheus also points out that Mayo’s argument that patents like Prometheus’s slow innovation and harm the quality of medical care is not based in reality.⁴⁷⁵ Prometheus cites examples to the contrary, including a Federal Trade Commission paper and an expert opinion.⁴⁷⁶

Prometheus also disregards Mayo’s argument that enforcing patents similar to the Prometheus patents will lead to the unethical practice of medicine.⁴⁷⁷ The availability and low cost of its test, Prometheus argues, makes it is essentially indistinguishable from other important innovations in the medical field, such as pharmaceuticals and medical devices.⁴⁷⁸ Prometheus also points out Mayo’s hypocrisy; Mayo continues to receive patents similar to the Prometheus patents.⁴⁷⁹

Finally, Prometheus’s focuses on Congress’s choice not to exclude medical processes from patent eligibility.⁴⁸⁰ According to Prometheus, *Congress addressed concerns over medical method patents by offering limited immunity from infringement to physicians without changing the eligibility of these methods for patent protection.*⁴⁸¹ Prometheus finishes the brief by asking the Court to disregard Mayo’s policy arguments and uphold the Prometheus patents.⁴⁸²

⁴⁶¹ *Id.*

⁴⁶² *Id.* (quoting *Reiner v. I. Leon Co.*, 285 F.2d 501, 503 (2d Cir. 1960).).

⁴⁶³ *Id.*

⁴⁶⁴ *Id.* at 50-51.

⁴⁶⁵ *Id.* at 51.

⁴⁶⁶ *Id.* at 52.

⁴⁶⁷ *Id.*

⁴⁶⁸ *Id.* at 53.

⁴⁶⁹ *Id.* at 53.

⁴⁷⁰ *Id.* at 54-55.

⁴⁷¹ *Id.* at 55 (quoting Lawrence M. Sung, Medical Alert: alarming challenges facing medical technology innovation, 6 J. bus. & tech L. 35, 58 (2001)).

⁴⁷² *Id.*

⁴⁷³ *Id.*

⁴⁷⁴ *Id.* at 55-56.

⁴⁷⁵ *Id.* at 56.

⁴⁷⁶ *Id.*

⁴⁷⁷ *Id.*

⁴⁷⁸ *Id.*

⁴⁷⁹ *Id.* at 57.

⁴⁸⁰ *Id.*

⁴⁸¹ *Id.* 57-58.

⁴⁸² *Id.* at 58.

12.21 Mayo reply brief

Mayo also filed a reply brief in response to Prometheus's brief.⁴⁸³ Mayo's reply brief is divided into five main arguments; 1) Prometheus's patent is invalid under § 101 under existing court precedent, 2) the Prometheus patents preempt a natural phenomena, 3) the invalidity of the patents cannot be avoided by Prometheus's defenses, 4) the Court's prior decisions render the Prometheus patents invalid and, 5) invalidating the patents would encourage innovation in personalized medicine.⁴⁸⁴

Mayo begins its reply brief with the argument that the Prometheus patents violate § 101 by preempting all uses of a natural law. Mayo compares the Prometheus patents to the patents invalidated in *Flook*, saying, "patents with such broad preemptive effect cannot be saved by adding the 'conventional' activities of administering a 'well known' drug and conducting a 'long prevalent' blood test."⁴⁸⁵

Mayo also argues that the Prometheus patents are not like the patents in *Diehr*, because the natural law is not confined in steps of the patent.⁴⁸⁶ Mayo alleges that the Prometheus patents prevent physicians and researchers from thinking about the correlation disclosed in the patents, even if they want to produce a new test.⁴⁸⁷

Allowing patents like the Prometheus patents to exist will result in an overflow of patents with "overreaching claims."⁴⁸⁸ According to Mayo, physicians will be forced to navigate patents covering every aspect of medicine.⁴⁸⁹ The fear, Mayo states, is that healthcare costs will increase because physicians must devote resources to patent searches and licensing agreements, coupled with a decrease in quality of care if doctors are forced to avoid patented practices.⁴⁹⁰

Mayo's first main argument focuses on the invalidity of the Prometheus patents in the face of prior court precedent.⁴⁹¹ Mayo argues that because the "administering" and "determining" steps were part of the prior art, the actual invention by Prometheus was the final step of the patent.⁴⁹² To support this argument, Mayo quotes the amicus brief filed by the United States in favor of neither party.⁴⁹³

Mayo focuses next on the *USPTO's assertion that the correlation by itself would not be patent eligible subject matter under § 101*.⁴⁹⁴ The addition of the correlation to a process, Mayo argues, does little to prevent the monopolization of the correlation.⁴⁹⁵ The focus should be on what the steps of the process actually claim, not on whether there are additional steps claimed in the patent.⁴⁹⁶ According to Mayo, because Prometheus's *patents claim prior and a step that involves thinking about numbers, there is nothing claimed in the patent that actually deserves patent protection*.⁴⁹⁷

Following this discussion, Mayo asks the court to disregard the arguments made in the United States brief, which suggests that the Prometheus patents could be rejected because they lack novelty and are obvious under § 102 and § 103.⁴⁹⁸ Mayo argues that the "government's proposal to reduce Section 101 to a rubber stamp that is easily satisfied with clever drafting, and to have the federal courts grapple instead with complex inquiries that are difficult to resolve, is flatly at odds with Congress's goals in this year's America Invents Act."⁴⁹⁹

Mayo's second argument focuses on the broad scope of the Prometheus patents.⁵⁰⁰ Mayo claims that the Prometheus patents, despite contentions by Prometheus, preempt almost all applications of correlations.⁵⁰¹ Limiting the subject matter claimed by the patents specifically to a number of diseases, or to a technological use does not suddenly make

⁴⁸³ See generally Reply Brief for Petitioners at 1 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S.Ct. 1289 (2012) (No. 10-1150).

⁴⁸⁴ *Id.*

⁴⁸⁵ *Id.*

⁴⁸⁶ *Id.*

⁴⁸⁷ *Id.*

⁴⁸⁸ *Id.* at 2.

⁴⁸⁹ *Id.*

⁴⁹⁰ *Id.*

⁴⁹¹ *Id.* at 3.

⁴⁹² *Id.*

⁴⁹³ *Id.* See generally Brief for the United States as Amicus Curiae Supporting Neither Party at 1 Mayo Collaborative Services v. Prometheus Laboratories, Inc., 132 S.Ct. 1289 (2012) (No. 10-1150).

⁴⁹⁴ *Id.*

⁴⁹⁵ *Id.*

⁴⁹⁶ *Id.* at 4.

⁴⁹⁷ *Id.*

⁴⁹⁸ *Id.* at 5.

⁴⁹⁹ *Id.* at 6.

⁵⁰⁰ *Id.* at 7.

⁵⁰¹ *Id.* at 8.

the subject matter patent eligible.⁵⁰² Mayo cites precedent from *Bilski*, *Flook*, and *Diehr* to support this statement.⁵⁰³ The effect, Mayo argues, is that these patents will interfere with the practice of medicine.⁵⁰⁴

Mayo dismisses the arguments made by Prometheus's amici that Mayo is attempting to invalidate patents for medical processes, diagnostic and therapeutic methods or medical correlations.⁵⁰⁵ Instead, Mayo argues, they are only attempting to show that the Prometheus patents are invalid because they claim ideas that are too abstract.⁵⁰⁶

Mayo then attacks some of the representations that Prometheus made to the Court. First, Mayo states that Prometheus claims to allow competitors to use numbers that vary by more than 15 %.⁵⁰⁷ However, Mayo points to Prometheus's successful argument at the district court level that the correlations claimed in the patent have no upper limit.⁵⁰⁸

Mayo also discusses the limitation of the Prometheus patents to a therapeutic setting.⁵⁰⁹ Mayo alleges that this argument also is contrary to Prometheus's arguments at the lower court level.⁵¹⁰ Prometheus successfully convinced the district court and the Federal Circuit to find infringement even when no dosage change was required to infringe Prometheus's patents; testing for metabolites in this manner is something that a non-treating physician would do during research.⁵¹¹

Additionally, Prometheus's suit against Dr. el-Azhary for researching the metabolite limits on thiopurine drugs for dermatology patients also is contrary to Prometheus's assertion that its patents are limited to a patient treatment setting.⁵¹² Mayo also points to Prometheus's argument about el-Azarhy's knowledge of the Prometheus correlations during her research.⁵¹³ Mayo states that Prometheus's stance on el-Azarhy's behavior has shifted.⁵¹⁴ Allegedly, Prometheus has abandoned its prior argument that el-Azarhy's behavior was infringing in favor of the stance that el-Azhary would not have infringed the Prometheus patents if she "ignored" or "disbelieved" the numbers.⁵¹⁵ This makes the ultimate question of infringement more difficult to answer, Mayo argues.⁵¹⁶

Mayo moves onto the defenses proposed by Prometheus to save the validity of its patents.⁵¹⁷ First, Mayo attacks Prometheus's assertion that the thiopurine drugs are not natural.⁵¹⁸ Mayo points out the thiopurine drugs are not new or the result of Prometheus's efforts, and that the correlation claimed in Prometheus's patents are the result of the body's response to thiopurine drugs.⁵¹⁹ The body's reaction to metabolize these drugs, Mayo argues, is a natural phenomena.⁵²⁰ Mayo then argues against the validity of the Prometheus patents, stating "Prometheus's *claims covering the physical phenomenon are not patentable simply because human intervention was necessary to develop and administer the drug.*"⁵²¹

Mayo moves on to discredit the holding of the Federal Circuit and Prometheus's argument that the thiopurine drugs "transform" the body of the patient and that the patients blood is "transformed" by testing for metabolite levels.⁵²² Mayo paraphrases *Bilski*, saying "transformation is only a "clue" to patentability: not every transformation satisfies Section 101."⁵²³ Mayo also states "conventional data-gathering steps do not create a patentable process out of a natural phenomenon."⁵²⁴ The administering and determining steps, instead of making this a patentable process, actually provide no limitation to the patent because without these two steps, there would be no data to measure.⁵²⁵

⁵⁰² *Id.*

⁵⁰³ *Id.*

⁵⁰⁴ *Id.* at 9.

⁵⁰⁵ *Id.*

⁵⁰⁶ *Id.*

⁵⁰⁷ *Id.*

⁵⁰⁸ *Id.*

⁵⁰⁹ *Id.*

⁵¹⁰ *Id.* at 10.

⁵¹¹ *Id.*

⁵¹² *Id.*

⁵¹³ *Id.* at 11.

⁵¹⁴ *Id.*

⁵¹⁵ *Id.*

⁵¹⁶ *Id.*

⁵¹⁷ *Id.* at 13.

⁵¹⁸ *Id.*

⁵¹⁹ *Id.*

⁵²⁰ *Id.*

⁵²¹ *Id.* at 14.

⁵²² *Id.*

⁵²³ *Id.* at 14.

⁵²⁴ *Id.* at 15.

⁵²⁵ *Id.*

Mayo dismisses Prometheus's argument that *the definition of "process"* in § 101 also encompasses a new use of a known machine or composition of matter.⁵²⁶ This is inapplicable, Mayo argues, because it has no impact on the physical phenomenon exclusion.⁵²⁷

Additionally, using thiopurines and metabolite testing in this way are not "new uses."⁵²⁸ Mayo states, "physicians have long known that thiopurine metabolite levels provide "valuable information" about dosage; that technology to measure metabolites has long existed; and that its claims merely posit a contestable range of numbers for those metabolites."⁵²⁹ Attaching these long standing practices to *a step telling physicians to think about a number range*, Mayo argues, adds *nothing new*.⁵³⁰

Next, Mayo argues that Prometheus's suit against Mayo are not allowed by Congress.⁵³¹ Congress specifically disallowed infringement suits against medical practitioners for performing medical procedures in 25 U.S.C. § 287(c).⁵³²

Mayo's fourth argument focuses on the invalidation of the Prometheus patents based on past precedent.⁵³³ First, Mayo distinguishes the multi-step process in *Deihr* designed to address a particular problem from the invention claimed in Prometheus's patents.⁵³⁴ Mayo states "The *Diehr* patent confined an equation within a particular manufacturing process which ensured that rubber molds were opened at the right moment to perfect the cure-a narrow but important solution to an industrial problem to which there is no equivalent in Prometheus's claims. Doctors knew how to administer drug, test blood and consider metabolite levels long before hearing from Prometheus."⁵³⁵ Then, Mayo makes the analogy between the patent in *O'Reilly* and the Prometheus patent.⁵³⁶ In *O'Reilly*, Samuel Morse attempted to expand his patent rights on the telegraph to encompass any use of electric current for transmitting messages.⁵³⁷ Like the *O'Reilly* patent, Mayo argues that the Prometheus patent attempts to control all activities relating to metabolite correlations in any field.⁵³⁸ Mayo also accuses Prometheus of treating *Flook* like dead letter law.⁵³⁹ This is not the case, because *Flook* was repeatedly quoted and applied in *Bilski*.⁵⁴⁰

The final argument made by Mayo focuses on the impact that invalidating the Prometheus patents would have on innovation.⁵⁴¹ Mayo argues that invalidating the Prometheus patents would have no impact on the patent eligibility of new inventions in the medical field.⁵⁴² This is because the Prometheus patents claim existing technology and the relationship between thiopurine metabolites and patient health, and not a new invention or medical treatment.⁵⁴³

Mayo finishes its brief by asking the court to invalidate Prometheus's patent in conjunction with the finding of the lower court.⁵⁴⁴

12.22 The Court Ruling

The Supreme Court in *Mayo v. Prometheus* invalidated the '623 and '302 patents because these patents claimed a law of nature.⁵⁴⁵ The Court found that the *relationship between the concentration of metabolites in the blood and the probability that the dose of thiopurine drug would be effective was a law of nature*, and therefore patent ineligible under § 101.⁵⁴⁶

The Court recognized that while the invention requires human action to administer the thiopurine drug, *the relationship between the metabolite concentration in the blood and the probability that the dose of the drug is effective is the result*

⁵²⁶ *Id* at 16.

⁵²⁷ *Id*.

⁵²⁸ *Id*.

⁵²⁹ *Id*.

⁵³⁰ *Id* at 17.

⁵³¹ *Id*.

⁵³² *Id*.

⁵³³ *Id* at 19.

⁵³⁴ *Id*.

⁵³⁵ *Id*.

⁵³⁶ *Id* at 20.

⁵³⁷ *Id*.

⁵³⁸ *Id*.

⁵³⁹ *Id* at 21.

⁵⁴⁰ *Id*.

⁵⁴¹ *Id* at 22.

⁵⁴² *Id* at 22.

⁵⁴³ *Id*.

⁵⁴⁴ *Id* at 23.

⁵⁴⁵ *Id*.

⁵⁴⁶ *Id* at 1296-1297.

*of how the body metabolizes thiopurine compounds.*⁵⁴⁷ The Court reasoned that this relationship is a law of nature because it exists apart from human interference.⁵⁴⁸

Following this finding, the Court considered whether the patents had sufficient “inventive concept” to be patent eligible.⁵⁴⁹

Although laws of nature are not patent eligible, the Court recognized that *select situations exist where laws of nature can be claimed as part of a patented invention.*⁵⁵⁰ In these situations, *the law of nature itself is not being claimed.*⁵⁵¹ Instead, *the application of the law of nature is claimed as part of a larger invention in combination with a number of elements.*⁵⁵² This is referred to as “inventive concept.”⁵⁵³ Under this precedent, a process patent that simply recites a law of nature and then states “apply the law” is not valid.⁵⁵⁴ This doctrine exists to avoid both the erosion of patent rights by the broad interpretation of the categories of patent ineligible subject matter, and patent claims that exist for the sole purpose of monopolizing a law of nature.⁵⁵⁵

To determine whether the patents claimed sufficient additional elements, *the court broke the patents down into three different steps*; the “*administering*” step, the “*wherein*” step, and the “*determining*” step.⁵⁵⁶

The “*administering*” step is the step requiring doctors to administer the thiopurine drugs to patients.⁵⁵⁷ The court dismissed the “administering step” as ineligible for patent protection because it only serves to restrict the relevant audience to doctors treating patients with thiopurine drugs.⁵⁵⁸ The court stated that the subject matter eligibility requirement cannot be circumvented by *limiting the technological environment in which invention is used.*⁵⁵⁹

The Court then went on to analyze the “*wherein*” step.⁵⁶⁰ The Court characterizes the “wherein” step as the step that *discloses the relevant natural law claimed by the patents.*⁵⁶¹ The Court found that this step was insufficient to establish subject matter eligibility, and *exists for the purpose educating the relevant audience* about the natural law with the hope that the audience would correctly apply that law.⁵⁶²

Finally, the Court considered the “*determining step.*”⁵⁶³ The “determining” step is the step that instructs the doctor to determine the level of thiopurine metabolites in the patient’s blood.⁵⁶⁴ The Court held that the “determining” step was insufficient to transform an unpatentable law of nature into a patent-eligible application of the law because it was a *conventional activity regularly engaged in by persons in the field.*⁵⁶⁵

The Court then considered these three steps together and found that *the combination of these steps add nothing to the law of nature to make it patent eligible.*⁵⁶⁶

The Court states, “any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.”⁵⁶⁷ In other words, the Court believes that these steps add nothing significant to the underlying natural law to would make it patent eligible.⁵⁶⁸

⁵⁴⁷ *Id* at 1297.

⁵⁴⁸ *Id.*

⁵⁴⁹ *Id.*

⁵⁵⁰ *Id.*

⁵⁵¹ *Id.*

⁵⁵² *Id.*

⁵⁵³ *Id* at 1294.

⁵⁵⁴ *Id* at 1297.

⁵⁵⁵ *NEED NOTE*

⁵⁵⁶ *Id.*

⁵⁵⁷ *Id.*

⁵⁵⁸ *Id.*

⁵⁵⁹ *Id.*

⁵⁶⁰ *Id.*

⁵⁶¹ *Id.*

⁵⁶² *Id.*

⁵⁶³ *Id.*

⁵⁶⁴ *Id.*

⁵⁶⁵ *Id* at 1298.

⁵⁶⁶ *Id.*

⁵⁶⁷ *Id.*

⁵⁶⁸ *Id.*

Following this analysis, the Court discussed past precedent on the issue. First, the court points to *Diamond v. Diehr*⁵⁶⁹ and *Parker v. Flook*⁵⁷⁰ as setting the boundaries of patent eligibility for processes that claim the application of natural laws.⁵⁷¹

In *Diehr*, the court upheld a patent that claimed a process for molding rubber.⁵⁷² The process required the use of the Arrhenius equation to determine the optimal time to open the rubber press.⁵⁷³ This equation was used in connection with a number of different steps, including a step that called for the monitoring of the temperature in the mold and entering the temperature into a computer.⁵⁷⁴ The computer would then calculate the time the mold should open using the Arrhenius equation, and signal for the opening of the mold at the appropriate time.⁵⁷⁵ The Court upheld the patent in *Diehr* because the Arrhenius equation was integrated into the process of molding the rubber.⁵⁷⁶ The Court also noted that *the existence of the patent did not stop others from using the Arrhenius equation itself*.⁵⁷⁷

The Court cites *Flook* as an illustration for the opposite purpose of *Diehr*.⁵⁷⁸ The patent in *Flook* claimed a method for adjusting “alarm limits” during the conversion of hydrocarbons.⁵⁷⁹ During the conversion of hydrocarbons, alarm limits must be adjusted according to certain variables, such as temperature, pressure and flow rate.⁵⁸⁰ To accomplish this goal, the patent disclosed the steps of a process to adjust the alarm limits.⁵⁸¹

This process called for measuring of the level of particular variables, calculating the alarm limits using an algorithm, and adjusting the system according to the new alarm limits.⁵⁸² The Court found that the method was un-patentable because it did nothing other than disclose a formula to determine the alarm limit without limiting the algorithm to a particular application.⁵⁸³ Additional steps disclosed in the patent, such as the monitoring of variable in the process, the use of alarm limits, the idea that alarm limits must be adjusted over time and the use of computers to monitor alarm limits, were all well-known in the art.⁵⁸⁴ As a result, the Court held that there was no “inventive concept,” stating “the discovery of such a phenomenon cannot support a patent unless there is some other inventive concept in its application.”⁵⁸⁵

In light of this precedent, the Court in *Mayo v. Prometheus* found that the process disclosed in the Prometheus patents is closer to the process in *Flook* than the process in *Diehr*.⁵⁸⁶ The Court held that attaching conventional steps to the application of a natural law is not sufficient to satisfy the subject matter eligibility requirement.⁵⁸⁷ Additionally, the Court cites three cases supporting this holding; *Neilson v. Hartford*⁵⁸⁸, *Bilski v. Kappos*⁵⁸⁹, and *Gottschalk v. Benson*⁵⁹⁰.

In these three cases the Court considered whether an abstract idea was eligible for a patent.⁵⁹¹ In the *Mayo* opinion, the Court characterizes each case in different ways to illustrate why the Prometheus patents are invalid. In *Neilson*, an English patent case, the court held that a patent claiming a machine that utilized the principle that hot air improves ignition was valid.⁵⁹² The court upheld the validity of the patent in *Neilson* because the patent did more than simply claim the idea that air temperature improved ignition; instead the patent claimed a machine that embodied this idea.⁵⁹³

⁵⁶⁹ *Diamond v. Diehr*, 450 U.S. 175 (1981).

⁵⁷⁰ *Parker v. Flook*, 437 U.S. 584 (1978).

⁵⁷¹ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012).

⁵⁷² See generally *Diamond v. Diehr*, 450 U.S. 175 (1981).

⁵⁷³ *Id.*

⁵⁷⁴ *Id.*

⁵⁷⁵ *Id.*

⁵⁷⁶ *Id.*

⁵⁷⁷ *Id.*

⁵⁷⁸ See *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1299 (2012). See also *Parker v. Flook*, 437 U.S. 584 (1978).

⁵⁷⁹ *Parker v. Flook*, 437 U.S. 584 (1978) (stating “An “alarm limit” is a number ... operating conditions ... are constantly monitored. When any of these “process variables” exceeds a predetermined “alarm limit,” an alarm may signal the presence of an abnormal condition indicating either inefficiency or perhaps danger.”).

⁵⁸⁰ *Id.*

⁵⁸¹ *Id.*

⁵⁸² *Id.*

⁵⁸³ *Id.*

⁵⁸⁴ *Id.*

⁵⁸⁵ *Id.* at 594.

⁵⁸⁶ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1299 (2012).

⁵⁸⁷ *Id.* at 1300.

⁵⁸⁸ See generally *Neilson v. Harford*, 151 ER 1256 (1841).

⁵⁸⁹ See generally *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

⁵⁹⁰ See generally *Gottschalk v. Benson*, 409 U.S. 63 (1972).

⁵⁹¹ See *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1300 (2012) (discussing these cases).

⁵⁹² *Neilson v. Harford*, 151 ER 1256 (1841).

⁵⁹³ *Id.*

The Court's opinion in *Mayo* characterized the process in *Neilson* as including "not only a law of nature but also several unconventional steps that confined the claims to a particular, useful application of the principle."⁵⁹⁴ In *Bilski*, the Court considered the validity of a patent for hedging the risk of price fluctuations.⁵⁹⁵

The Court held that *the concept of hedging risk was unpatentable because it was an abstract idea*, and that any claims that limited the concept to different markets did not make the idea patent eligible subject matter.⁵⁹⁶ In *Benson*, the court discussed the patentability of using a computer to employ a mathematical process for converting binary coded decimals into binary numbers.⁵⁹⁷ The Court found that this process was unpatentable because it only claimed the *implementation of a mathematical principle without any substantial application*.⁵⁹⁸

After discussing this precedent, the Court states that *granting patent rights in laws of nature, physical phenomena, and abstract ideas would slow scientific progress by restricting access to the tools necessary for innovation*.⁵⁹⁹ The Court points to precedent in *Benson*, *Bilski*, and *Flook* as past instances where the Court refused to allow patent rights to exist in patent ineligible subject matter.⁶⁰⁰

The Court emphasizes why laws of nature cannot be patented, stating "And so there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to "apply the natural law," or otherwise forecloses more future invention than the underlying discovery could reasonably justify."⁶⁰¹

The Court also explicitly states that the narrow application of a particular law of nature does not suddenly make the law patent eligible.⁶⁰² The narrowness of the Prometheus patents cannot save their validity, the Court argues, because they have the potential to prevent doctors from making appropriate treatment decisions and prevent the development of improved treatment standards.⁶⁰³ Additionally, the Court found that the "determining" step claims all processes that use the Prometheus correlations, even processes that may be discovered later, and processes that measure the metabolite levels in new ways.⁶⁰⁴

After this extensive analysis *the Court struck down several of Prometheus's arguments in favor of the validity of its patents*.⁶⁰⁵

First, the Court addresses the Federal Circuit's findings in favor of Prometheus.⁶⁰⁶ The Federal Circuit upheld Prometheus's patents using the machine-or transformation test.⁶⁰⁷ Applying this test, the Federal Circuit found that the processes disclosed in the patent transform feature two transformations; 1) the transformation of the human body with a thiopurine drug (the "administering" step), and 2) the transformation of the blood during the testing of the blood for metabolite levels.⁶⁰⁸

The Court disregards this argument, stating that the first transformation is irrelevant because the "administering" step serves only to limit the application of the law of nature.⁶⁰⁹ This limitation does not weigh on the patent eligibility of the invention.⁶¹⁰ The Court then rejects the Federal Circuit's holding that the second transformation is patent eligible.⁶¹¹ The Court states that the *machine-or-transformation test cannot overcome the law of nature exclusion*.⁶¹²

The Court next addresses Prometheus's argument that the narrowness of the claimed law of nature renders it patent eligible.⁶¹³ The Court rejected this argument because the patenting of narrow laws of nature can still inhibit future

⁵⁹⁴ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1300 (2012).

⁵⁹⁵ See *generally* *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

⁵⁹⁶ *Id.* at 3231.

⁵⁹⁷ *Gottschalk v. Benson*, 409 U.S. 63 (1972).

⁵⁹⁸ *Id.*

⁵⁹⁹ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1301 (2012).

⁶⁰⁰ *Id.*

⁶⁰¹ *Id.*

⁶⁰² *Id.* at 1302.

⁶⁰³ *Id.* at 1302.

⁶⁰⁴ *Id.*

⁶⁰⁵ *Id.*

⁶⁰⁶ *Id.*

⁶⁰⁷ *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 628 F.3d 1347 (Fed. Cir. 2010).

⁶⁰⁸ *Id.*

⁶⁰⁹ *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1302-1303 (2012).

⁶¹⁰ *Id.* at 1303.

⁶¹¹ *Id.* at 1303.

⁶¹² *Id.*

⁶¹³ *Id.*

innovation.⁶¹⁴ Traditionally, the patenting of laws of nature does not depend upon the law of nature's narrowness, and for good reason; courts are traditionally not good at making such distinctions.⁶¹⁵

The Court goes on to reject the argument in the United States's *amicus* brief that these claims should be rejected for lack of novelty and obviousness.⁶¹⁶ The Court states, "[t]his approach, however, would make the 'law of nature' exception to § 101 patentability a dead letter. This approach is therefore not consistent with prior law."⁶¹⁷ The Court recognized that this shift would only serve to create greater uncertainty in patent law.⁶¹⁸ Also, the Court claims that *adopting this principle would make all inventions unpatentable because all inventions would fail the obviousness test when reduced to principles of nature.*⁶¹⁹

The Court next addresses that argument that striking down this patent will remove the economic incentive from medial research.⁶²⁰ The Court rejects this argument by citing many sources that say otherwise, including the American Medical Association, the American College of Medical Genetics, the American Hospital Association, the American Society of Human Genetics, the Association of American Medical Colleges and the Association of Molecular Pathology.⁶²¹ The Court states that *allowing the patenting of these types of medical discoveries would create a patent thicket that would slow research and prevent physicians from providing adequate care to patients.*⁶²²

The Court finishes the opinion by emphasizing that patent law covers many different fields of science and technology, and that *adjusting patent law to suit one particular field could have a huge unforeseen impact on another field.*⁶²³ The Court finishes the opinion by reiterating its holding and invalidating the Prometheus patents.⁶²⁴

⁶¹⁴ *Id.*

⁶¹⁵ *Id.*

⁶¹⁶ *Id.*

⁶¹⁷ *Id.*

⁶¹⁸ *Id.* at 1304.

⁶¹⁹ *Id.*

⁶²⁰ *Id.*

⁶²¹ *Id.* at 1304-1305.

⁶²² *Id.* at 1305.

⁶²³ *Id.*

⁶²⁴ *Id.*

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This book is founded in part on deliberations among the participants in the NSF workshop, chapters that some of them submitted to us, and follow up discussions among members of the editorial board. This chapter provides important information on the breadth and depth of subject matter experience and expertise of this illustrious group. As the diverse topics that this book addresses continue to evolve through scientific discovery and innovation, this chapter also provides website and contact information for readers interested in exploring them further.

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Biography: Dr. Klang completed his doctorate in pharmacology in 2000, researching colloidal formulations as a vehicle in ophthalmology at the Hebrew University in Jerusalem. From 1998 to 2000, he joined the Israeli Ministry of Health, the Pharmaceutical Administration as a senior assistant responsible for health technology assessments of new medications to be reimbursed in the national health services. In 2000 he was appointed as the Chief Pharmacist and Pharmacologist of Clalit Health Services (CHS) which insures more than half of the population of Israel. He initiated the development of the personalized medicine concept in CHS, leading to Clalit becoming the first health services organization outside of the U.S. to fund Oncotype DX as part of the basket of services. He is also the main partner in all of Clalit's medical interventional programs for the community.

Dr. Alexander Kuhn, PhD

Post-Doctoral Researcher, Molecular Genetics, Max Planck Institute; Co-founder and Head of Modeling, Alacris Theranostics GmbH, Berlin, Germany

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Biography: Dr. Kühn studied computer sciences at the Humboldt University, Berlin, biochemistry at the Free University, Berlin and business studies at the Distance University, Hagen. He received his PhD degree at the Free University, Berlin, studying the functional properties of pathway development in the model organism *Strongylocentrotus purpuratus* and applying modeling techniques to elucidate pathway interactions in this organism.

Dr. Kühn is currently a postdoctoral fellow at the Max Planck Institute for Molecular Genetics (MPIMG), in the department of Prof. Dr. Hans Lehrach. He is focusing on applying novel molecular modeling technologies in clinical applications and is involved in several research project aiming the development of comprehensive models that can be used in medical and pharmaceutical research for the establishment of a personalized medicine: TREAT20 projects within the CancerSys program; PREDICT project within the MedSys program, both funded by the German Federal Ministry of Education and Research (BMBF); and "Systems biology of prostate cancer" project funded by the Austrian Nationalstiftung and the Austria Wirtschaftsservice GmbH in

the framework of the IMGUS research program.

For his work on computational modeling of cancer using deep sequencing data Dr. Kühn received the Annemarie Poustka Poster Award for Medical Genome Research from the National Human Genome Research Network (NGFN) committee. He is Co-founder of Alacris Theranostics GmbH, a MPIMG spin-off, where he is leading the modeling department.

Ms. Elva Ngai-Yu Lei

PHD Candidate, Chemistry, City University of Hong Kong, Kowloon, Hong Kong SAR

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Biography: Ms. Lei is currently pursuing her doctorate at the City University of Hong Kong. She was a recipient of the University Research Tuition Scholarship and the Outstanding Academic Performance.

Prof. Derek LeRoith, MD, PhD

Professor at Diabetes and Metabolism Clinical Research Center of Excellence, Legacy Heritage Clinical Research Institute at Rambam (LHCRIR); Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

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Biography: Prof. Leroith has been involved in research in the field of obesity and Type 2 diabetes for a number of years. Initially, while at the NIH as Chief of the Diabetes Branch, he studied insulin and IGF-1 action through their respective receptors. These studies included the normal signaling pathways as well as those pathways affected by disease states including insulin resistance. Prof. Leroith created mouse models such as diet-induced obesity and genetically manipulated mice that resulted in insulin resistance and diabetes for my studies. As Division Chief of the Endocrine Division and Director of the Metabolic Institute at Mt Sinai, Prof. Leroith has for the past few years also been involved in the clinical aspects of obesity and Type 2 diabetes, correlating to his basic research and has published review articles on these topics.

Dr. Nicky Lieberman, MD

Head of Community Medical Division, Clalit Health Services, Tel Aviv, Israel

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Biography: Dr. Lieberman specialized in Internal Medicine (1982-1988) at Meir Hospital (Kfar Saba), becoming chief resident after 6 months and Deputy Director of the Hospital at the end of his fifth year of specialization. He was Deputy Director of Meir Hospital (700 beds regional hospital) until 1993 and then became Medical Director of the Sharon-Shomron District in Clalit Medical Services. During his time at Clalit, one of the largest HMOs in the world, Dr. Lieberman introduced risk management, quality assurance, and disease management in his district. He carries expertise in Personalized Medicine (especially in oncology), Diabetes & Gestational Diabetes management, Cardiology, Pharmacoeconomics, and in general, creating and implementing health programs in the community. In 2011, Dr. Lieberman was elected as president of the Israeli chapter of ISPOR (International Society for Pharmacoeconomics and outcomes research).

Ms. Ann Liebschutz, JD

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Biography: Ann Liebschutz is the Executive Director for the United States Israel Science & Technology Foundation [USISTF]. As the organization's lead Executive, she directs the organization's operations, programs, and staff in addition to leading new initiatives to facilitate R&D cooperative opportunities among U.S. and Israeli government programs and private institutions.

Ann joined the USISTF after serving as Legislative Assistant and Counsel to United States Senator Jim

Bunning. While working as Senior Staff in the U.S. Senate, she managed a diverse legislative portfolio which included Commerce, Science & Technology, Homeland Security, Aviation, Transportation and Infrastructure, and Workforce Development issues. Prior to her service in the U.S. Senate, she served on campaigns and practiced law in Chicago, Illinois.

In addition to having a degree in Physics, Ann is a licensed Attorney holding a Juris Doctor degree from the John Marshall Law School in Chicago, Illinois, which is internationally known for its top Intellectual Property Law Program. A Kentucky native, in her free time, Ann enjoys competitive swimming and running marathons

Prof. Andreas Linninger, PhD

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Biography: Prof. Linninger received his PhD in Chemical Engineering from the Vienna University of Technology. His educational family tree continued at University of Cal Berkeley and finally at the Massachusetts Institute of Technology. He has received distinctions including the Best Paper of 2008 from Computers and Chemical Engineering Journal, the UIC College of Engineering Teaching Award in 2009, and was a Keynote Lecturer at the International Symposium on Process Systems Engineering.

Dr. Yoav Livney, PhD

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Biography: Dr. Livney received his PhD degree from Technion, where he currently is a senior lecturer. His research interests are in physical chemistry, specifically water-structure effects of low molecular weight solutes, and its impact on macromolecules. He also has academic pursuits in nanotechnology, studying nature-inspired nano-delivery systems for nutraceuticals and drugs based mainly on proteins and polysaccharides.

Dr. Tajana Lucic, MD

Director of Medical Informatics, NOA, Inc., Miami Beach, Florida, USA

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Biography: Dr. Lucic received her MD degree from the University of Zagreb in 1988 and went on to serve in the Peace Corps organizing relief for war-devastated populations. She has been leading NOA Inc.'s Medical Informatics projects, since 1996. Dr. Lucic is a member of the Industrial Advisory Board of the NSF Industry-University Cooperative Research Center for Advance Knowledge Enablement

Dr. Alberto Magi, PhD

Assistant Professor, Faculty of Medicine, University of Florence, Firenze, Italy

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Biography: Dr. Magi's main research interests are the development of algorithms for the analysis of large scale genomic and proteomic data and computational methods for the integration and analysis of gene/protein interaction networks.

From 2003 to 2005 Dr. Magi worked on his PhD in "Nonlinear Dynamics and Complex Systems" developing novel algorithms for microarray data analysis and for predicting the function of uncharacterized genes by exploiting the topology of gene networks. After receiving the PhD from Florence University in 2006, he has been a postdoc at the Department of Medical and Surgical Critical Care of the University of Florence (2006-2010). From 2011 he is Assistant Professor at the Faculty of Medicine of the University of Florence.

He has published about 20 papers in international peer-reviewed journals. He is referee of several international

journals spanning fields from numerical analysis to genomic informatics.

Prof. Manuel Mayr, MD, PhD

Professor of Cardiovascular Proteomics, Cardiovascular Division, The James Black Centre, King's College, University of London, London, UK

Associate Editor, Journal of Molecular and Cellular Cardiology

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Biography: Prof. Manuel Mayr received his first degree in medicine from the University of Innsbruck, Austria, where he graduated “sub auspiciis presidentis rei publicae”, the highest distinction awarded for academic education. From 1996-1998 he worked with Prof. Georg Wick at the Institute of Experimental Pathology, Innsbruck, Austria on the role of heat shock proteins in atherosclerosis. Beginning his postdoctoral studies, he joined Prof. Qingbo Xu’s group at the Institute of Biomedical Aging Research of the Austrian Academy of Sciences, working in the area of animal models and cellular signaling in response to biomechanical stress. In 2001, he moved together with Prof. Xu to London. At St. George’s, he developed his proteomic skills and obtained his PhD, entitled “Cardiovascular proteomics: Linking proteomic and metabolomic changes” from the University of London in 2005. In 2006, he spent a sabbatical in Prof. Peipei Ping’s laboratory at the University of California, Los Angeles, to further advance his skills in mass spectrometry. He is now in charge of the new proteomics facility at the James Black Centre that will provide a technology platform for cardiovascular research

Prof. Mayr is a member of the Editorial Board for Proteomics - Clinical Applications and was recently appointed as Associate Editor for the Journal of Molecular and Cellular Cardiology. He is serving on the American Heart Association Program Committee (Council on Functional Genomics & Translational Biology) and the Management Committees of the British Atherosclerosis Society (BAS), the British Society for Proteome Research (BSPR) and the London Vascular Biology Forum (LVBF).

His research interests include Proteomics and Metabolomics Combined with Genetic Manipulation, and Stem Cell Differentiation into Vascular Cells.

Dr. Robert Mennel, MD, FACP

Director of the Baylor Health Care Systems Precision Medicine Institute; and Oncologist, Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, Texas USA

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Biography: Dr. Mennel specializes in medical oncology and hematology with board certification in both internal medicine and medical oncology. He is a Diplomate of the American Board of Internal Medicine with subspecialty certification in medical oncology.

Dr. Mennel received an MD degree from the University of Pennsylvania Medical School in 1970. He completed training in internal medicine at the University of Rochester, Strong Memorial Hospital, in 1974, and a fellowship in hematology and oncology at Johns Hopkins Oncology Center in 1979.

He is member, American College of Physicians, American Society of Clinical Oncology, American Institute of Ultrasound, Texas Society of Medical Oncology; board member, Dallas Chapter of the American Cancer Society; elected to Nu Sigma Nu (National Jesuit Honor Society); received the Navy Commendation for spontaneous work in medical education and healthcare delivery; won the Baylor House Staff Outstanding Teacher Award, 1980, 1983, 1991 and 1994; professor of oncology and internal medicine at Baylor University Medical Center, Dallas, Texas; director of data management Sammons Cancer Center, Dallas Texas; foundation board member at Baylor University Medical Center; member of Medical Advisory Board of the Sammons Cancer Center and associate director of medical oncology at the Sammons Cancer Center, Dallas, Texas. In 2009 D Magazine elected Dr. Mennel as one of the best hematology oncologists in Dallas, Texas.

Prof. Ariel Miller, MD, PhD

Associate Professor of Medicine/Neurology, Head of the Center for Multiple Sclerosis & Brain Research at Carmel Medical Center and co-director of the Pharmacogenetics & Personalized Medicine Center, The Rappaport Faculty of Medicine & Research Institute at the Technion-Israel Institute of Technology, Haifa, Israel.

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Biography: Prof. Ariel Miller holds MD degree from the Sackler school of Medicine, Tel-Aviv, Israel and PhD degree in Experimental Sciences (Neurobiology) from the Hebrew University of Jerusalem, Israel. From 1989 to 1992 he was a research fellow at the Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School in Boston, MA as Fogarty International Research Fellowship scholar (NIH).

Dr. Jessica Nadler, PhD

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Biography: Dr. Nadler is a Manager with Deloitte Consulting, Kennedy's #1 Global Healthcare Consulting firm. Before joining Deloitte, she was an American Association for the Advancement of Science (AAAS) Science & Technology Policy Fellow. During her fellowship, Dr. Nadler served in the Personalized Health Care Initiative at the US Department of Health and Human Services (HHS). As Research Assistant Professor in the Department of Genetics at the University of North Carolina at Chapel Hill, her research focused on gene expression networks associated with social and cognitive behaviors relevant to autism spectrum disorders. Dr. Nadler earned her PhD in Genetics at the University of Washington in Seattle.

Dr. Yousef Najajreh, PhD

Dean of Scientific Research; Assistant Professor, Faculty of Pharmacy; Head of the Projects Department, Planning and Development Office; and Head of the Anticancer Drugs Research Lab, Al Quds University, Jerusalem, Palestine.

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Biography: Dr. Najajreh completed his Post-Doctorate at the Department of Pharmaceutics/School of Pharmacy-Hebrew University and Post-Doctor Researcher at Bethlehem University on Gene Therapy and Pharmacogenic Delivery for Treatment of Restenosis in 2004. In 1999 - 2000 he was Researcher at the Department of Medicinal Chemistry in cooperation with Prof. Joshua Katzhendler developing new antisense and antigene agents with improved properties based on peptide nucleic acids (PNAs). Dr. Najajreh was Teaching Assistant, Department of Medicinal Chemistry at the School of Pharmacy in 1994-1998; and Science Lecturer, El-A'roob Teacher College, El-A'roob-Hebron in 1991 – 1993.

Dr. Najajreh's industrial experience includes Scientific Advisor for PHARMASENSE Ltd., Naiot Technological Center Ltd., Technological incubator in Nazaret Ellit, Israel; and Scientific Advisor to Bioline.

He was PhD fellow at the Department of Medicinal Chemistry, School of Pharmacy, Hebrew University-Jerusalem in 1991 – 1993. His thesis was Methods in Site-Specific labeling of Oligodeoxyribonucleotides (ODNs) with Platinum Anti-Cancer Drugs. He earned Masters Degree in 1991 in Pharmaceutical Sciences. Medicinal Chemistry, Department of Medicinal Chemistry, School of Pharmacy, Hebrew University. His thesis was Synthesis, Characterization and Biological Activity of Platinum-Anthraquinone Complexes. He earned Bachelor Degree in Chemistry, The Hebrew University and was BSc Student/Faculty of Science-Bethlehem University.

Dr. Najajreh's won Prize for Excellent PhD student in 1998; Prize of the Faculty of Medicine for Excellent Master's degree Dissertation in 1993; and Prize for Excellent MSc student from the School of Pharmacy in 1993.

Mr. Abhishek Narain Singh

ICT Associate at University Medical Centre, Groningen, Netherlands.

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Biography: Mr. Singh previously held a position at Aby-O-Tech Solutions in Delhi, India where he was the

Scientific Officer working on various life sciences technologies writing on grant proposals. He also worked as an Associate Professor of Engineering at Institute of Professional Studies and Research, IPSR, teaching courses on genetics, electrical, mechanical engineering, and operations research in interim to gain teaching skills.

Prof. Christopher Newgard, PhD

Director of the Sarah W. Stedman Nutrition and Metabolism Center and the W. David and Sarah W. Stedman Distinguished Professor of Pharmacology and Cancer Biology at the Duke University Medical Center, Durham, North Carolina, USA

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Biography:

Prof. Newgard has served as director of the Sarah W. Stedman Nutrition and Metabolism Center since March 2002. Prior to coming to Duke, he was the Gifford O. Touchstone and Randolph G. Touchstone Distinguished Professor and co-director of the Touchstone Center for Diabetes Research at UT Southwestern Medical Center in Dallas. Before his appointment as director of the Stedman Center, the Stedman Center was recognized as a clinical research center. Since taking over the leadership of the center, Prof. Newgard has combined a strong basic science research program in metabolism with a new clinical research program focused on nutrition, metabolism, and obesity. To these programs he has added a comprehensive metabolic and biomarker profiling program to put the Stedman Center on an entirely new trajectory for success.

A pillar of the basic science research program of the Stedman Center is his own laboratory. His laboratory focuses on understanding metabolic regulatory mechanisms and applying this knowledge to gain insight into chronic conditions and diseases such as obesity and diabetes.

Key projects in the lab include the following: 1) mechanisms involved in the regulation of insulin secretion from pancreatic islet β -cells by glucose and other metabolic fuels; 2) mechanisms involved in obesity-related impairment of β -cell function; 3) development of methods for protection of β cells against environmental insults, including elevated lipids and inflammatory mediators; 4) studies on spatial organization and regulation of systems controlling hepatic glucose balance; 5) studies on the mechanisms involved in lipid-induced impairment of insulin action in obesity and diabetes.

Dr. Joanna Ng, PhD

Head of Research at IBM Canada Software Laboratories, Center for Advanced Studies; and Senior Technical Staff Member, IBM Software Group, Markham, Ontario, Canada

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Biography: Dr. Ng directs the organization to conduct applied research and manages innovative incubation projects in collaboration with academic researchers; researchers and software technologists in IBM. Dr. Ng has held various senior management and architect positions within IBM. She is an IBM Master Inventor with a long track record of profitable innovations. Under her leadership in software strategy and in software product development, she has conceived and led incubation projects with a proven track record of nurturing them into commercialized products.

Dr. Ng has published and edited a book, "The Smart Internet"; and authored/co-authored 27 publications. She has been granted 22 patents, of which, four were world wide patents. In addition to Canada and United States, these patents were also granted by China; France; Germany; Ireland; Italy; Japan; Korea; Netherland; Spain; Sweden; Switzerland; Taiwan and United Kingdom. These patents and publications were in the research areas such as mobile technologies; web related technologies; commerce portal; voice-enabled portal; retail industry solutions; service oriented architecture; semantic and ontology technologies and asset repository related technologies.

Efrat Recanati, MSc

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Biography: A graduate of Hebrew University of Jerusalem Faculty of Medicine School of Pharmacy, Ms. Recanati was Deputy Pharmacist at a community Pharmacy of Clalit Health Services and participated in a Clinical Research of Hepatitis C. She interned at Ichilov Hospital Tel-Aviv

Dr. Ron Ribitzky, MD www.linkedin.com/in/ronribitzky

Work on this book was in his former role as CEO, R&D Ribitzky, Newton, MA USA and Visiting Professor, Kigali Health Institute (KHI), Kigali, Rwanda. Presently Sr. Vice President, Product Management, Symphony Performance Health.

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Biography: Dr. Ribitzky is a physician executive with global experience in healthcare I.T. and life-sciences informatics. He specialized in bringing together medical, technology, and business to shape strategy and drive execution throughout the product, project, and program lifecycle. His engagements included 23 developed and emerging economy countries; and all regions of the US. He published, presented, and led workshops around the world in industry, public sector, and academia.

In 1990 he published the world's first peer-reviewed article on using search engine to enable clinical documents lifecycle management; and near-real-time case-based clinical decision support for patient care and knowledge-management to accelerate scientific discovery in healthcare and life sciences.

Dr. Ribitzky's informatics career developed rapidly from clinical practice to Senior Programmer-Analyst, Director of Applications at Boston Children's Hospital, and Chief Information Officer (CIO) at UMass Medical Center; from medical sales support to VP Prototype Development and VP Advanced Research at Eclipsys; and Senior Healthcare Strategist at Intel where he developed and successfully led worldwide marketing campaign to advance adoption of mobile technology in healthcare.

Focusing on applied research and accelerating the cycle from innovation to practice, Dr. Ribitzky's major interests include the role of user experience in driving adoption of IT, big-data analytics, knowledge management, personalized medicine and translational research informatics, mHealth, national and global eHealth, multi-level interoperability, IT value modeling. He is the inventor of a US patent on component-based object-relational database infrastructure and user interface.

His work in emerging economy markets focuses on accelerating ICT capacity building and addressing the adoption challenges specific to these markets.

Dr. Ribitzky's academic appointments included Visiting Scientist at IBM Science Center and Weizmann Institute's Applied Mathematics; Research Fellow, Medical Informatics at Harvard Medical School; Assistant Professor, Pediatrics at University of Massachusetts Medical School; Assistant Professor, Center for Clinical Evaluation Sciences at Emory University School of Public Health; Visiting Professor, Rockefeller Center for eHealth at Kigali Institute of Science and Technology (KIST) and Visiting Professor, eHealth at Kigali Health Institute (KHI).

Prof. Naphtali Rische, PhD

Professor of Computer Science, Florida International University and Director, NSF Industry/University Cooperative Research Center for Advanced Knowledge Enablement (I/UCRC-CAKE), Miami, Florida

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Biography: Prof. Rische is the Author of 3 books on database design and geography; Editor of 5 books on database management and high performance computing; Inventor of 4 US patents on database querying, semantic database performance, Internet data extraction, and computer medicine; Author of 300 papers in journals and proceedings on databases, software engineering, Geographic Information Systems, Internet, and life sciences; Awardee of over \$45 million in research grants by Government and Industry, including NASA, NSF, IBM, DoI, USGS; Architect of major industrial projects -- both prior to his academic career, and as a consultant since; Founder and Director of the High Performance Database Research Center at FIU (HPDRC); Director of the NSF Center for Research Excellence in Science and Technology at FIU (CREST) and of the NSF International FIU-FAU-Dubna Industry-University Cooperative Research Center for Advanced Knowledge Enablement (I/UCRC); Mentor of 70 postdocs, PhDs and MS; the inaugural FIU Outstanding University Professor.

Prof. Rische's TerraFly project has been extensively covered by worldwide press, including the New York Times, USA Today, NPR, Science and Nature journals, and FOX TV News. Of the 53,000 NSF-funded projects in 2009, it chose 120, including Rische's TerraFly, for the NSF annual report to Congress. Current NSF grants under Rische's P.I.ship include: \$2.9M Moving Objects Databases for Exploration of Virtual and Real Environments; \$800K Ecosystem to Pipeline Research; \$5.2M Center for Innovative Information Systems Engineering; \$300K I/UCRC; \$1M Development of a High-Performance Database Appliance for Geospatial Applications; \$700K Development of an Integrated, Geospatial Analytics Research Instrument; \$750K Instrument for Information Science and Computing in Neuroscience; and over \$1M in smaller current NSF grants. Rische's current industrial grants include \$300K from ALTA Pix, \$1.5M membership fees in the I/UCRC; \$300K in subcontracts from NSF SBIR companies; \$1M in auxiliary income; and \$200K in donations.

Prof. Stefano Ruffo, PhD

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Biography: Prof. Ruffo earned "Laurea" in Physics from Florence University (Italy) in 1977. Before obtaining his permanent position as an Assistant Professor at Pisa University (1981), he got a fellowship from the National Institute of Nuclear Physics in Pisa (1978-1981). From 1987 to 1991 he has been Associate Professor of condensed matter physics at the University of Basilicata. He joined the Faculty of Engineering, University of Florence, in 1991.

Prof. Ruffo's main fields of research are nonlinear dynamics and statistical physics, specifically: hamiltonian dynamics; cellular automata; coupled map lattices and space-time chaos; long-range interactions. He has studied applications of physics to biology: immune system modeling, DNA models. He has published about 150 papers in international refereed journals. He is an editor of Communications in Nonlinear Science and Numerical Simulations (Elsevier) and associate editor of Physica A (Elsevier). He is the chairman of the C3 (Statistical Physics) commission and the vice-president of the International Union of Pure and Applied Physics for the term 2011-13. He is Weston visiting professor at the Weizmann Institute of Science (2010-11) and Chaire d'Excellence at ENS de Lyon (2011-12).

Dr. Joel Saltz, MD, PhD

Chair of the Department of Biomedical Informatics and Director of the Center for Comprehensive Informatics at Emory University, Atlanta, Georgia USA

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Biography: Dr. Saltz's biomedical computing efforts have included development of high-end computing and grid-based systems to support microscopy image analyses, leadership of the design and development effort for the cancer Biomedical Informatics Grid (caBIG®), along with development of frameworks to support data intensive semantically enabled query and computations. His biomedical efforts have spanned cancer, heart disease and infectious disease areas.

His research vision and objectives are to develop principles, techniques and tools that can be used by biomedical researchers to assemble a coherent biomedical picture by integrating information from multiple complementary data sources. The approach is to develop knowledge and data-management middleware so that investigators can explore different ways of synthesizing information from multiple, disparate data sources. This middleware will allow researchers to generate and test biomedically-meaningful hypotheses.

Dr. Saltz's team leads the development of informatics infrastructure designed to support integrated management and analysis of clinical, molecular, pathology and image data. In addition to work with biomedical research teams, they will continue the development and evaluation of computer science techniques, tools and algorithms motivated by deep integrative research applications.

Prof. Eliot Siegel, MD

Professor of Diagnostic Radiology and Nuclear Medicine, Vice Chairman of Radiology Department of Diagnostic Radiology and Nuclear Medicine, and Associate Vice Chairman for Informatics, University of Maryland School of Medicine, Baltimore, Maryland, USA

Director, Baltimore Veterans Affairs Medical Center Radiology, Baltimore, Maryland, USA

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Biography: Prof. Siegel has been recognized internationally for his work in imaging informatics and currently serves as the National Cancer Institute Cancer Biomedical Informatics Grid (caBIG) Imaging Workspace lead, lead for the National Biomedical Imaging Archiving, chair of the Radiological Society of North America Medical Imaging Resources Center (MIRC) committee, and is a designated informatics lead within the national VA network. He has testified before Congress on the crisis in electronic health care records and image interoperability.

Prof. Siegel holds federal and industry funding support for his lab's activities. His teams lead in diagnostic care through CT Scans, Drainages, Ultrasound, Nuclear Medicine, Digital Radiology, Interventional Biopsies, and Doppler Duplex Sonography. Under his guidance, the VA Maryland Healthcare System became the first filmless healthcare enterprise in the US. He has written over 200 articles and book chapters about PACS (Picture Archiving and Communication Systems) and digital imaging, and has edited six books on the topic, including Filmless Radiology and Security Issues in the Digital Medical Enterprise. He has made more than 1,000 presentations throughout the world on a broad range of topics involving the use of computers in medicine.

Prof. Siegel has been named as Researcher of the Year, received multiple awards for innovation, including the Smithsonian award, and was selected as runner up Educator of the Year for Diagnostic Radiology. The readers and editorial board of Medical Imaging have selected Dr. Siegel as one of the top ten radiologists for two consecutive years. He was symposium chairman for the Society of Photo-optical and Industrial Engineers (SPIE) Medical Imaging Meeting for three years, is currently chair of Publications for the Society of Computer Applications in Radiology (SIIM) and has been honored as a fellow in that organization.

His areas of interest and responsibility at local and national levels include digital imaging and PACS, telemedicine, the electronic medical record, and informatics.

Prof. Siegel is board certified in Radiology and in Nuclear Medicine and a fellow of the Society for Imaging Informatics in Medicine as well as a fellow of the American College of Radiology. He received his medical degree and completed his residency at the University of Maryland.

Prof. Alan Shuldiner, MD, PhD

John L. Whitehurst Professor of Medicine and Associate Dean for Personalized Medicine at the University of Maryland School of Medicine; Director, UMSOM Program in Personalized and Genomic Medicine; Head of the Division of Endocrinology, Diabetes and Nutrition in the Department of Medicine; and Investigator at the Baltimore Veterans Administration Geriatrics Research and Education Clinical Center, Baltimore, Maryland USA

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Biography: Prof. Shuldiner received his BA degree (Chemistry) from Lafayette College and his MD degree from Harvard Medical School. He was a resident in internal medicine at Columbia-Presbyterian Hospital in New York City and a Medical and Senior Staff Fellow in Endocrinology and Metabolism in the Diabetes Branch at the National Institutes of Health.

Prof. Shuldiner's major research interests lie in the genetics of age-related diseases, including of type 2 diabetes, obesity, osteoporosis, and cardiovascular disease - common disorders that contribute significantly to mortality, morbidity, and health care costs in the US and world-wide. He also works on the pharmaco- and nutrigenomics of these disorders, with a goal of making genomic discoveries that lead to more effective individualized treatment and prevention of these diseases.

Prof. Shuldiner is best known for his studies in the Old Order Amish, a homogeneous founder population ideal for genetic studies. He leads a large multidisciplinary research team that uses state-of-the-art molecular genetic statistical and epidemiological methods, including both candidate gene and genome wide approaches.

Prof. Shuldiner's group reported the first null mutation in the APOC3 gene which validates apoCIII as a novel target for the treatment of hypertriglyceridemia. Most recently, through a genome-wide approach, his group identified a common gene variant in CYP2C19 that is associated with poorer response to clopidogrel that many cardiologists now use to individualize anti-platelet therapy. This research is supported by the NIH

Pharmacogenomics Research Network and other NIH and foundation grants.

He is the recipient of a number of awards, including the prestigious Paul Beeson Physician Faculty Scholar award, the Ellison Medical Foundation Senior Scholar award, and the 2006 University of Maryland Founders Day Researcher of the Year award.

Dr. Christoph Wierling, PhD

Head of Systems Biology Group, Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany

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Biography: Dr. Wierling's research interest is in the mathematical modeling of cellular processes with respect to development and diseases. His group develops different systems biology resources and tools for the modeling and simulation of biological systems has been designed and implemented. These tools are used in current projects for the modeling of cancer-related signal transduction pathways and their subsequent gene regulatory network, and the effect of mutations on the model behavior. The group is also working on the modeling of stem cell biology and host-parasite interaction. The research is driven by the integration of diverse omics data that is generated by high-throughput technologies.

Prof. Yaacov Yesha, PhD

Professor, Computer Science and Engineering, University of Maryland Baltimore County, Baltimore, Maryland USA

Website: <http://ebiquity.umbc.edu/person/html/Yaacov/Yesha>

Contact: yayesha@umbc.edu

Biography: Prof. Yesha joined the Department of Computer Science and Electrical Engineering at the University of Maryland Baltimore County in 1989. From 1984 through 1989 Dr. Yesha was on the faculty of the Department of Computer and Information Science of the Ohio State University.

Prof. Yesha's research interests include SSME (service science, management and engineering), Web services, personalized medicine, computational complexity, mobile computing, wireless networks, parallel computing, distributed systems, and software testing. He has many publications in refereed journals and proceedings, and has received substantial external research funding from NSF, NSA, NIST, SAP, IBM, and Aether Systems Inc. He published over 50 refereed articles in these areas, was a program committee member of several conferences, and served as program chair of the International Conference on Parallel and Distributed Computing Systems

He received his BSc degree in Chemistry from Tel-Aviv University, Tel-Aviv, Israel in 1973; and MSc and PhD in Computer Science in 1974 and 1979, respectively, from Weizmann Institute of Science, Rehovot, Israel.

Prof. Yelena Yesha, Ph.D.

Verizon Professor, Department of Computer Science and Electrical Engineering, University of Maryland Baltimore County; Associate Director of the National Science Foundation's Center for Hybrid Multicore Productivity and Research (CHMPR) at UMBC; and Site Director of the Multicore Computational Center (MC2), Baltimore, Maryland USA

Website:

<http://ebiquity.umbc.edu/person/html/Yelena/Yesha>

Contact: yeyesha@umbc.edu

Biography: Prof. Yesha oversees a research center comprised of unique multicore computation resources. Established in 2007, the center aims to apply its cutting-edge multicore computing facility to prototype challenging scientific and business applications. In addition, MC2 serves as an invaluable learning tool for students with an interest in high performance multi-core computing.

Prof. Yesha joined University of Maryland Baltimore County in 1989. During 1994 she was the Director of the Center for Applied Information Technology at the National Institute of Standards and Technology. From 1994 to 1999 she served as the Director of the Center of Excellence in Space Data and Information Sciences at

NASA. She is a senior member of IEEE, and a member of the ACM.

Her research interests are in the areas of distributed databases, distributed systems, mobile computing, digital libraries, electronic commerce, and trusted information systems. She published 8 books and over 100 refereed articles in these areas.

Prof. Yesha was program chair and general co-chair of the ACM International Conference on Information and Knowledge Management and a member of the program committees of many prestigious conferences. She is a member of the editorial board of the Very Large Databases Journal, and the IEEE Transaction on Knowledge and Data Engineering, and is editor-in-chief of the International Journal of Digital Libraries.

Prof. Yesha received her BSc degree in Computer Science from York University, Toronto, Canada in 1984; and MSc and PhD in Computer and Information Science from The Ohio State University in 1986 and 1989, respectively.

We are also grateful to contributions made by Dr. Hussein Hallak, Sean Szeja, Prof. Ondrej Topolman, Ying Hsu, Minh Tran, and Ava L. Caffarini.

14 Organizations that influenced this book

The contributors to this book represent wide range of organizations and research groups, academic departments, and business units within them having broad and deep interest in personalized medicine informatics. The purpose of this chapter is to foster international multidisciplinary collaboration on this increasingly important and rapidly evolving subject.

14.1 Healthcare industry

Baylor Health Care System Precision Medicine Institute, Dallas, Texas USA

www.baylorhealth.com/SpecialtiesServices/PrecisionMedicine/Pages/Default.aspx

Carmel Medical Center Department of Neurology Multiple Sclerosis & Brain Research Center, Haifa, Israel

www.reformedms.org/ccsvi-treatment-locator/israel/department-neurology-carmel-medical-center-haifa

Clalit Health Services Community Medical Division, Tel-Aviv, Israel www.clalit-global.co.il/en

Clalit Health Services Health Policy Planning, Tel-Aviv, Israel www.clalit-global.co.il/en

Clalit Health Services Office of the Chief Pharmacist, Tel-Aviv, Israel www.clalit-global.co.il/en

Clalit Health Services Research Institute, Tel-Aviv, Israel www.clalit-global.co.il/en

RAMBAM Medical Center Institute of Endocrinology, Diabetes and Metabolism, Haifa, Israel

www.rambam.org.il/Home+Page/Departments+and+Clinics/Division+of+Medicine/Endocrinology+Diabetes+and+Metabolism/default.htm

RAMBAM Medical Center Diabetes and Metabolism Clinical Research Center of Excellence, Legacy Heritage Clinical Research Institute, Haifa, Israel http://md.technion.ac.il/lecturers/lecturer_desc.asp?lecturerId=697

Texas Oncology Baylor Charles A. Sammons Cancer Center, Dallas, Texas USA

www.texasoncology.com/location-results.aspx?id=80

US Department of Veterans Affairs Maryland Health Care System Department of Radiology, Baltimore, Maryland, USA <http://www2.va.gov/directory/guide/facility.asp?id=181>

14.2 Public sector research and development organizations

Max Planck Institute for Molecular Genetics, Berlin, Germany www.molgen.mpg.de

Max Planck Institute for Molecular Genetics Department of Vertebrate Genomics Systems Biology Group, Berlin, Germany www.molgen.mpg.de/~sysbio

National Science Foundation Center for Hybrid Multicore Productivity and Research (CHMPR) at University of Maryland Baltimore County, Baltimore, Maryland, USA <http://mc2.umbc.edu>

National Science Foundation Industry/University Cooperative Research Center on Advanced Knowledge Enablement, Miami, Florida, USA <http://cake.fiu.edu>

US-Israel Science and Technology Foundation (USISTF), Washington, DC USA www.usistf.org

14.3 Private sector companies

Alacris Theranostics GmbH, Berlin, Germany www.alacris.de

Deloitte Consulting, LLP, Washington, DC, USA www.deloitte.com

Galil Center for Medical Informatics, Telehealth and Personalized Medicine, Haifa, Israel. www.galilcenter.org.il

IBM Canada Lab Center for Advanced Studies, Markham, Ontario, Canada www-927.ibm.com/ibm/cas/canada/research

IBM Software Group, Markham, Ontario, Canada <http://www-01.ibm.com/software/>

Journal of Molecular and Cellular Cardiology, www.journals.elsevier.com/journal-of-molecular-and-cellular-cardiology

NOA, Inc. Medical Informatics, Miami Beach, Florida, USA <http://Polymedicine.com>

R&D Ribitzky, Newton, MA USA www.RDRibitzky.com

The Rappaport Family Institute for Research in the Medical Sciences Central Nervous System in Health and Disease Research Group, Haifa, Israel
www.rappinst.com/Rappaport/Templates/showpage.asp?DBID=1&TMID=84&FID=76&PID=169

14.4 Higher learning institutions

Akdeniz University, Antalya, Turkey <http://biyo.fen.akdeniz.edu.tr/tr.i48.yrd-doc-dr-mehmet-akif-kilic>

Al Quds University Faculty of Pharmacy Anticancer Drugs Research Lab, Jerusalem, Palestine
www.alquds.edu/en/faculties/faculty-of-pharmacy.html

Al-Quds University Mathematics Museum, Jerusalem, Palestine www.alquds.edu/en

Al Quds University Planning and Development Office, Jerusalem, Palestine www.alquds.edu/en

Al-Quds University Science Discovery Center Jerusalem, Palestine www.alquds.edu/en

Ben-Gurion University of the Negev Faculty of Health Sciences Epidemiology Department, Béér-Shéva, Israel
<http://in.bgu.ac.il/en/fohs/Pages/Depts/Epidemiology.aspx>

Ben-Gurion University of the Negev National Institute of Biotechnology Bioinformatics Core Facility, Béér-Shéva, Israel <http://web.bgu.ac.il/Eng/Centers/nibn/Research/ComputationalBiotechnology>

City University of Hong Kong Department of Biology and Chemistry, Kowloon, Hong Kong SAR
<http://www6.cityu.edu.hk/bhdbapp/deptweb/index.html>

Duke University School of Medicine Sarah W. Stedman Nutrition and Metabolism Center, Durham, North Carolina, USA http://stedman.mc.duke.edu/modules/stedman_team/index.php?id=6

Emory University Center for Comprehensive Informatics, Atlanta, Georgia USA
<http://cci.emory.edu/cms/index.html>

Emory University School of Medicine Department of Biomedical Informatics, Atlanta, Georgia USA
www.bmi.emory.edu

Florida Atlantic University Department of Electrical and Computer Engineering and Computer Science, Boca Raton, Florida, USA www.ceecs.fau.edu

Florida International University School of Computing and Information Sciences High Performance Database Research Center, Miami, Florida <http://hpdrc.fiu.edu>

Kigali health Institute (KHI) Regional E-Health Centre Of Excellence (RECHE) Master Of Science In Health Informatics, Kigali, Rwanda www.khi.ac.rw/index.php?option=com_content&view=article&id=146&Itemid=118

Technion Israel Institute of Technology Department of Biotechnology and Food Engineering Laboratory of Biopolymers and Food-Nanotechnology, Haifa, Israel <http://biotech.technion.ac.il>

Technion Israel Institute of Technology Department of Chemical Engineering Laboratory for Nanomaterial Based Devices, Haifa, Israel LNBD.technion.ac.il

Technion Israel Institute of Technology Rappaport Faculty of Medicine, Haifa, Israel <http://md.technion.ac.il>

University of Firenze Faculty of Engineering Centro Studi Dinamiche Complesse, Firenze, Italy
www.csdc.unifi.it/CMpro-v-p-51.html

University of Firenze Faculty of Medicine, Firenze, Italy <https://sites.google.com/site/compbiofirenze/home>

University Medical Centre Groningen, Groningen, The Netherlands
www.umcg.nl/en/corporate/the_university_medical_center/pages/default.aspx

University of Illinois at Chicago Laboratory for Product and Process Design, Chicago, Illinois USA
<http://vienna.bioengr.uic.edu>

University of London King's College School of Medicine Cardiovascular Division James Black Centre, London, UK www.kcl.ac.uk/medicine/research/divisions/cardio/about/jamesblack.aspx

University of Maryland School of Medicine Clinical Informatics Group, Baltimore, Maryland, USA
www.umcg.com

University of Maryland School of Medicine Department of Diagnostic Radiology and Nuclear Medicine, Baltimore, Maryland, USA <http://medschool.umaryland.edu/radiology.asp>

University of Maryland School of Medicine Division of Endocrinology, Diabetes and Nutrition, Baltimore, Maryland, USA <http://medschool.umaryland.edu/endocrinology>

University of Maryland School of Medicine Program in Personalized and Genomic Medicine, Baltimore, Maryland, USA <http://medschool.umaryland.edu/genetics>

University of Maryland Baltimore County Department of Computer Science and Electrical Engineering, Baltimore, Maryland, USA www.csee.umbc.edu