THE 2029 PROJECT

Achieving an Ethical Future for Biomedical R&D

INSTITUTE FOR ALTERNATIVE FUTURES

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Finally, I need to thank all of the scientists who joined us on our quest to discover how biomedical R&D could best contribute to global health by 2029. The real credit for what is best in this report belongs to the people who joined our meetings and shared their thoughts through interviews. Special thanks goes to Paul Blasche for arranging the Draper Labs meeting described in the appendix. All of the scientists named in the appendix and quoted in the report provided a depth of knowledge that we have done our best to represent. I made large, intuitive leaps off the base of their knowledge to come up with the forecasts in this report. If these forecasts prove spectacularly wrong, that is my responsibility. If over the next twenty four years the best of these forecasts prove fortunately right, it will be these scientists with their bold visions for biomedical R&D who we can all thank once more.

Jonathan C. Peck
Futurist

EXECUTIVE SUMMARY

Introduction

In *The 2029 Project: Achieving an Ethical Future for Biomedical R&D,* the Institute for Alternative Futures (IAF) provides a sweeping preview of the greatest advances coming through biomedical R&D. The report forecasts that a wide array of achievements in science will be enabled by an ethical evolution. After scanning the scientific literature, interviewing dozens of scientists and holding meetings focused on 2029, IAF anticipates a culture change. An emerging ethical concern for global health will create the context for medical science to realize its full potential, which will culminate in a Health Advocate Avatar.[1] IAF offers seven recommendations to bring science and ethics together through the Avatar.

The 2029 project explicitly pushes the boundary of optimism because an accelerating rate of change can deliver a cascade of surprising successes in science. IAF contends that scientists who can imagine such success will be all the more likely to achieve it over the next twenty-four years. As a rule scientists want their work to improve the quality of life in this world, and this report shows how such a highly ethical endeavor can unfold.

Futures Methodology

IAF began this project in 2004 using a forecasting method to help scientists imagine success in 2029. The project used literature scans to develop forecasts describing the breadth of change that biomedical R&D promises. IAF used its provocative forecasts to interview dozens of leading scientists who explored the most promising areas for improving health. IAF organized workshops with selected scientists from various disciplines and interest areas to develop further foresight across different fields. To help scientists share common ground in this

[1] In this report the term avatar refers to a computer interface that personifies collective knowledge. The word has been adapted in computer game cultures from a Sanskrit term referring to the incarnation of a Hindu God. (See http://en.wikipedia.org/wiki/Avatar_%28disambiguation%29.)

exploration, IAF prepared multiple briefing papers on potential breakthrough areas.[2] IAF then revised its forecasts after working with farsighted scientists on February 10, 2005 to develop timelines showing how biomedical R&D can develop its greatest contributions to global health.

Health Advocate Avatar

The most exciting forecast is the Avatar. The scientists at the February meeting concluded that IAF should bring them back together with others who have the expertise and capability to help create this Avatar. Basically the Avatar is a knowledge interface that can mediate interactions between individuals and the world of medical knowledge. The Health Advocate Avatar is envisioned as a secure and discreet agent for the individual that also represents a highly ethical learning technology for collective knowledge. A variety of developments and new technologies will be required to provide components for the Avatar, including natural language search engines, truly effective voice recognition, haptic devices and high resolution displays. The Avatar is envisioned to be a coach, educator and health manager that draws on the experience of large populations. The Avatar can provide individuals with control and personalized advice while serving health worldwide. More than just a technological wonder, the Avatar is an ethical development that can facilitate the health of both individuals and society.

Four Timelines

The promise of the Health Advocate Avatar is supported by a large number of forecasts IAF arrayed along four timelines. They anticipate short term (2005-2010), mid term (2011-2020) and long term (2021-2029) developments in biomedical R&D. Each timeline is thematically distinct, yet they flow together to offer patterns of opportunity that the Avatar can synthesize into a growing capability to achieve health. The four timelines are:

- Turning data into information, knowledge and wisdom: Science will have extraordinary tools and immense amounts of data to support knowledge creation.

[2]See http://www.altfutures.com/2029.asp.

- The union between East and West: Bringing together Eastern and western ways of understanding will lead to a unifying theory of biology.
- Moving beyond boundaries: Greater connectivity will accelerate learning around the globe, into communities and by individuals.
- Shift from disease to health potential: Medicine will shift from managing the risks of disease to promoting the potential for health for individuals and society.

Turning Data into Information, Knowledge and Wisdom

Knowledge is power, and more people will gain access to this power. Over the next five years, the flood of data from genetics, proteomics and electronic medical records will be converted into an overwhelming amount of health information. Scientists will use new knowledge tools, such as intelligent agents, to create the context that converts this information into knowledge. By the mid-term the accelerating spread of knowledge will include biomarkers that illuminate cellular pathways. Systems biology will take these pathways into new assessments of individual health potential based on signals of pre-disease. By the 2020s, a prognostic system will emerge and begin to replace the diagnostic systems of the past. Remarkable knowledge tools, such as immersive interactive environments and virtual brains will support the creation and dissemination of knowledge. By 2029 more people will be looking beyond knowledge and asking how to create wisdom.

The Union between East and West

Wisdom can arise from different cultures that will bring their particular gifts together in the decades ahead. Over the next five years Eastern philosophies and practices will be further adopted in the West, complemented by a growing base of Asian scientists bringing their worldview to biomedical R&D. By 2020, this combined knowledge will merge science and ancient beliefs into a new understanding of health that recognizes subtle effects, chaos theory and energy fields. At all levels prevention will become the favored intervention, with pre-disease displacing disease as the focal point for research. Death will become another focal

point, bringing the idea of spiritual health to the fore. By 2029, systems biology with advanced models and simulations will fuse with Eastern philosophies to achieve a unifying theory of biology no less significant than the breakthroughs in physics of the early 20th century.

Moving Beyond Boundaries

Learning will accelerate worldwide over the next twenty-four years as networks grow across such divisions as country, sector, institution and discipline. By 2010, boundaries will blur as open source networks rapidly create and spread knowledge. Fed by a major short-term success against malaria, grid communities and distributed research projects will help open source science create continuous risk assessment for individuals, families and communities. By 2029, complete connectivity between researchers and patients who actively collaborate in science will reinforce a global ethic. The political impact of this ethic will be clear in new intellectual property rules negotiated to speed innovation and diffusion. Biomedical R&D will serve the poor as well as the rich, worldwide. Healthcare can be fully personalized by 2029 to achieve gains in individual and population health that will also create greater wealth.

Shift from Disease to Health Potential

When more disease can be prevented, interest will grow in how health can be created. The shift starts in the near term with regulators accepting the validity of surrogate markers and suites of biomarkers that individuals will use for continuous risk monitoring. As more people learn to interpret biological signals, prevention will take center stage. A low-dose combination therapy will prove successful against heart disease by 2010. This success will lead to a "predict and prevent" approach that fosters global learning cooperatives as people with shared risk factors pool their knowledge. By 2020, risk research will identify indicators for families, communities and societies showing their health potential. Healthy communities will grow in number, and will focus on the role of compassion in creating health. The global health agenda created by these healthy communities will be supported by science and ethics.

Biomedical Research and Development Advances

IAF's 2029 forecasts propose a preferred future for biomedical R&D that is based on what scientists currently recognize as the probable future. The 21st century is poised for many potential advances to improve health, quality of life and longevity that will change how people live and die by 2029. These probable advances include:

Using Knowledge Technologies to Transform Healthcare

Researchers and patients will gain access to greater computing power, new user interfaces and miniature biomonitors that continuously collect data. Knowledge will be created, challenged and changed at a faster rate to "support a purity of thought we've not had before." Key technologies will include:

- Grid computing to supply the power and the storage capacity, enabling endeavors such as the Human Proteome Folding Project.
- Data management tools that mine the vast repositories that can be made available on the "deep web" of dynamic web pages opening up to information retrieval systems.
- Natural language processing that helps computers "understand" human languages at the same time it democratizes scientific knowledge.
- Intelligent agents with increasingly friendly, intuitive interfaces that help both scientists and citizens engage in research.

Developing Knowledge of Health and Disease

Remarkable advances in diagnostics provide new insights into the biology of the mind and the nature of disease. Medical science will predict changes in health status and prevent many illnesses through developments that include:

- Diagnostics capable of distinguishing between sub-classes of diseases and identifying pre-disease states to create new categories of health, including "super healthy."
- Molecular imaging that peers into cellular processes, and uses probes that can be armed with therapeutic agents to address problems such as cancer.

- ‘Omics sciences focused on the study of genes (genomics), proteins (proteomics), sugars (glycomics) and other biologically crucial molecules.
- Systems biology that understands the dynamics within cells based on cross-disciplinary research building up systems knowledge from the cell to tissues, organs and organisms.

Developing an Infrastructure for Personalizing Risk

The ability to continually monitor individuals and create personal risk assessments will lead to individualized therapy. The platforms for assessing risk will define therapeutic selection, meaning the platforms will prove more valuable than the medicines, thanks to:

- Measuring risk using new methods such as adaptive trials with Bayesian statistics used in environments with electronic personal health records.
- Modeling and simulations that work at different levels, from digital models of “virtual patients” down to the more granular levels of genes and proteins. Computer models and simulations will speed experimentation and help predict safety and efficacy for each patient.
- Open source research which increases collaboration across organizational structures and geographies to develop new research tools and incentives for addressing the health needs of the developing world.
- Biomonitors that make it cheaper and easier to continuously measure change in health status so that healthcare is addressed in the home through risk reduction.
- Developing “N of 1” clinical trials which incorporate bioengineered tissue scaffolds identical to a patient for pre-clinical safety assessment as well as combinations of therapies given in low dose to identify the best therapeutic effect for a given patient.

Looking at Potential Breakthroughs

Four specific advances hold the greatest breakthrough potential that will create new hope for patients and new pressures for healthcare systems. Progress on these new therapies will come from both East and West:

- Stem Cells hold the potential for decisively addressing heart disease, diabetes, cancer and neurological diseases such as Alzheimer's and Parkinson's.
- Gene Therapy/Silencing therapeutics are emerging as new delivery technologies target specific cells. A number of Eastern countries are pursuing this promising technology. If scientists can comprehend the complexity of cellular systems there is great potential for RNAi drugs across many diseases.
- Nanomedicine has achieved initial successes in medical devices and diagnostic tests, but a far larger number of applications could come within the decade. Nanotechnology is bringing valuable research tools and clinically useful devices. A breakthrough could come from implantable devices that diagnose, deliver therapies and monitor effects.
- Implants and Drug Delivery devices will improve dramatically as new advances in microelectromechanical systems (MEMS), nanotechnology and other technologies are combined to create new ways of delivering drugs that improve patient care and mobility.

The Evolution of Ethics and Healthcare

While the 2029 project intended all along to forecast scientific breakthroughs, the cultural breakthrough in ethics surprised both the scientists and futurists exploring future possibilities. A global ethic of concern for life worldwide will evolve over the next twenty-four years. Natural selection will favor this ethical position in healthcare, economics and politics. As in nature, human systems are organized as a hierarchy of systems nested in more complex systems. When healthcare creates health, it fosters economic and political advantages. Evolutionary pressure works toward higher global value propositions, and the most advanced communities and societies will adopt the highest level of ethical concern by 2029. This emerging ethical convention will direct law and economics so that science can fulfill its promise to deliver global health.

Seven Recommendations

IAF proposes seven steps to promote the most ethical advances from biomedical R&D, expand knowledge of health and disease, and improve health for everyone.

1. Set a goal for U.N. adoption of a minimum health standard for all.
2. Create personalized risk profiles.
3. Initiate a global discussion of ethical positions for intellectual property.
4. Move from healthcare focused on treating disease to promoting health.
5. Change healthcare regulations to promote information sharing and new methods beyond clinical trials.
6. Foster an open-source system for health research, including drug discovery.
7. Create a collaboration of stakeholders to design and develop the Health Advocate Avatar.

Conclusion

The report concludes that biomedical R&D can contribute more to global health in the future than history suggests is possible. Science is delivering remarkable technologies that can improve the health of billions of people around the world. Knowledge of health and disease will increase dramatically, affecting how biomedical research is performed and healthcare is delivered. The deeper question is how do we unlock the full potential of science? The answer is to evolve our ethical positions so that whole societies gain from the coming knowledge revolution. The Health Advocate Avatar is an exciting way to tie the evolution of healthcare, economics and ethics together. The 2029 Project ends with a call to enhance health, to leap beyond existing strategies and to promote the highest level of global health.

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Introduction

"Any useful statement about the futures should seem ridiculous."[3] The Institute for Alternative Futures (IAF) **2029 Project: Achieving an Ethical Future in Biomedical R&D** may seem ridiculous for its optimism. Why is such an unabashedly positive statement about science and ethics in the future useful? Because an accelerating rate of change leads scientists, policy makers and the public to underestimate rather than overestimate the future contributions of biomedical R&D. In 1980, scientists did not anticipate that they would largely map the human genome by 2005. They could not see how a World Wide Web would link researchers and information. People did not expect that a global biotechnology industry could clone animals and create stem cells and more momentous changes are now before us. Change may be coming faster than we realize. So this report risks overestimating rather than underestimating the potential that biomedical R&D holds for the next 25 years.

There is another, more important reason for pushing the boundaries of optimism rather than just predicting what scientists now think is most likely. People who can imagine surprising success are more likely to achieve it. It fires the imagination to think science can prevent disease, improve global health and bring greater wealth to billions of people who will live on this planet over the next twenty-five years. Science holds this promise. Pessimists are generally more realistic about what can be achieved, but optimists are more successful.[4] So this report portrays the remarkable potential of scientists who by striving together for a noble purpose may surprise the world with their success.

This report is based on more than just optimism. **Section 1** describes the **Futures Methodology Employed for the 2029 Study**. IAF began with an initial research framework

[3] Jim Dator, quoted from Hawaii Research Center for Futures Studies web site (http://www.futures.hawaii.edu).
[4] Martin E.P. Seligman. (1998) Learned Optimism. Simon & Schuster, Inc. New York: New York.

for a literature scan that sought evidence for potential breakthroughs.[5] This scan helped IAF develop an initial set of forecasts intended to prompt and provoke knowledgeable scientists.[6] IAF then conducted dozens of interviews along with a forecasting session at Draper Labs. The interviews helped IAF focus on key changes which became the basis for a meeting with far-sighted scientists that IAF gathered for the 2029 Project.

Section 2 presents the **Vision of a Health Advocate Avatar**, which emerged from this meeting. This Avatar can be a new knowledge interface between individuals and the ever expanding world of biomedical R&D. The vision shows an ethical evolution inciting a scientific revolution to serve both individual and collective health. Readers are invited in this section to imagine a trusted intelligent agent helping each person use the global knowledge base to achieve better health. Just as significantly, this Avatar can help each person contribute to better global health.

Section 3 describes **Forecasts and Trends** anticipating the scientific and technological advances that support the vision of a Health Advocate Avatar. Four timelines bind multiple advances together thematically to show the major changes anticipated by 2029. One theme is *Transforming Data into Information, Knowledge and Wisdom,* which shows a remarkable knowledge revolution coming. A second theme, *The Union Between East and West* describes how future science can support global health advances. The third, *Moving Beyond Boundaries,* anticipates networks overcoming the silos that constrict innovative science in departments, disciplines and sectors. The fourth theme, *Shift from Disease to Health Potential,* takes prevention from the margins of healthcare onto center stage.

Section 4 covers the **Biomedical Research and Development Advances** identified in the extensive research that IAF conducted through literature reviews and interviews with leading

[5] The initial framework, forecasts and a series of background research papers are available on the IAF website: http://www.altfutures.com/2029.asp.
[6] See IAF website: http://www.altfutures.com/2029/2029_Forecasts.pdf.

scientists. This section highlights many specific developments, including knowledge technologies, molecular imaging, systems biology, biomonitors, stem cells and nanomedicine. Many of the advances are revolutionary for healthcare. However, by putting them together the 2029 Project invites a larger recognition that a new capability for health can emerge.

Section 5 addresses **The Evolution of Ethics and Healthcare** with the forecast that our ethical positions will evolve toward a greater human concern for life globally. This report asserts that this higher ethical position will support economic success and improvements in healthcare by guiding science over the next 25 years. The theory of evolution helps explain the rise of this global ethic. Natural selection works on the evolution of healthcare, political economies and ethical positions as well as genes and species.

Section 6 offers **Seven Recommendations** that IAF makes for initiating action in 2005 that can make the optimistic picture of 2029 most likely. We invite readers to take these actions on their own, support others or join IAF as it organizes efforts to make this vision for 2029 real.

Section 7 provides the report **Conclusion**. The central question we ask of science has a surprising answer. How do we make sure the full potential of science is unlocked over the next 25 years? We evolve our ethical position to serve global health. The Health Advocate Avatar is the most exciting step we see to take us up the path that puts science in the service of a higher ethical calling.

This report was informed by many scientists. **Appendix A** lists **Experts and Meeting Attendees** who helped IAF throughout the 2029 Project. **Appendix B** provides **The Draper Laboratory Report** which offers a specific set of forecasts highlighting bioengineering advances.

While many scientists helped to develop the ideas in this report, the Institute for Alternative Futures is responsible for the vision and forecasts. IAF explicitly seeks to push the limits of

possibility for biomedical research and development. Our challenge is to see the brightest future for biomedical R&D and then show the possibilities to those who can help make this healthier future come about.

Section 1: Futures Methodology Employed for the 2029 Study

The 2029 project began in 2004 with an ambitious work plan to study the future of biomedical research and development with selected thought leaders across many scientific disciplines and institutions. Learning is a journey and IAF sought fellow travelers who could identify and understand potential advances in biomedical research. The stated goal was to identify the most important developments that could contribute to improving global health by 2029. Readers will meet the remarkable scientists and healers who guided IAF through quotes and citations in the report. Their words reflect deep insights and a farsighted view of exciting possibilities.

Scanning the Literature

IAF's first step was to create a research framework that would support an extensive literature scan. The scan quickly revealed that dynamic change tends to blur previously distinct topics. Converging sciences and technologies such as biology and informatics can form whole new fields, as in the case of bioinformatics. The scan showed an expansive array of new knowledge and technologies emerging. The challenge was to put it together comprehensively and coherently. Highlights from this literature scanning process are summarized in the **Biomedical Research and Development Advances** section of this report.

Forecasting Potential Developments

From the initial scan IAF created a preliminary set of fourteen forecasts. These were statements designed to be "stalking horses" that would elicit responses from people with informed opinions. IAF sought to be provocative with some of the forecasts, but found in many cases that thought leaders regarded some statements about the future to be too cautious and some too far-fetched.

These forecasts were continually reworked based on additional comments received from our interviewees, as well as 2029 forecasting meetings. These forecasts intentionally pushed the boundary of what is probable both in biomedical research and in healthcare. The forecasts presented in the **Forecasts and Trends** section of this report represent the most exciting of the forecasts developed during the project.

Interviewing Leading Experts

After the initial literature review, we interviewed experts in different fields of biomedical R&D. These interviews clarified and confirmed much of our learning, while taking us into completely new, unanticipated insights. The scientists helped us see what we now regard to be the most promising areas for progress over the next 25 years. Based on these interviews, IAF performed a deeper level scan in selected areas of biomedical R&D to create a series of overview papers that would provide a common framework for our February meeting with selected scientists.[7]

IAF also held a joint meeting with Draper Lab to explore the preliminary forecasts. The Draper Lab workshop produced deep insights into future advances in microelectromechanical systems (MEMS), and nanotechnology. While many of the insights from this joint meeting were carried forward into the February 2005 meeting with leading experts and into this report, more detailed discussion can be found in the meeting report. This Draper Laboratory Report is therefore included in Appendix B.

February 2005 Meeting with Leading Experts

On February 11, 2005, IAF invited 16 experts in the field of biomedical R&D and medicine for a full day meeting to identify the most promising areas of progress over the next 25 years. Based on the previous research and interviews, five overview papers were distributed to stimulate the participant's thinking. The participants were encouraged to think out into the

[7] See the five overview papers on molecular imaging, nanomedicine, open source research, the nervous system and knowledge technologies on the IAF website: http://www.altfutures.com/2029.asp.

future and identify the most promising areas for progress over the next 25 years. Over the course of the day, a surprising shift occurred. The focus of the discussion moved from science to ethics and from the problem of disease to the opportunity for health. The discussions of ethics formed the basis of the **Evolution of Ethics and Healthcare** section of this report. The most exciting breakthrough idea of the meeting was the concept of the Health Advocate Avatar. Based on their thinking, we developed the **Vision of the Health Advocate Avatar.**

Disseminating Learning

Our final stage of the project is disseminating the learning from IAF's Biomedical Research 2029 project to a wider audience. IAF will distribute the report electronically to selected scientific and policy organizations, while inviting the public to download the report from the IAF website.

Section 2: Vision of the Health Advocate Avatar

To explore the scale of change that may be possible by 2029 as advances in many areas converge, consider the concept of the Health Advocate Avatar. Imagine that you are in the future and this knowledge interface is mediating your interactions with the healthcare system. It uses natural language processing to present complex medical information to you in an easy to understand and intuitive way. It allows you to choose the best possible care and helps motivate you to live a healthier life. But it is also a comprehensive intelligent network linking you to providers and global information resources. Through sharing knowledge of your health with the Health Advocate Avatar, you also contribute to greater health for others all around the world.

The Avatar is secure and discreet and is always protecting your privacy and keeping your interests foremost. It works for you and you have control over it. You are comfortable that this Avatar knows all about you—your personal health history, your health-related behavior, your values and your dreams. You know it will use all its knowledge to help you be healthy. When you allow the Avatar to share your information with others on the network your information is presented anonymously. It is only used to identify ways to make you, your community and world healthier. When you interact with your Avatar you are gaining knowledge while giving information.

You might interact through myriad interfaces. You could talk to your avatar, use gestures that communicate via motion, perhaps transmit via neural implants or even use the old fashioned keyboard. You could continuously feed data to the Avatar through monitors, some of which you wear all the time and some of which you pass by periodically. The Avatar would be able to draw relevant information from your personal records, whether medical or financial.

The concept of this Avatar is not so futuristic when you consider the capabilities now available and those likely to emerge over the next 25 years of biomedical progress. Potential components of this avatar are in development now. Natural language search engines and knowledge repositories can already be put into play. Pioneers in personal health records already can provide useful formats, as could other systems now developing electronic medical records. Monitoring technologies now on the market could be part of the initial construction of the Avatar. People are experimenting with exciting prototypes that make the human-computer interaction more friendly and natural. The field of haptics research is combining computer graphics and video display with devices that respond to touch.[8] Once voice recognition and graphic displays become better you may simply talk to the Avatar, which is represented on a high resolution display as a favorite figure now, perhaps as a hologram in the future.

The Avatar would listen to learn what you value most and scan for evidence that confirms how your expressed values align with your actions. The Health Advocate Avatar might scan your purchases and other evidence of lifestyle choices. Monitors could show multiple physiological parameters, such as pulse and calories expended today. Many more biomarkers will be available in the coming years. The Avatar could cross-check all this personal information with leading knowledge centers to provide personalized knowledge about your health status and potential health improvements.

The Avatar will be your coach, educator and health manager. It can draw on the cumulative experience of others with similar needs, wants and values to guide decisions and provide incentives to encourage healthy behaviors. Individuals could keep the locus of control, and this might mean someone could knowingly lie to the Avatar and diminish its ability to help that person reach full potential for health. However, the Health Advocate Avatar would operate under ethical constraints designed to assure that it conveys the best available knowledge back to the individual.

[8] See http://haptic.mech.northwestern.edu/PaperArchives.html for examples and background.

The Avatar has a dual role as an agent for the health of both individuals and society. As it connects to sources of knowledge for you, it also is contributing knowledge needed for the collective health of society. For example, the Avatar could pick up signals showing health trends, such as obesity or depression. Avatars might reveal new threats such as pathogens that emerge in our changing ecology. Using the knowledge they generate, Health Advocate Avatars could coach policymakers and public health leaders responsible for decisions and investments in collective health.

The knowledge of collective health will expand as individual information flows into a variety of collecting pools. Whenever any individual puts knowledge into his Avatar it could benefit everybody in the system that interacts with the Avatar. You could empower your Avatar to exchange data, information or knowledge that adds to the collective pool, while drawing from the pool in order to bring more health knowledge to you. Working like today's search agents only with a good deal more intelligence, the Health Advocate Avatar could be empowered to negotiate entrance into health data bases, sources of information and knowledge. These pools of shared information might include electronic medical records in healthcare provider systems or the growing number of genetic records collected by countries such as Iceland.

The Health Advocate Avatar is as much an ethical opportunity as it is an opportunity for science and technology advances. The Avatar can help people evolve their ethics so they become more knowing contributors to better health at all levels--their families, their communities and people everywhere. Any individual wanting to make the most out of his life in 2029 would gain a knowledgeable guide with the Avatar. The family and neighborhood working for health would find a great resource for community health in the Avatar. The Director-General of the World Health Organization in 2029 could gain knowledge from Avatars around the world to help steward resources toward health for all. Finally, whether in America or Zimbabwe an individual could use the Avatar to learn how personal use of resources affects

everybody else. As the interface for this knowledge, the Health Advocate Avatar can help grow an ethic of responsibility toward ever larger social units beyond the individual.

As individuals, communities and societies become more knowledgeable about their impacts, the ethical demand to create health at all levels should take precedence over short-term, self-centered concerns. The Health Advocate Avatar is thus the facilitator for visions long articulated by health leaders. Whether it is "healthy people in a healthy world" [9] or "health for all"[10] the Health Advocate Avatar can take us much closer to these visions. The Avatar can be a knowledgeable advocate for evolving and achieving the health potential of individuals and societies globally over the next 25 years.

[9] See Institute for Alternative Futures, *The Belmont Vision* articulated by C. Everett Koop and other U.S. healthcare leaders (1992) (http://www.altfutures.com/pubs/belmontvision.pdf).
[10] See the World Health Organization vision and values at http://www.euro.who.int/aboutwho/20021122_3.

Section 3: Forecasts & Trends

The Health Advocate Avatar encompasses many different advances that can shatter the status quo in healthcare. The forecasts that follow describe many capabilities that we foresee which could be integrated into the Avatar's offering. The forecasts are arrayed along four timeline showing important developments through brief narratives and more specific forecasts for the near term to 2010, mid-term to 2020 and long-term to 2029.

Turning Data into Information, Knowledge and Wisdom

Gene sequencers, protein sequencers, video monitors and a host of other technologies have flooded biomedical researchers with new data in 2010. Much of the data gets converted into information about health through high quality studies. More studies become widely available and easier to access each year. Data from electronic medical records (EMRs—owned by systems) and personal health records (PHRs—owned by individuals) help fuel this logarithmic growth of information. The growing databases are converted into health information through epidemiological studies that incorporate genomic, proteomic and phenotypic biomarkers. Advances in molecular imaging, biomonitoring, nanobiotechnology, and the many –omic sciences continue to expand the amount of data available to biomedical researchers.

Short-Term Forecasts: 2005 to 2010

- **Genetic & Proteomic Analysis:** It becomes feasible to determine the entire base sequences of an individual promptly and cheaply. Proteomics has characterized the protein folding structures for many of the most important proteins implicated in disease.

A large number of diagnostic tests quantify the proteins to create a "phenotype profile" showing what is going on in the body at a given time.[11]

- **In-Silico Simulations:** Models and simulations of various cellular, tissue and organ systems use data from genomics and proteomics to represent known physiology. Experiments with these simulations identify safety information that informs scientific development. Electronic Medical Records (EMRs) begin to incorporate personalized models and simulations that help assess individual risk and contribute to safety studies in large populations.
- **Theory of the Brain:** A theory of the brain accurately predicts experimental results showing how the brain works to create many aspects of intelligence.[12] Ongoing studies of the mind also demonstrate to western scientists that eastern meditation techniques can alter emotional states and enhance mental health.[13] Studies of both the brain and mind build a strong case for making mental health the central focus in healthcare.

Scientists working with new tools, such as intelligent agents, are able to quickly organize, understand, and place into context torrents of new information. The resulting scientific knowledge spreads beyond the biomedical R&D community as an interested public takes advantage of the new knowledge tools. Accelerating knowledge creation and exchange propels systems biology up from understanding cells to characterizing whole organisms. Models and simulations embed this understanding into a growing infrastructure for studying risk in both individuals and populations. People monitor biomarkers continuously for changes in cellular pathways. Systems biology takes thousands of these measurements to assess the resilience of systems or "host robustness," which corresponds closely with health potential.

[11] Lee Hartwell (February 28, 2005) Telephone interview.
[12] Jeff Hawkins. (2004). On Intelligence. Henry Holt and Company. New York: New York.
[13] Daniel Goleman. (2003). Destructive Emotions. Bantam Dell. New York: New York.

Medium-Term Forecasts: 2011 to 2020

- **Pre-Disease Recognized:** The gene control and protein systems are sufficiently characterized by 2015 to help scientists predict many disease states. These predictions lead to treatments of "pre-diseases" that can be either modified or prevented through combinations of drugs.
- **Pre-clinical Risk Assessment:** Pre-clinical studies typically use computer models and simulations to predict therapeutic response based on knowledge from molecular and cellular biology. Predictive safety and efficacy studies account for individual variation in risks. Pre-clinical research supports studies of combinations of compounds. Computer models also become more important for ongoing safety studies for approved medicines on the market. Most EMRs include in-silico models that take continuous data from biomonitors to create ongoing personalized risk assessments that also can be aggregated for population studies.
- **Immersive Interactive Environments:** Collaborations of global colleagues are equipped with individualized "immersive interactive environments." (IIE's are multi-media platforms with advanced user interfaces) Using these tools scientists explore, assimilate, model, simulate, predict, and gain understanding to formulate hypotheses for experimentation.[14]

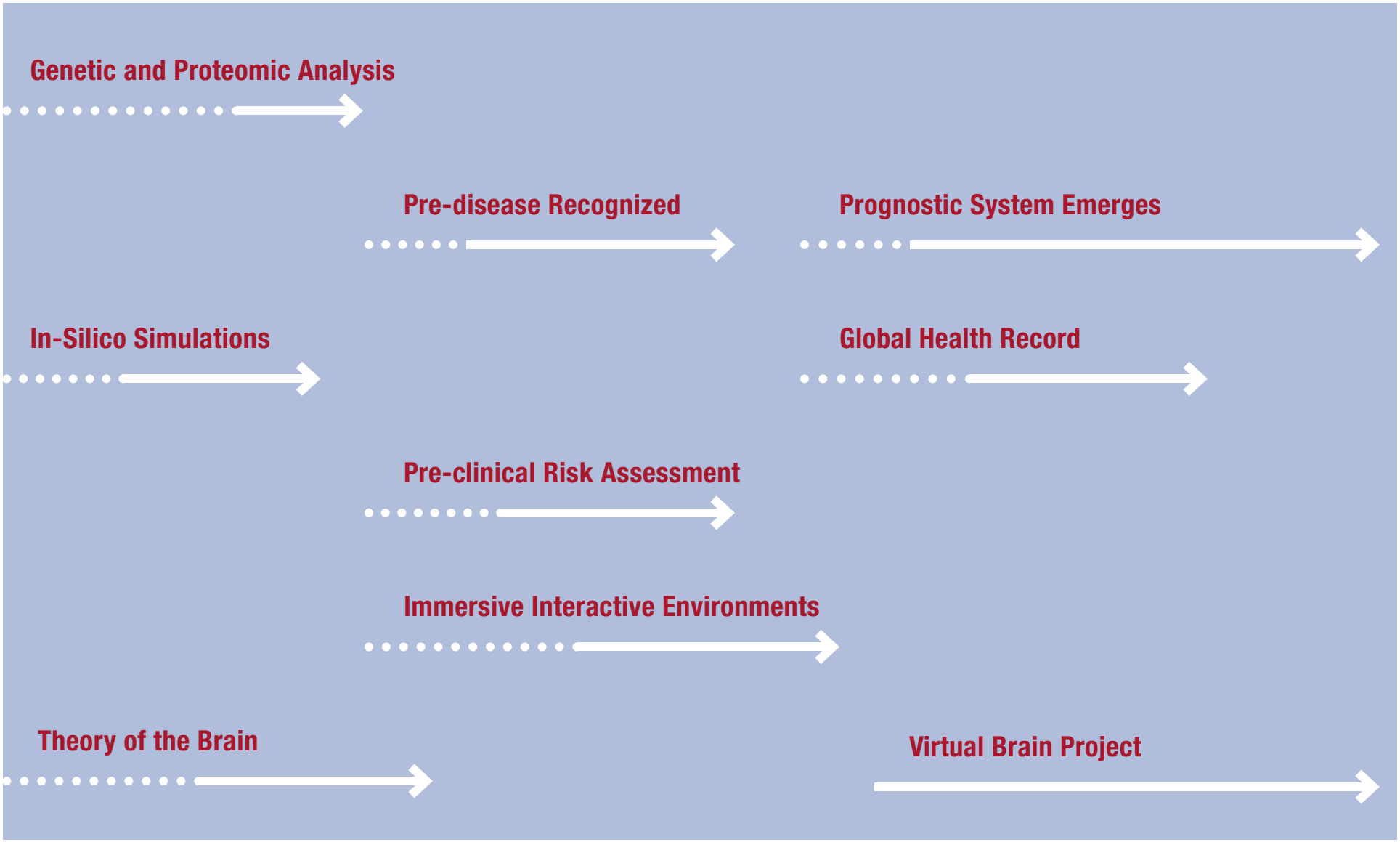
The knowledge revolution passed the tipping point when scientific exchanges reached such a high velocity that researchers find each morning that collective knowledge advanced while they slept. Biomedical researchers have created a working knowledge of biology that comprehends most of the changes in the body, much of the brain and creates new ideas about the human mind. The knowledge of mental states is closely linked to the human health potential of individuals and communities. Risk assessment tools help individuals, families, communities, nations and global alliances predict health status.

[14] Mark Williams. (February 11, 2005) IAF 2029 Meeting.

Long-Term Forecasts: 2021 to 2029

- **Prognostic System Emerges:** Systems biology has developed a new nomenclature for health potential. Clinicians use this predictive system rather than diagnoses to explain the prospects for illness and death to patients. Risk statements are based upon cellular, tissue and organ system measurements along with behavioral assessments and environmental monitors. The frontier of systems biology has shifted from disease to health and from studies of individuals and populations to learning about communities and ecosystems. Both individual and collective health outcomes are predicted with some accuracy in 2029.
- **Global Health Record:** Electronic Medical Records (managed by organizations) and Personal Health Records (managed by individuals) from around the world are merged by an international consortium into a Global Health Record. The vast array of available genomic and phenotypic data helps characterize the diversity of populations and supports surveillance for new health threats that emerge.
- **The Virtual Brain Project:** The Virtual Brain Project is working on the only human organ yet to be well characterized through models and simulations.

TURNING DATA INTO INFORMATION, KNOWLEDGE AND WISDOM



The Union Between East and West

Global conferences, torrents of email across time zones and a burgeoning global traffic in ideas brings East and West closer together in scientific understanding in 2010. China, India, Japan, Korea and Singapore produce a growing number of Asian scientists who are in senior positions across many disciplines in the "hard sciences." Europe and the U.S. have a growing number of scientists in the "soft sciences" who explore Asian health concepts and health improvement methods. For example, studies of cardiovascular rhythms initiated in the brain lead researchers to investigate how older understanding of energy forces such as chi energy also explain physiological phenomenon. New research strategies combine knowledge from East and West so that science validates many ancient beliefs.

Short-Term Forecasts: 2005 to 2010

- **West Adopts Eastern Practices:** Eastern philosophies and practices continue to be adopted by a growing number of Western educated citizens through Yoga, Tai Chi, various martial arts and healing traditions. This phenomenon opens more Western scientists to Eastern views and the dialogue between Eastern and Western scientists continues to grow.
- **Focus on Health:** Health becomes a growing focus. Western research budgets include more studies on host variation (e.g., genetic differentiation) and understanding optimally healthy people such as athletes, long-lived elders and people with stronger immune responses.
- **East Grows Western Science Base:** Eastern science makes a strong in-road into Western medicine. The number of scientists, and the scientific capability in Asian countries, especially Japan, South Korea, China, and India, continues to grow. Asian labs take the lead in stem cell research. The Eastern worldviews coming to biomedical R&D fosters research into subtle effects, chaos theory and the body's energy fields.

Constant exchanges of ideas between East and West create a remarkably fertile decade from 2010 to 2020. Systems level knowledge thrusts up from the cellular, organ and organism levels to explain the dynamics of community health and evolution of ecosystems. Just as remarkably, the ability to manipulate molecules and model cellular pathways creates powerful interventions to address pre-disease states of risk and decisively prevent many diseases. The dynamic interplay between new knowledge of the very small and very large creates a growing demand for biological theories to make sense of it all.

Medium-Term Forecasts: 2011 to 2020

- **Western Culture Shift:** Western culture moves markedly away from its historical emphasis on the individual, toward community and a collective consciousness. Eastern culture moves away from its traditional emphasis of cultural harmony toward a growing fascination with individual expression and accomplishment. A growing number of Asian Nobel Laureates achieve "rock star" status.
- **Research on Healthy Death:** The rising number of Baby Boomer deaths in America feeds a new interest in studies that focus on the experience of death. Interest in the spiritual dimensions of health visibly rises in both the East and West.
- **Young Asian Scientists:** The increasingly large number of educated youth in Asia creates a great drive to excel in science and technology. Asian scientists take leadership in nanotechnology, stem cell research and bioinformatics. The drive toward understanding the smallest units of nature carries with it a growing interest in empowering the individual with technology throughout Asian societies.

A new evolutionary theory unites the more reductionist sciences with systems biology.[15] The decade fosters a new paradigm of biomedical research that integrates ethics and science to

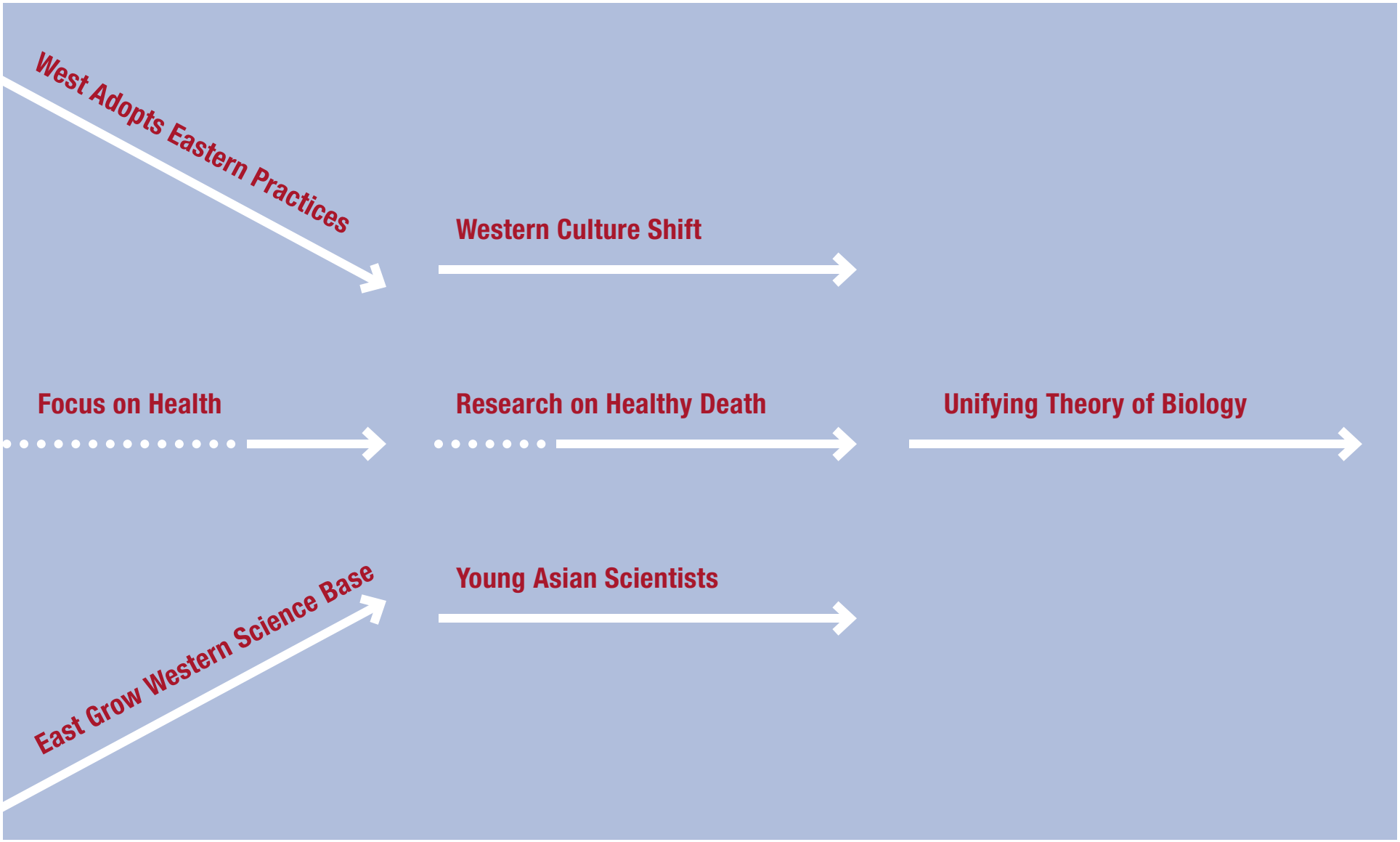
[15] Denis Noble. (2002). Computational Biology. Encyclopedia of Life Sciences. London: Nature Publishing Group, pp. 6-7. Available online: http://www.els.net.

shape new hypotheses and experimentation. New methods of research include new branches of statistics that evolve from large-scale adoption of Bayesian methods used to direct data streams flowing from billions of individuals around the planet. Biomedical research over the decade to 2029 achieves advances in theory no less significant than the shift from Newtonian physics to Quantum physics.

Long-Term Forecasts: 2021 to 2029

- **Unifying Theory of Biology:** The fusion of reductionism, systems biology, and Eastern philosophies with advanced modeling and simulation capabilities achieves a new unifying theory of biology.

UNION BETWEEN EAST AND WEST



KEY: Growing Awareness Growing Acceptance

Moving Beyond Boundaries

Blurring boundaries between disciplines, institutions and geographies accelerates learning. Ideas get rapidly exchanged and enlarged by globally networked scientists. Corporations become intertwined with joint ventures and licensing agreements. Many scientists now have more loyalty to their project partners than to the company paying their salaries. The speed of exchange makes the old boundary between basic, translational and applied research fuzzier, until it disappears altogether. The remarkable success against malaria, using open source research, propels the formation of dedicated networks that challenge old institution-based approaches. Companies spend more externally to work within networks in order to keep up with innovations that are coming faster and from more diverse locations outside their organizational boundaries.

Short-Term Forecasts: 2005 to 2010

- **Merging Organizations:** Large scale research projects in biomedicine bring together industry, academia, NGOs and government to create faster transfers “from bench to bedside.” Successful consortia make the headlines in genomics, proteomics and nanomedicine.
- **Embrace of Open Source:** Developing countries embrace open source research. Universities around the world link-up students and professors in open source networks. Self-organizing networks create instantaneous peer review and rapid dissemination for seminal ideas. Open source research into neglected diseases includes a major success against malaria, which encourages more scientists to try to replicate the approach in a host of research areas.

- **Patient/Provider Dyad:**[16] Healthcare delivery research incorporates new understanding of the patient interactions with healthcare providers in order to better predict outcomes. Healthcare delivery is understood in a new dynamic in which the patient and the provider are viewed as an integral unit. This "dyad" of patient and provider is a well characterized factor in achieving health gains.

Any new idea, product or service for improving health engages scientists and citizens in continuous risk assessment. The most advanced societies and enlightened communities look at risk in a global context. Risk studies link individuals and communities worldwide. Sometimes studies impose the artificial boundaries of controlled clinical trials, but generally research takes advantage of multiple study designs. Scientists work vast data flows with an array of analytic tools. Typically clinical trials are short-lived and generally superseded by other research approaches including continually monitored observational studies. Most patients and "pre-patients" (people at risk for illness) are experimenting actively with combinations of medicines, foods, behaviors and environments. These experiments are typically observed by hundreds of scientists looking at data, generating and testing hypotheses on a continuing basis. Most scientists are themselves research subjects in many experiments as well.

Medium-Term Forecasts: 2011 to 2020

- **Grid Communities:** Researchers who gather online in grid communities collaborate around audacious goals and share research data and ideas for new experiments. Linkages between grids grow quickly across all boundaries.

[16] Dr. Michael Murphy provided the original insight for this forecast during the IAF 2029 Project Meeting, saying "the fundamental unit of interest, even in an experimental setting, becomes the physician-patient unit, not just the patient. You are generating data that becomes actionable information and the leverage point is the interaction between the patient and the physician. The issues in the future, therefore, are not just technological, but they are psycho-social."

- **Distributed Research Projects:** Open source research is the most common method for drug discovery and development. Virtual pharmaceutical companies then take these drug compounds through research phases that are transparent and overseen by networks of scientists, clinicians and patient activists. Patients enroll directly into research studies via the web and become active and knowing participants in clinical research. Health records become the basis for continuous study of drugs in the marketplace with large-scale data exchanges for constant monitoring of safety and efficacy.
- **Social Unit Health:**[17] The Patient/Provider Dyad expands to include teams of providers, family and community. Each social unit is recognized as a contributor to health. Dysfunctional relationships within and between social units are recognized risk factors.

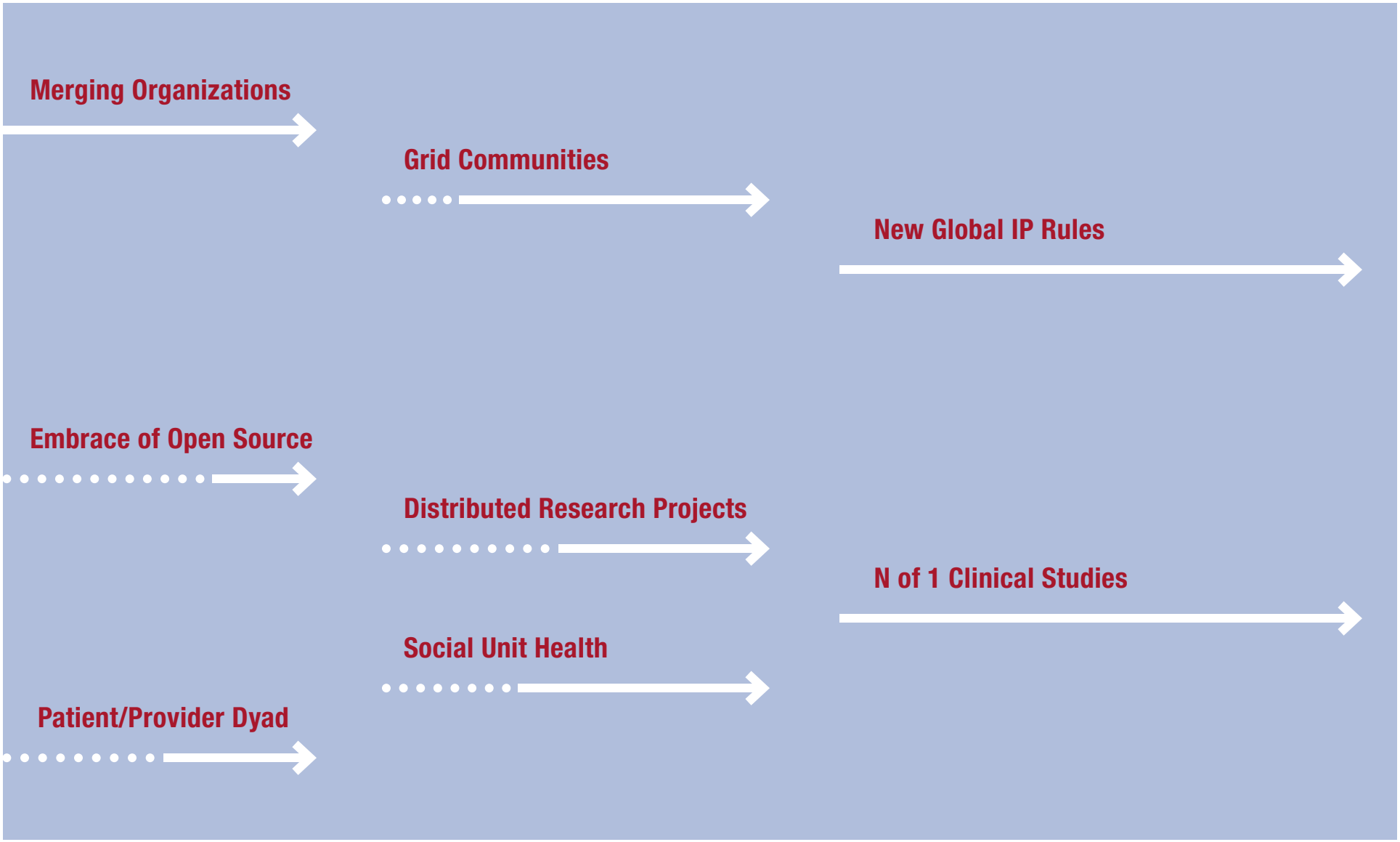
By 2029, institutional and professional barriers begin to weaken and in some cases disappear. Complete connectivity helps researchers and active patients collaborate jointly from anywhere in the world, which reinforces the interest in a global ethic. Institutions become less important as open source research connects scientists from across the world in important projects. Advances in natural language processing and expert systems enable lay people to comfortably access biomedical knowledge whenever the interest arises. Individuals can participate fully in their health decisions confident that they have the knowledge that they need.

[17] Dr. Wayne Jonas provided the insight for this forecast at the IAF 2029 Project Meeting , saying: “I would like to expand the dyad of the healthcare team to include their family or community, nurse, and alternative health practitioners.”

Long-Term Forecasts: 2021 to 2029

- **New Global IP Rules:** The balance between rewarding innovation and encouraging diffusion is re-engineered. The faster rate of innovation produced by global networks using open source agreements encourages an ethical commitment to expand access quickly so that the whole world, including the poor, benefit from biomedical R&D.
- **N of 1 Clinical Trials:** Personalized medicine evolves into tens of millions of human trials where each patient develops combinations of therapies to address his or her unique risk profile. Knowledge of what works is rapidly and universally shared.

MOVING BEYOND BOUNDARIES



Shift from Disease to Health Potential

Regulatory approval and market success for the first major "prevention combo" spurs scientists to seek similar approaches for other diseases.[18] Regulators accept that a suite of proteins measured with an approved diagnostic provides a valid surrogate marker for prevention studies. New studies show that suites of biomarkers can predict risk of multiple diseases. Diagnostics come flooding onto the market to help personalize risk measures, showing finely tuned individual responses to therapeutics and preventives. People who are interested in their health stay alert to their biological signals which provide continuous assessment and feedback to help them achieve their potential for physical and psychological well being.

Short-Term Forecasts: 2005 to 2010

- **Sub-Categories for Disease:** Better diagnostic tools help differentiate between people in disease groups, leading to a wide range of sub-categories for disease. People in these sub-groups link up in global learning cooperatives that support ongoing research into ever more granular risk assessments.
- **Disease Management Expands:** Disease management programs improve through research into behavior change (smoking, nutrition, rest, exercise and meditation). These programs evolve into health management programs that are effective at both preventing disease and achieving measurable health gains.
- **New Biomarkers & Rx Combos:** New biomarkers create the opportunity to prevent heart disease as well as other leading causes of morbidity and mortality through combinations of low-dose therapeutics.

[18] Anthony Rodgers. (28 June 2003). A Cure of Cardiovascular Disease? British Medical Journal, 326: 1407-1408. Available online: http://bmj.bmjjournals.com/cgi/content/full/326/7404/1407.

By 2020, the research question has become "what are the main avenues for communities and countries to help families and individuals achieve their greatest health potential?" Many communities boost their health status by erecting walls against social pathologies and environmental degradations known to hurt health. A number of pioneering communities find they can improve their health status far more by partnering with disadvantaged communities. The more inclusive the ethic of health grows, the more people are positively affected. This finding is consistent with studies from neuroscience showing that compassion, joy and good health are highly correlated.

Medium-Term Forecasts: 2011 to 2020

- **24/7 Risk Monitoring:** Wearable biomonitors that can transmit and store data are widely used to monitor risks and conduct research. Many people rely on the rapid feedback from biomarkers that detect the risk of health perturbations.
- **Community Health Grows:** Research illuminates the pathways through which the brain and mind interact with the body and the social environment.[19] With better understanding of the emotional and cognitive landscape that people live in, the ability to create healthy communities grows. Many communities focus on the development of compassion, collaboration and learning that demonstrably improves the health within and around the community.[20]
- **Prevention Combos:** Cadres of scientists race to discover new ways to predict and prevent disease using combinations of low-dose therapeutics as well as behavioral and alternative medical practices that focus on the mind along with the body.

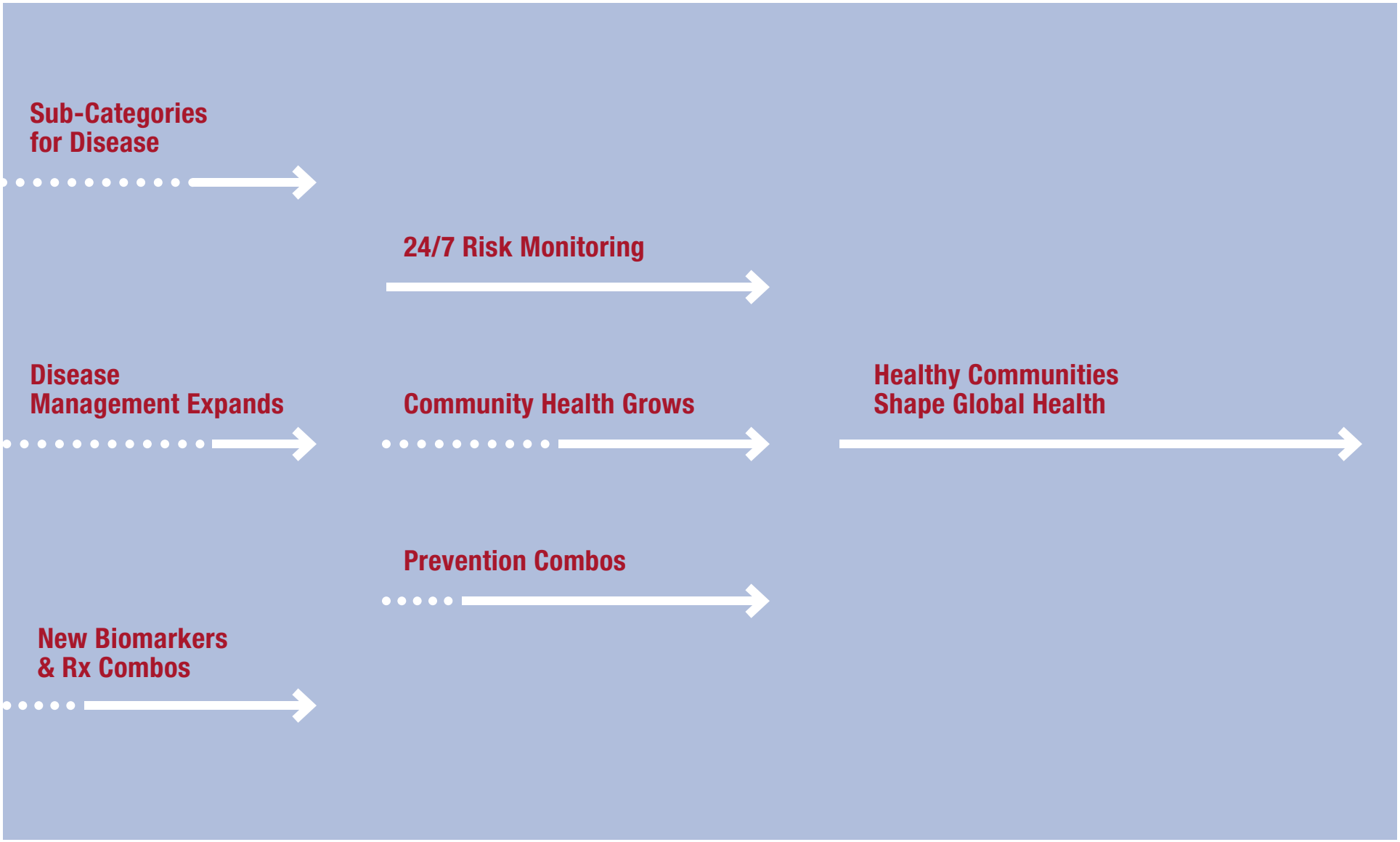
[19] R. Stein. (1 May 2005). "Study Links Discrimination, Black's Health—Stress From Persistent, Subtle Slights May Increase Heart Disease Risk in Women," The Washington Post, A17. See also Robert M. Sapolsky. (1998). Why Zebras Don't Get Ulcers: An updated Guide to Stress, Stress-Related Diseases, and Coping. New York: W.H. Freeman and Company, pp. 37-52.
[20] Daniel Goleman. (2003), Destructive Emotions—How Can We Overcome Them? Bantam Dell. New York: New York.

By 2029, people understand that their health status depends less on avoiding the diseases of yesteryear and more on the many systems factors that diminish health potential. The measurement of health potential goes beyond individual measures to include indicators for families, communities, different societies and global health. Finely calibrated measures of risk help focus attention on both new knowledge and new stressors. Research proves cultural and social dynamics are significant stressors. New pathogens are closely monitored and factored through environmental simulations that predict mutations and transgenic problems.

Long-Term Forecasts: 2021 to 2029

- **Healthy Communities Shape Global Health:** Developing healthy lifestyles becomes a community activity. These healthy communities create a global health agenda to lift up the least healthy in order to improve the health potential of the wealthy as well as the poor. Both science and ethics support this agenda.

SHIFT FROM DISEASE TO HEALTH POTENTIAL



Section 4: Biomedical Research and Development Advances

Futurists use forecasts to describe future conditions that could emerge from current events and capabilities. The forecasts described above are a progression of possibilities that can be anticipated in the present using the lens of a preferred future. IAF gathered the views of many scientists from the literature and from interviews to identify what they believe is the probable future. This section of the report presents the highlights from that research while pointing to important ways in which the Health Advocate Avatar can make the probable future evolve into the preferred future.

When IAF gathered experts to imagine what could emerge from current capabilities, they envisioned the Health Advocate Avatar. They could see the need for a platform to develop the potential for biomedical research and development (R&D) to ethically serve global health. As you review IAF's scan of a 2029 future for biomedical research, you may see other promising patterns and possibilities. The Health Advocate Avatar is just one powerful idea that could transform the future of global health. You may find others in this assessment of capabilities and opportunities. We organized our learning in this comprehensive scan into these areas:

- Using Knowledge Technologies to Transform Healthcare
- Developing Knowledge of Health and Disease
- Developing an Infrastructure for Personalizing Risk
- Looking at Potential Breakthroughs

Using Knowledge Technologies to Transform Healthcare

> AI that makes inferences based on the contingent acceptance of facts is in commercial development. The mathematical basis for it already exists. The challenge is that we have a collection of trillions of alleged facts. To make progress a critical next step is to identify authoritative sources to identify those that are credible. Only from such facts can one create a sound basis for any kind of automated reasoning.
>
> Lucian Russell, Ph.D.
> Enterprise Architect, Computer Sciences Corporation

Biomedicine and biology are in the midst of a revolution. The convergences of information technology with advances in molecular biology have created a surging flood of data. Computer systems are needed to analyze and manage data, improve user interfaces, and create detailed models and simulations. Advances in data management tools are turning raw data into accessible information for biomedical researchers. The challenge is assembling massive amounts of information into the right context, which turns information into knowledge.[21]

User interface advances will democratize biomedical knowledge allowing researchers to collaborate across disciplines, organizations and the globe. Better user interfaces will also enable patients to actively be part of this process. The union of biomedical researchers across disciplines with informed patients will bring wisdom into the healthcare system by uniting the needs and goals of both researchers and patients in an ethical framework.

Computing Power

Bioinformatics is benefiting from the exponential increase in power and reduction in cost of computing power. Biomedical research tasks that could only be done on a supercomputer decades ago can now be done in the lab on a personal computer. In the next few years, these

[21] Mark Williams, (February 8, 2005) Telephone interview.

personal computers will have the speed and accurate algorithms to analyze the large amount of data generated by genomics and related sciences.

Computer chips have migrated into a wide variety of consumer products. Combined with advances in microelectromechanical systems (MEMS), such as sensors and actuators, there will soon be everyday devices able to monitor physical health. These self-contained biomonitors will be able to give us a greater understanding of environmental impacts on health. Improvements in the cost and performance of information storage as well as wireless networking technology have also increased dramatically and will help enable biomonitoring.[22]

Over the next few years grid computing will increase the computing power available for biomedical research projects by distributing tasks among computers over a network. Grid computing allows large numbers of different computers in geographically dispersed locations to combine their processing and storage capacities so that a user essentially sees a single, enormously powerful virtual computer. Grid computing allows everyday people to contribute to the research process by donating computing time on their personal computers. IBM has started the World Community Grid project to network thousands of computers for biomedical research. The first project is the Human Proteome Folding Project that seeks to identify all the proteins in the human body and their functions. The computer grid will be used to compute how new genes fold into proteins and then match those shapes against a three-dimensional protein database, looking for similarities that provide clues about what specific genes do in the body.

[22] National Science Foundation. (2002). Chapter 8: The Significance of Information Technology. Science and Engineering Indicators. Accessed online at http://www.nsf.gov/sbe/srs/seind02/c8/c8s1.htm#top

As a biomedical researcher in 2029 what might knowledge technology allow me to do? Advances in individualization, speech recognition, and haptics provide me with an immersive interactive environment that gives me ready access to relevant pieces of captured knowledge (multimedia, not just text) and it connects me, via sight and sound to similarly equipped colleagues. We can collaboratively explore, assimilate, model, simulate, predict, and gain understanding of the changing knowledge landscape. We can plan and shape the focus of joint investigations, we can even formulate and test hypothesis.

Distributed information architectures, knowledge representation, and symantec interoperability enabled by ontologies will effectively manage vast amounts of information that is produced and published by organizations and individuals. We'll worry about the policy issues: who has access and how much it costs to get access. Enhanced computational power, enabled by such technologies as grid computing and cellular computing, will transform subsets of information into more meaningful and useful forms. AI and intelligent agent technologies will aggregate and assimilate pieces of knowledge and collect information relevant to my specific interests and current work.

Developments like these and technologies for knowledge collection, knowledge management, access and exploitation will facilitate our ultimate goal of collective cognition. An educated consumer/patient will also have access to this technology.

Mark Williams, Ph.D.
Chief Technology Officer, Eastport Analytics

The climb from information to knowledge is happening. I was in the camp of people trying to drink from a fire hose for the last six or seven years, and the omics is still pushing information out the fire hose. With every information flow vector people first get flooded, but then they figure out how to organize the information. They pick their spot and get their head around it. The tools are maturing to enable us to get access to the people who get their heads around the information.

Harold Schmitz, Ph.D.
Director of Science and External Research
Mars, Inc.

Data Management Tools

Large scale data collection techniques are shifting molecular biology from a small highly skilled industry with close ties to academic research into a larger scale industrial operation. This shift is driving exponential growth in the amount of data being generated. Examples of the data explosion include data from systematic DNA sequencing of a growing variety of organisms; micro-array gene expression data from the simultaneous measurement of the expression levels of tens of thousands of genes; 3D data on both small molecular structures and large macromolecular structures (proteins, RNA, DNA); and data for modeling and visualizing biological pathways (metabolic, signaling, genetic control).

Data mining will become more important as the amount of data available on the web increases. The surface web, the web pages we are most familiar with, are primarily collected by search engines "crawling" across hyperlinks. A large amount of research data is hidden from these search engines in the "deep" web"[23] since they are only accessible by direct query and posted as dynamic web pages. It is estimated that the information resources in the deep web are over 500 times larger than those in the surface web. In the decade ahead, database architectures and information retrieval systems will make data in the deep web available to researchers and patients.

Proactive patients are using the internet to access information about health and using that information to make better decisions. The Consumer's Union has already opened a Best Buy Drugs website to help patients choose the most cost-effective beta-blockers, anti-depressants, and statins.[24] Over the next few years, natural language processing combined with large databases of scientific peer-reviewed journals will go beyond online websites to democratize scientific knowledge and provide better assessments of risk. Patients will be able to access

[23] This information has also been called the "invisible" web. We use the term deep web because the data is not invisible, merely hard to find.
[24] For more information see: http://www.crbestbuydrugs.org

the latest scientific research through online libraries cheaply and easily, making them more informed and better able to choose their healthcare. This new audience for scientific journals will demand scientifically rigorous and understandable assessments of risk that they can personalize.

> The semantic web is feasible and likely to emerge but how long will the knowledge be right? Medicine is about to go through a period when conclusions are going to be found to be wrong at a faster rate. Conclusions made from one situation will not apply to other situations. Regulatory systems make it slower. It takes 20 years to move new knowledge to the point that it changes the practice of medicine….The healthcare community is not ready for the amount of empowerment that the web is about to give the consumer. When I think about what I can find in the primary literature and on WebMD, I can see both good and bad in what the consumer can do with information. Either way it is a significant revolution. There are not significant market forces driving quality in healthcare. That is going to change. Even now I can find reports on the Internet that let me compare how many procedures have been done at Mayo and at the Cleveland Clinic. When I can see practice data I will be making decisions. Doctors will still be relevant for the human component, but if they cannot accept consumer empowerment they may be pushed aside.
>
> Martin L. Ferguson, PhD
> Founder and Senior Vice President
> Ardais Corporation

Natural language processing helps computers "understand" human languages. Computers that are better able to "understand" human queries are better able to manage and present information in a context that leads to knowledge. Natural language processing is proving extremely valuable in biomedical research where large electronically accessible bodies of text are today's main repositories of new knowledge. The MEDLINE database, for example, contains over six million abstracts of articles going back to 1966. PubMed Central and other initiatives will increasingly provide access to full articles. Large medical libraries will become

available online as Stanford, Harvard, the University of Michigan, Oxford, and the New York Public Library work with Google Inc. to digitize millions of volumes in their collections. New tools for searching and analyzing these large bodies of text are accelerating research progress and democratizing access to biomedical information.

Ontologies work well for data integration when used in a single discipline for capturing concepts expressed as nouns, but work less well across disciplines when there is a conflict in terminology. They are also ineffective when concepts are expressed by verbs. The new direction is to use both nouns and verbs, and the new technology is called automated question answering. It is where natural language processing will next be applied on the web. However, inside companies there is a lot of gold to mine using Ontologies. The risk, however, is that each organization will make its own Ontology. The result would be to formalize quasi-independent cultures with their own world views, reflected in the different nomenclatures. The benefit, however, is realized by allowing this to occur as the first of two steps. Reviewing these as a collection will reveal where functional groups have different priorities, organizational views, and focus on levels of! process. It will also reveal where there are missing pieces. The second step is to identify the concepts that are common throughout an organization and to publish them. By doing this, and insisting on their use, the great strength of Ontologies is realized: the company can make visible its way of working and leverage the strengths of its component parts to make a stronger whole.

Lucian Russell, Ph.D.
Enterprise Architect, Computer Sciences Corporation

Artificial intelligence (AI), in the form of expert systems, has proven disappointing, primarily because these systems are 'brittle': they cover only narrow domains of knowledge and lack key aspects of 'common sense.' As knowledge gained from research is increasingly reported directly as structured formats that facilitate computational analysis, AI combined with ontologies[25] will become a powerful tool in data mining for patterns of significance within large

[25] Ontologies are exhaustive and rigorous conceptual maps of concepts and their relationships within a domain of knowledge.

bodies of data. A current example of making knowledge available in machine readable formats is the sequence information in GenBank.

By mining and correlating information from the literature in multiple disparate fields, AI systems may be able to generate hypotheses and propose experiments that otherwise would not be developed. Mikhail Blagosklonny has argued, for example, that all the information necessary to understand the feedback control of the p53 chromosome function was available in MEDLINE ten years before it was finally explicated.[26]

As more knowledge from research is placed directly into machine readable formats, opportunities will expand for "automated learning" in which AI systems generate hypotheses and, where possible, test them against appropriate data. As a result, the basic approach to research in biomedicine will begin to shift. In the past, the field was dominated by the conventional scientific approach in which researchers formulate hypotheses, devise and conduct experiments to test the hypotheses, and evaluate the results. In the emerging approach, vast amounts of data are collected and stored. This data is then mined by computers for new hypotheses, and researchers choose the most interesting hypotheses to test using other data, experiments, or simulations.

Over the next few years, intelligent agent technology will enable biomedical researchers and patients to focus less on manipulating data for information and more on placing that information in context to create knowledge. They will be able to gather and sort, filter and connect relevant information. Intelligent agents will do much of the "finding the dots" as well as "connecting the dots" so that biomedical researchers and patients can focus on understanding what they mean.[27] In doing so they help biomedical researchers and patients move from data to wisdom.

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[26] Mikhail V. Biagosklonny and Arthur B. Pardee. (2002). Conceptual Biology: Unearthing the Gems. Nature, 416: 373.

[27] Mark Williams. (February 8, 2005). Telephone interview.

These knowledge tools will be available to develop the Health Advocate Avatar. AI systems will be able to sift through vast amounts of biomedical data to highlight and analyze data that is important to specific patients. Better biomonitors, biomarkers and genomic information will enable the Health Advocate Avatar to apply that data to the patient's unique circumstances. This kind of tailored healthcare is likely to be much more efficacious and cost-effective than current treatments.

> The knowledge problem will need a new infrastructure for learning with tools that support a purity of thought that we've not had before. The internal infrastructure for science is geared toward getting data and putting it somewhere. Now with ontologies we find that people who ask the right question can get to the data, but many people cannot get to the right question. With the right question the knowledge is there for people who get to the fundamental issues involved.
>
> Sheryl Torr-Brown, Ph.D.
> Director of Knowledge Management
> Pfizer Global Research and Development

User Interfaces

User interfaces for computers will become progressively more user-friendly and intuitive. These interfaces will make it easier for researchers to access and use the latest information to create scientific knowledge. Advances in individualization, speech recognition, and haptics will provide an immersive interactive environment for computer researchers. Retrieving and interpreting captured knowledge (including multimedia) will be easy and intuitive and it will be easy to connect with similarly equipped colleagues from around the world. This will allow biomedical researchers to shape joint investigations and even formulate and test hypothesis

online. Combined with advances in knowledge management and acquisition, the biomedical researcher will be able to collaborate on increasingly complex and sophisticated problems.[28]

Over the next few years, grid communities, where biomedical researchers meet online to exchange ideas, knowledge, and research findings, will become important ways for biomedical researchers to increase their reputation in their professional fields and update knowledge and skills. Grid communities will become more valuable as user interfaces make interacting and collaborating online easier. Over the next ten to twenty years, grid communities will be transformed into virtual bazaars where biomedical researchers from around the globe specializing in different disciplines can conduct research.

In the long-term, researchers and patients will have access to "immersive interactive environments."[29] Advances in individualization, speech recognition, and haptics will provide researchers and patients with an immersive interactive environment that gives them ready access to relevant pieces of captured knowledge (multimedia, not just text) and connects them, via sight and sound to similarly equipped colleagues in grid communities. They can collaboratively explore, assimilate, model, simulate, predict, and gain understanding of the changing knowledge landscape. They can also plan and shape the focus of joint investigations. They can even formulate and test hypotheses.[30]

These same advances will be available to patients and incorporated into the Health Advocate Avatar. Patients will be able to join and contribute to research conducted in grid communities as a partner in the research process. The Avatar will provide patients access to the knowledge needed to participate in research endeavors. The Avatar's facilitation should help patients overcome the linguistic and cultural barriers that now separate researchers from patients. This

[28] Mark Williams (February 11, 2005) IAF 2029 Meeting.
[29] Immersive Interactive Environments (IIEs) are multi-media platforms with advanced interfaces and knowledge representation tools.
[30] Op.cit. Mark Williams

union of patients and researchers can create genuine wisdom in the research process by aligning the needs and goals of both researchers and patients.

Developing Knowledge of Health and Disease

> There is a convergence between different technologies and disciplines, but at the heart of it is a merging of our perceptions of health and disease. This fundamentally is the recognition that we are both simultaneously healthy and diseased at all times. The decision becomes how tolerant are you of disease and how desirous are you for health. How much are you willing to pay to shift your place on the continuum? And that ultimately becomes the question of health and healing capacity, not simply choosing a drug to treat a disease.
>
> Wayne B. Jonas, M.D.
> Director, Samueli Institute

As therapies evolve from focusing on diseases to centering on prevention, the healthcare system will also need to evolve with the science. Biomedical R&D will expand to integrate various "soft" factors that influence health, including mental states, lifestyle choices, and environmental factors. Clinical researchers will broaden their interests beyond frequency statistics and individuals to account for variations in the family, community, and physical environment. Cheap bio-monitors and genomic tests will help provide the needed data to researchers. Various electronic technologies will help analyze and synthesize these "soft" factors to inform a patient's choices of therapies.

Advances in diagnostics could greatly expand the range and depth of disease sub-categories. Instead of diagnosing a broad class of cancer, for example, doctors will be able to diagnose sub-categories of the same cancers based on their unique molecular profiles. As these sub-categories become better defined treatments will become more personalized. Eventually,

treatments for many diseases will be tailored to the individual. These advances will herald a change in thinking, over the next five to ten years, from a disease-oriented approach to a health-oriented approach. The “one disease, one cure” model of medicine will be replaced with a framework where there are multiple diseases or pre-disease states and a variety of therapies that have different risks and costs.

Growing knowledge of individual and community health, enhanced by the Health Advocate Avatar, will enable both patients and health policymakers to focus on a “best buys first” strategy based on costs, benefits, and risk assessments. A “best buys first” strategy would focus on the health advances that deliver the most benefit for the least cost and the lowest risk. Increasing the knowledge of health and disease will open up many areas where health can be improved and resources can be preserved. For the individual patient this means focusing on the most effective therapies at the lowest cost. In many cases the best buy will be in community healthcare.

Advances in Imaging

It is possible that some individuals, particularly those that might be regarded as "high risk" start on the path toward Alzheimer's disease in the decade of the 30s when the first histopathological evidence of Alzheimer's disease might be detected. In the intervening years from initial biochemical insult to the clinical manifestation of dementia one might say that the brain is engaged in an epic struggle, developing compensatory mechanisms and coping strategies that mitigate awareness of disability. Since a large percentage of neurons might be lost prior to that day when a disease becomes an illness, biomarker and imaging technologies are vital to detect, and ultimately prevent these debilitating diseases well in advance of their clinical expression.

Michael Murphy, M.D., Ph.D.
Chief Medical Officer and Senior V.P. for Drug Development
TorreyPines Therapeutics

Advances in imaging technologies have transformed how doctors diagnose patients. Imagining technologies developed since the 1970s, such as Computed Tomography (CT), Positron Emission Tomography (PET) and, later, Magnetic Resonance Imaging (MRI) have helped doctors diagnose disease early in its progression and differentiate disease more effectively. These imaging technologies have also been vital to increased understanding of the brain and mental states. Over the next ten years, these technologies will continue to evolve and diffuse as the technology becomes smaller, more robust, and cheaper.

MRI scans have become more common as the technology has improved. Scans that used to take hours can now be completed in seconds. Researchers are already working on smaller MRI units able to perform imaging on individual body parts. By 2020, it should be possible to perform real time MRI scans on moving patients. An entire room could be magnetized to produce resonance. Patients inside the room would wear special helmets that send information to the scanning unit of the position, angle, and speed of the moving head. The processor inside the scanning unit can then compensate for the movement of the patient when processing the images. Real time scanning of moving patients will create new knowledge of how the brain functions during social interactions. This will translate into new insights on learning and behavior that can be used to improve learning environments in schools and even improve mental and social cognition.[31]

The frontier in imaging technology is currently molecular imaging. Molecular imaging allows noninvasive visualization in space and time of normal as well as abnormal cellular processes at a molecular or genetic level of function. It can also be used therapeutically by adding therapeutic agents onto the imaging probes used. The discipline of molecular imaging has

[31] Magoroh Maruyama. (2003). New Technologies for Brain Study: A Meeting Ground for Social, Biological, and Psychological Sciences. Futures Research Quarterly, 19 (2): 13-22.

evolved rapidly over the past decade through the integration of cell biology, molecular biology and diagnostic imaging.[32]

A key component in molecular imaging is the imaging probe which hones in on the specific target of interest in the body. The probe is visualized by a scanner. Although the concept is simple, the process is complex and requires extensive expertise and equipment. The probe must be safe, not alter the disease process being studied, be able to reach the target in sufficient concentration, and not accumulate in other tissues. The probe must also be retained long enough to be detected. Currently there are over 500 probes with many more in development.[33]

Molecular imaging will become more important as genomics and proteomics expand the number of relevant molecules to visualize. Systems biology and knowledge management tools will also help scientists and clinicians interpret the growing number of molecular images. Futurists anticipate that scanners could become so small and inexpensive that they will move from research settings to doctors' offices and then homes—think of the handheld tricorder like device on Star Trek. Molecular scans which could only be done in a few research centers a decade ago (e.g., PET) have since become widely disseminated. The same can be expected of future molecular imaging technologies, especially as nanotechnology investments bring about smaller devices that can diffuse rapidly into research and clinical settings.

Advances in imaging will support the union of Eastern and Western approaches to science by allowing researchers to study meditation, health, and energy flow. Already, brain scans show that advanced meditation can create remarkable neurological changes that energize areas of the brain associated with happiness. Our interviews and meetings with experts found many scientists anticipate that molecular imaging will illuminate a large number of biomarkers to

[32] Ronald G Blasberg and Juri Gelovani Tjuvajev. (2003). Molecular-genetic imaging: current and future perspectives. Journal of Clinical Investigation, 111:1620-1629.
[33] Claude Nahmias. (2002). Molecular imaging: the next frontier. Canadian Association of Radiologists, 53(5): 255-7.

mark disease processes. Beyond disease, some see that molecular imaging could prove even more important for revealing healthy and "super healthy" biological processes as well. Molecular markers for other parameters such as resiliency, stress levels, immune function, balance and energy flow could help us shift from a disease treatment focus to a prevention and even a health enhancement focus.

The Brain and Mental States

> If we had measures to precisely manage the mind via the brain-- including neurological emotion measures--we could develop an empowering approach to mind and self-management. This has implications beyond health into the areas of well-being, individual joy, family function, community wellness and even perhaps social peace.
>
> Wayne B. Jonas, M.D.
> Director, Samueli Institute

The biology of the mind is capturing the imagination of the scientific community in the 21st century much as the gene did in the 20th. Biologists are using structural biology to show a molecular basis for what the nervous system does in everything from individual molecules, DNA, proteins and neurons to living organisms. But the brain may be the most complex structure in the universe, and we do not have good principles for understanding how all these billions of neurons assemble into a biological wonder that can process information to create knowledge and even wisdom.

Advances in brain imaging have illuminated the brain's processes. Positron Emission Tomography (PET) scans, and the more recent functional Magnetic Resonance Imaging (fMRI) scans have allowed researchers to study activity in the brain as a person thinks or acts. These advances have allowed cognitive neuroscience to identify patterns related to more complex thoughts, emotions, and character traits such as extroversion. In the next five years,

the advances in cognitive neuroscience could enable a host of non-medical technologies that can be used for neuromarketing, detecting lies, and job screening. Creating new ethical agreements to address the use of cognitive neuroscience will be especially important.[34]

Until recently it was assumed humans were born with all the neurons they were ever going to have, and that the addition of new ones would be disruptive to established neural pathways. Researchers now know that there are concentrations of neural stem cells in the hippocampus and ventricles of adults and that the body uses them for neurogenesis. Development of humeral factors and techniques to manipulate neurogenesis could be therapeutically important as some diseases, such as stroke, Parkinson's, Alzheimer's, and Huntington's, are due to the unnatural death of neurons.

Scientists have also learned more about synaptic plasticity and the formation of memories over the last three decades. Memory storage arises in the synapses between neurons and passes through two phases to form short and long-term memory. The processes involved are complex and require extensive dialogue between the synapse, nucleus and maybe even surrounding support cells. The postsynaptic NMDA receptor is a key to synaptic plasticity and is the center of a vast scale-free network of proteins. These proteins work together as a "molecular machine" regulating the conversion of electrical signals to cellular changes. Understanding of "molecular machines" and networks shifts thinking away from simple gene-protein linear biochemical pathways to a regulatory dynamic model. This will be important in devising therapies for the complex factors causing human psychiatric disease and enhancing cognitive function.[35]

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[34] David Dobbs. (January 25, 2005). Brain Scans for Sale: As brain imaging spreads to nonmedical uses, will commerce overtake ethics? Slate. Accessed online at http://slate.msn.com/id/2112653

[35] R. Douglass Fields. (February 2005). Making Memories Stick. Scientific American: 75- 81.
Seth G.N. Grant. (2003). Synapse signaling complexes and networks: machines underlying cognition. BioEssays 25:1229-1235.
Erik R. Kandel (2001). The Molecular Biology of Memory Storage: A Dialogue Between Genes and Synapses. Science 294:1030-1038.
Eric Klann and Tomas E. Dever. (2004). Biochemical Mechanisms for Translational Regulation in synaptic Plasticity. Nature Reviews Neuroscience. 5:931-942.

Neurological disorders cause more than one quarter the total disease burden in the U.S. About half of human genes are expressed either exclusively or preferentially in the brain, but genetic relationships are complex, and the hope for identifying protein products for targeting new drugs has yet to be successful. Progress is being made in understanding degenerative neurological diseases such as Parkinson's, Alzheimer's and Huntington's. It is likely that effective drugs, vaccines, or gene therapies will control some of these diseases in the next 10 to 15 years. Neuropsychiatric disorders, such as schizophrenia, appear to be a complex interplay of genetic and environmental factors, possibly resulting in several protein abnormalities and producing developmental defects early in life. They are likely to be much more of a challenge to understand and control. Major advances in treating neuropsychiatric disorders are unlikely before 2029.[36]

Some of the drugs developed to treat these neurological disorders could also be used to enhance cognition. New drugs for enhancing cognitive function with fewer side effects are already being tested. Patients given the drug propranolol have been shown to blunt the formation of painful memories involved in post-traumatic distress disorder. Donepezil, a cholinesterase inhibitor developed for the treatment of dementia, has been shown to improve the performance of airline pilots in computer simulations. Modafinil has been shown to improve the performance of helicopter pilots when they have been sleep deprived and improve the concentration, learning capacity, and mental agility of healthy volunteers. Other drugs, including cyclic adenosine monophosphate affect memory modulation and are also being researched for enhancing cognition. These drugs could lead to a "cosmetic" neurology that

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James L. McGaugh. (2000). Memory – a Century of Consolidation. Science, 287:248-251.

[36] R. Douglass Fields. (February 2005). Making Memories Stick. Scientific American: 75- 81.

Seth G.N. Grant. (2003). Synapse signaling complexes and networks: machines underlying cognition. BioEssays 25:1229-1235.

Erik R. Kandel (2001). The Molecular Biology of Memory Storage: A Dialogue Between Genes and Synapses. Science 294:1030-1038.

Eric Klann and Tomas E. Dever. (2004). Biochemical Mechanisms for Translational Regulation in synaptic Plasticity. Nature Reviews Neuroscience. 5:931-942.

James L. McGaugh. (2000). Memory – a Century of Consolidation. Science, 287:248-251.

focuses on enhancing cognition to improve the performance of highly skilled professionals and students.[37]

While science has made great strides in understanding neurons at genetic and molecular levels and mapping localized brain activity during different mental states, there has been a reluctance to develop productive theories for how the brain works as a whole. Even though this is a daunting task, it is essential for trying to make sense out of the complex details. Jeff Hawkins' "memory-prediction framework" is an example of a comprehensive theory. He states the crux of intelligence is the ability to make predictions about the future, and this ability evolved with the development of the neocortex in mammals. Hawkins hopes to apply the knowledge of the "memory-prediction framework" to computer programming to create tools able to mimic some of the higher level functions of the human brain.[38]

The advances in neuroscience mentioned above will create greater knowledge of how mental states influence physical health. Researchers have already established links between stress and positive outlooks and some chronic conditions including heart disease.[39] Advances in neuroscience will also create opportunities to treat disease and enhance cognition. Creating an ethical balance between what is acceptable enhancement and what is unethical will become more important moving forward. Advances in understanding the brain will also shift to a more Eastern focus on the mind and its links to health. This will shape new research approaches to studying both the brain and mental states.

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[37] Anjan Chatterjee. (2004). Cosmetic neurology: the controversy over enhancing movement, mentation, and mood. Neurology, 63: 968-974.
Colby Strong. (2004). New Therapies Blur the Line Between Treating the Sick and Aiding the Healthy. Neurology Reviews.com, vol. 12, no. 11. Accessed online 5/2005 at http://www.neurologyreviews.com/nov04/nr_nov04_therapies.html

[38] Jeff Hawkins. (2004). On Intelligence. Times Books, New York: New York.

[39] Op. Cit. Sapolsky (1998).

Learning about health may tend to begin with the mental state. So we learn about states of mind, from mental health to high energy…. You don't have to go as far as Buddhist studies and eastern religions to see the relationship between mental health and resilience with religion. Twenty five years from now I think we will know more about the relationship right down to the molecular level. Accepting that meditation and prayer affect health and have a molecular pathway, we will see the multi-dimensional, multi-faceted relationship between health and disease.

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Worldwide V.P. Drug Safety Sciences
Pfizer Global Research and Development

The Rise of the –Omics

The intensive study of genes and other molecules using high throughput screening and advanced software for analyzing massive amounts of data have been loosely described as the –omics. These scientific studies will play a critical role in the future of biomedical R&D. Genomics, the first and most well known –omic science, studies genes and their role in health. The Human Genome Project held the promise of creating a bewildering array of new treatments. Many researchers believed that understanding the genome would help identify new targets for drugs and how patients would react to drugs. Genomics was expected to predict disease susceptibility, and allow biomedical researchers to alter or silence genes that cause hereditary diseases. Biology no longer looks that simple. Five years after the rough draft of the human genome was published, scientists understand more about the genome and its role in the cell. It is becoming clear that more knowledge is needed about other molecules and their role in cellular regulation to turn knowledge of the genome into new therapies.

The problem is the sheer complexity of the genome and its interactions with other molecules inside the cell. Many strands of what was originally labeled "junk" or "dark" DNA are proving to have much more of an impact than previously thought. In the next five to ten years, advances in genomics will shed more light on the role of "dark" DNA in the cell. The interactions of other

molecules, such as proteins and sugars, are instrumental to how the genomic information is expressed. Developments in proteomics, glycomics, and other molecular sciences will increase knowledge of the genome's function inside the cell.

Genomics has produced some early successes. Genomics is stimulating the development of new therapeutics by revealing new targets for drug development and by giving scientists new ways to develop drugs, vaccines, and diagnostic devices. For example, current DNA microarray technology, commonly called DNA chips, can measure the expression levels of tens of thousands of genes. About 22,000 protein encoding genes have been identified and more than 1,400 human genes have been directly correlated with disease. So far, more than seven million variants to the genome have been catalogued.[40]

These advances from DNA microarray technology will provide researchers with lots of new data about the genome and individual differences between genomes that predispose and cause disease in individuals. Genetic testing already can identify more hereditary diseases. Turning this data and information into knowledge and wisdom that can be used for improving health is the next step. Combined with advances in other –omic sciences, systems biology, and risk assessment, genomics will help biomedical researchers assess risk and create new targets for drugs and vaccines. For example, a cancer risk and response to therapy could be determined to a large degree by variations in the patient's genome.[41]

As genomics allows a more precise knowledge of how genetics predisposes individuals to disease, it is likely that what are now considered single disorders with a common set of symptoms will be further refined into more precise classifications. This has been referred to in the literature as a molecular taxonomy of disease. Also, some diseases, including cancers,

[40] D.R. Bently. (2004). Genomes for Medicine. Nature, 429: 440-445.
[41] Lee Hartwell. (February 28, 2005) Telephone interview.

develop into diseased tissue that has a different genetic make-up than the patient in which it resides. Identifying these differentiated genes can help determine the optimum treatment.[42]

Genomics will also reveal more about nutrition and health: functional foods and nutraceuticals are beginning to merge and offer foods that heal. The next step is for food science departments and food product companies, to develop nutragenomics, or structuring diet around genomic information. An early indicator can be seen in popular diets such as *Eat Right for Your Type*, which structures your diet around your blood type.

However, understanding the genome is only the first step in developing new treatment options. A more complete understanding of the role of proteins and sugars is required to understand the system of molecular interactions inside a cell. From a systems perspective, each of the molecules inside the cell form a piece of a jigsaw puzzle and with each piece that is better understood and placed in context, the knowledge of the cell grows larger.

Like genomics, proteomics --the study of proteins and their role in the cell-- must be placed in the context of the larger cellular system since the function of proteins is closely tied to their cellular, tissue and physiological context. Recent developments in protein sequencers have allowed a hundred fold improvement in identification of proteins.[43] Over the next few years, advances in protein diagnosis will improve biomarkers for diseases such as cancer, and create new targets for drug therapies. Over the next five to ten years, proteomics will play a large role in developing a systems level knowledge of the cell. This will make it possible to create better models and simulations and overcome research barriers to gene therapy and gene silencing.

Sugar chains, like DNA and proteins also play an important role in the cellular network. Sugars are involved in everything from embryonic development to regulation of the immune

[42] Nuffield Council on Bioethics. (2003). Pharmacogenetics: ethical issues. Retrieved Online 2/2005 at http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf on page 13-18.
[43] Leroy Hood. "Systems Biology: Changing Biology, Medicine, and Society." Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.

system. Like genomics, and proteomics, developing a better understanding of the interaction of sugar molecules could lead to new therapies or improve existing therapies. Glycomics can play an important role in cancer research. Sugars help to transmit the signals that prompt unchecked cell growth. Glycomics could create new ways of disrupting or slowing the progression of cancer in the next five years by disrupting the signals of cancerous cells.

Environment

> We need a diagnostic of normal rather than of sick. We are hung up on the belief that we have errant notes in an orchestra, and we go about seeking that note to fix it. If we try to understand the whole, we may be better able to re-architect the understanding of disease to fit into the context of health. We will then see pre-disease and etiology more clearly. Today we can see a disease like SARS and respond, but tomorrow we may see that a sick chicken is a signal of an ecological illness leading to SARS. Whether it is sick chickens or sick trees, they signal an imbalance in our plant-animal interactions that tell us we are at risk and in a pre-disease state. We are dependent upon nature. So if we depend on a food system that is not healthy it will either make us sick or prevent us from being fully healthy.
>
> Brian Lovatt, M.D.
> Vision Healthcare Consultancy, Ltd.

Environmental factors also play a role in both drug response and health. Advances in the –omics, systems biology, and epidemiology will allow biomedical researchers in 2029 to better understanding how an individual's genotypes interact with its environment and lifestyle to produce physical traits (i.e. phenotypes). Understanding phenotypes will allow doctors or the Health Advocate Avatar to recommend precise therapies that include not only medicine, but also changes in lifestyle and environmental factors that are individualized to the patient.[44]

[44] J.A. Robertson, B. Brody, A. Buchanan, J. Kahn, and E. McPherson (2002). Pharmacogenetic Challenges for the Health Care System. Health Affairs, 21(4): 155-167.

Advances in biomedical R&D will also have a large impact on environmental health. Currently, only a handful of the eighty thousand chemicals in commerce have been tested. This is due in part to the expense and length of time necessary for toxicity studies. For example, the chronic rodent bioassay, the gold standard for toxicity testing, costs upwards of 3 million dollars and three to four years to complete. DNA chips can be used to examine the changes in gene expression in a cell after exposure to toxic chemicals. It only takes a few days and a couple hundred dollars to test a chemical using a DNA chip.[45]

Within a decade DNA chips will revolutionize toxicology. It will be possible to analyze all of the chemicals in commercial production and test chemicals early in the research and development process. Since most chemicals are likely to pose some risk it will be important to determine what constitutes an acceptable environmental risk. Genomics will also enable biomedical researchers to determine which individuals are more susceptible to environmental pollution. Since individuals will have more knowledge of how pollution affects their health, they may push for more environmental regulation. This could either shift many types of production to closed loop systems, where environmental pollution is minimized, or further concentrate polluting industries in low income areas. It is likely that environmental justice issues will move even further into the decisions of health policymakers and biomedical researchers.[46]

The relationship between individual benefits and collective risks will create an ethical imperative for industry as knowledge and transparency increase. Communities will reshape the agreements with the companies that reside within their borders so that liability for environmental health is clear and fair.[64] By 2029, achieving health gains for the individual will require improving the health of the entire community and vice versa.

[45] Gary E. Marchant. (2005). Genetics and the Future of Environmental Policy. In R. Olson and D. Rejeski (Eds.) Environmentalism & The Technologies of Tomorrow (pp. 11-19). Washington: Island Press.
[46] Gary E. Marchant. (2005). Genetics and the Future of Environmental Policy. In R. Olson and D. Rejeski (Eds.) Environmentalism & The Technologies of Tomorrow (pp. 11-19). Washington: Island Press.

Systems Biology

> The relative contribution of systems biology toward a basic understanding about molecular contributions in disease makes me wonder if systems biology will be the genomics of the next decade. If you look at all the major academic centers in the world there are no major centers for genomics or proteomics—no departments. That's because they are tools. There are departments now forming for systems biology and that is because there may be disciplines behind this knowledge. So I wonder if systems biology will do the same thing as genomics. The rise of heavy computing power may generate new knowledge that we are not equipped to understand…. The emergence of the quantum biologist who does not think the same way as the classic biologist and chemist makes me wonder if we will see parallels between them and traditional practitioners. Look at Ki Kong practitioners who are describing pathways. Maybe the essential concepts of Asian medicine are an alternative way of thinking about systems biology. Rather than looking for molecular and cellular correlations we need to think about systems differently. Maybe the Eastern philosophies are manifestations of Leroy Hood's notion of perturbing systems back to health.
>
> Wayne Rosenkrans, Ph.D.
> Business Strategy Director, Astra-Zeneca Pharmaceuticals

The human body is an incredibly complex set of interconnected systems with an array of feedback loops and emergent properties. The previous scientific approach of reducing this complex system to its component parts in the search for cures for disease has produced remarkable results over the last fifty years and is likely to produce more. However, there is even more to be gained by aggregating this knowledge into a system level understanding.

The advances in molecular biology, particularly in genome sequencing and high-throughput measurement, have sparked interest in understanding cellular functions at a systems level. Advances in biology, but also advances in computer science, engineering, mathematics and

statistics are vital to systems biology. These advances are allowing biomedical researchers to develop an understanding of cellular processes from the ground-up.

Systems, however, are more than just the sum of their parts, and systems biology is developing an understanding of system structures and dynamics inside the cell. A better understanding of cellular systems will allow detailed models of cell regulation and the multiple pathways of various proteins that interact within a cell. Better models of cell regulation will also make it easier for researchers to run certain aspects of drug discovery in-silico and identify the sources of adverse drug reactions. A lack of systems biology knowledge may be an important reason why many drug candidates, especially for complex diseases, fail in preclinical and clinical trials. It is quite possible that the Food and Drug Administration may one day demand that drugs be screened using simulations.[47]

Systems biology quite naturally leads to predictive and personalized medicine. Understanding the cellular system will allow researchers to make probability statements about disease. In the next 10 to 15 years, for example we will be able to look at individual genes and make mathematic models to compare them to defective genes. Understanding how those genes affect the cell could allow researchers to predict emergent behavior and identify perturbations in the cell. Identifying perturbations in the complex system inside the cell will allow researchers to identify pre-disease states. [48]

Advances in models and simulations combined with advances in systems biology will allow patients to get a “predictive health history” for diseases with root causes in the cell. Blood will be the window into health and disease and a drop every month will provide the information

[47] Hiroaki Kitano. (2002). Systems Biology: A Brief Overview. Science, 295:1662-4.
[48] Leroy Hood. “Systems Biology: Changing Biology, Medicine, and Society.” Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.

needed for prevention. Prevention is likely to include combinations of drugs since there will be more than one factor contributing to a perturbation in the system.[49]

The potential for a systems level understanding of biology is not limited to the cell. The same advances in biology, computer science, engineering, mathematics, and statistics that are helping to create a systems level understanding of cellular processes could also be used to develop a systems level understanding up the transcending levels of biological holarchy. Creating a systems level understanding of cellular processes will allow biomedical researchers to develop better models of other systems including organ systems. Combined with advances in understanding neurological function, mental states, and environmental factors, it will be possible to create models of organisms to predict individual health.

Developing an Infrastructure for Personalizing Risk

> Signals and information will be where biology goes. Information is order in biological systems and our understanding of signals will make our understanding of disease obsolete. Understanding how other cultures understand disease will also help. The science of chaos will be how we understand whole organism effects. The idea of an etiology of disease will go away. We will also see that mono-drug therapy, and possibly drug therapy as we know it will fade. Randomized clinical trials will also diminish. Randomized, controlled trials sensitive enough to pick up systems information will be too expensive. We will do large, observational studies that have thick enough information to understand probabilities, model interactions and cause.
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> Wayne Jonas, M.D.
> Director, Samueli Institute

[49] Leroy Hood. "Systems Biology: Changing Biology, Medicine, and Society." Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.

Advances in information technology and biomonitoring will make it easier to monitor an individual's risk continuously. In the next ten to fifteen years, managing risk will be more important than managing disease. Risk profiles of patients will vary even among patients with the same disease. Therefore, it will be the patient and not the category that will matter. In the long term, the focus of healthcare will shift from treatment of disease to management of quality and wellness. In this scenario the patient and the doctor are a dyad where each is responsible for personalizing and managing a patient's risk.[50]

> The main idea: continuous monitoring means continuous learning which means continuous feedback and synergy between the continuous monitoring and the patient. You can also add to that predictive modeling. The FDA process will no longer be an on/off switch. There will be a continuous re-assessment of risk and benefit for any individual.
>
> Timothy Ferris, MD, MPH
> Senior Scientist
> MGH Institute for Health Policy

Personalized risk assessment will create the need for open databases and personalized packages of therapies, which combine multiple compounds under patent protection. In order to take full advantage of the differing risk profiles of sub-populations and patients, a more open and collaborative process of biomedical research is needed. Overly strict patent protections on upstream research and products will make it difficult to combine and alter therapies. For the patient to receive the best care possible, open source research and better technologies for testing drug toxicity and efficacy will prove crucial. Then personalized risk assessments could support a transformation of clinical trials. The new approach could be "N of 1" clinical trials, in which the line between research and development, as well as between researcher and patient, blurs (See also page 70). In this scenario, it is not the therapy that adds the highest value to the patient, but the platforms used to identify risk and modify therapies.

[50] Wayne Jonas. (February 11, 2005) IAF 2029 Meeting.

Measuring Risk

> Drug development focused on a small number of patients brings two things to mind. One is that drug development will be personalized to focus on subsets with individual risk profiles and pathogenesis that differs from individual to individual despite common downstream disease symptoms. We could also say that our ability to measure the effects of drugs will be improved with proteomics and genomics so we won't need such big trials. These are both true… The marketplace can also give us new learning based on the EMR. The FDA process looks increasingly like they will move towards an approval that is no longer all or nothing. A conditional approval will let them release drugs into the marketplace with sustained marketplace presence depending on post market surveillance.
>
> Timothy Ferris, MD, MPH
> Senior Scientist
> MGH Institute for Health Policy

New ways of measuring safety, efficacy, and risk will develop over the next ten to twenty years to accommodate changes in healthcare. Randomized controlled trials will be challenged as the gold standard of evidence. They are poorly sensitive and do little to advance understanding of individual risk.[51] In the short term, developing adaptive clinical trials using Bayesian statistics will enable trials to move seamlessly from phase II to phase III. Adaptive trials allow researchers to learn efficiently while patients receive more effective treatment. Another advantage of adaptive trials is the ability to compare distinct, but related therapies as different arms of a trial. This ability allows researchers to study multiple drugs and select the most efficacious ones for commercialization.[52] In the next ten to twenty years, Bayesian statistics combined with knowledge gained from genomic profiles and adaptive personal health records could help personalize therapies in the marketplace.

[51] Wayne Jonas (February 11, 2005) IAF 2029 Meeting.
[52] Donald A. Berry. (Winter 2001). Adaptive Trials and Bayesian Statistics in Drug Development. Biopharmaceutical Report, vol. 9, no. 2.

Adaptive trials can be entirely rigorous and we don't have any fundamental philosophical problem with them as long as the P values are adjusted. We make some suggestions about the ones we see, but we don't see many of them. They are fine, but they are not radical changes. We are getting used to the idea of including Bayesian approaches, but we see very little of them. In the sense that Bayesian is about taking into account what you already know, we already do that. If we see a class effect we don't ask for two studies because we have the information we need. How much formal Bayesian methods will help I don't know. They lighten the load because you have a strong prior. But it's hard to see how much they will change. The great thing is that in a formal way they quantify the likelihood that something you predict will come true.

Robert Temple, M.D.
U.S. Food and Drug Administration

Some patients will have a higher health potential than others who will have a significant risk for disease. Health and risk will be seen in three dimensions with multiple causes and multiple points of influence to return people to their highest health potential. Risk then becomes a conscious decision. Patients won't use a therapy or treat a pre-disease because it is considered abnormal; they will use a therapy or treat a disease because they want to maximize their health potential. Since there will be multiple points of influence to affect health potential there will be multiple therapies used in conjunction to treat pre-disease and maintain health. Since there is no simple correlation between a single therapy and a single disease there will be no reason for maintaining a clear distinction between research on therapies and established medical practice. Research on new therapies will be ongoing and continuous in the post-market stage as they are continuously adapted to fit the unique needs of individual patients.[53]

[53] Wayne Carter, James Mayne, and Wayne Rosenkrans. (February 11, 2005) IAF 2029 Meeting.

Insurance companies will still play a role in managing individual risk, but patients will become much more responsible for adapting their lifestyles and behaviors to shift themselves away from disease and towards health. Since insurance companies will be able to predict pre-disease states earlier there will need to be new ethical agreements between patients and the larger community to care for those who have a low starting health potential. Patients will also desire to enhance their health beyond their existing health potential through performance-enhancing technologies. New ethical agreements will also be important on which performance enhancing technologies are worthwhile and should be subsidized by the community through insurance, as well as which are detrimental to society and should be restricted.

In the next fifteen to twenty years, the market power of those who make and provide therapies will shift to those that provide the platforms, such as the Health Advocate Avatar, needed to assess patient risk and combine therapies to maintain a patient's health potential. The Health Advocate Avatar will help individuals manage risk and make knowledgeable health choices. Regulatory regimes and research methods will need to change over the next ten to fifteen years to accommodate the knowledge represented by the Avatar. Regulation of therapies will shift from an absolute standard of safety to a relative standard of safety, since it will be easier to determine the risk of a food or drug to individual patients. The intellectual property system will also need to allow more open source methods to allow patients to modify and combine therapies to maximize their health potential. Institutional resistance to change both in the regulatory agencies and in industry will slow down the pace of these reforms, but the expense and restrictions of current practices will prove untenable in the long run.

Modeling and Simulations

> Simulations will be more central. I'll be able to see my own body on a screen by 2029. There will be massive data bases by the millions. The patient will be able to see their own information routinely in five years time on their TV screens and have a much more active role in their treatment. They will have a lot of feedback.
>
> George C. Butler, Ph.D.
> V.P. for Customer Partnerships, AstraZeneca Pharmaceuticals

Models and simulations of biological processes are an important method for turning data into intelligence. Data mining techniques can help biomedical researchers turn data into intelligence by separating the "noise" from the signal they are looking for. Models and simulations help biomedical researchers interpret complex data, test hypothesis and discover novel information. Models allow researchers to "fail" under controlled conditions. This allows biomedical researchers to test out ideas and anticipate problems in a systematic way, allowing them to test a hypothesis in a controlled virtual environment and avoid expensive real life studies.[54]

The logical starting place for building biological models is from the bottom-up. Building biological models and simulations from the bottom-up is a complex task. Nowhere is this more apparent than molecular and cellular biology. As molecular biologists are continuing to discover, the interactions of cellular regulation are incredibly complex. Designing models that simply capture data from gene chips and other data sources without a systems level perspective of how the cell works may create useful information, but not useful knowledge.[55] Advances in the field of systems biology, which is explained in greater detail below, will create

[54] Dennis Noble (2002). Biological Computation. Encyclopedia of Life Sciences. London: Nature Publishing Group.
[55] W. Wayt Gibbs. (August, 2001). Cybernetic Cells. Scientific American, p. 53-7.

a systems level understanding of cell regulation to create detailed computer models of cell regulation.[56]

Another approach is to model cellular systems from the top down through computer simulations. Biomedical researchers could reverse engineer a disease to identify known and unknown biological pathways. This kind of simulation can help biomedical researchers identify new areas of research. The company Entelos already uses similar models to run pre-clinical simulations of drug compounds using "virtual patients." These "virtual patients" have digital models of various organ systems built on the latest biomedical research published in scientific journals. The parameters of the models can be changed based on weight, age, sex, and disease severity. This information can help drug developers determine dosage and toxicity effects before clinical trials.[57] This saves on R&D costs, quickens the drug discovery process and potentially saves lives during clinical trials.

In the short-term, the most success will be seen in developing models and simulations from the middle-out. Biological systems are complex with multiple feedback loops running parallel, from the bottom-up and from the top-down. A middle-out approach models a biological system in a functional area between the genome and the whole system. This might be an organ, a tissue, a cell, or cell signaling mechanism. The choice of area to be modeled is based on what areas have the most detailed information to build models from.[58]

In the next ten years, advances in the knowledge of biological systems will become quantitative enough that most biological hypotheses will be expressed in mathematical form and tested through computer simulations. These same advances will create principles of biology that will be used as a platform to develop a theoretical biology over the next 25 years.[59]

[56] H. Kitano. (2002). Systems Biology: A brief overview. Science, 295: 1662-4.
[57] Gary Stix. (January, 2003). Reverse-Engineering Clinical Biology. Scientific American.
[58] Dennis Noble (2002). Biological Computation. Encyclopedia of Life Sciences. London: Nature Publishing Group.
[59] Dennis Noble (2002). Biological Computation. Encyclopedia of Life Sciences. London: Nature Publishing Group.

Creating a theoretical understanding of biology will be the final step in turning the vast amounts of data developed from the genomic revolution into usable wisdom from biology.

In the next ten to fifteen years, advances in computer simulations and systems biology could allow researchers to develop medicines based almost entirely on computer simulations. Depending on safety regulations and developments in genomics, this would allow compounds to be developed and modeled for smaller sub-populations of patients. The most costly and time consuming part of drug research and development--clinical trials--could be reduced or augmented and transformed.

In the long term, it will be possible to produce compounds or variations on compounds for individual patients. Computer simulations based on genomic profiles, and informed by systems biology, would be used to predict safety and efficacy of the compound for each patient. The clinical trial would then consist of only one person, the patient, and would be continually adapted to the patient as the doctor receives more information on the effect of the compound on the patient and feeds it back into the simulation (See also “N of 1” clinical trials on page 70).

Open Source Research

> Systems biology is looking for a signature of health through a variety of measures. We are working in the gene expression and protein areas, but are really interested in any endpoint that is a biomarker. Any measure that tells us about physiology or pathology can also give us a better idea of the health state…. We are devoting millions to develop biomarkers, and very little of this is for IP because we want these diagnostics used by academics. We are very interested in trying to move discovery forward in an open pursuit that leads to new products. A lot of universities have been trying to open up the disciplines so that learning crosses the boundaries. Systems biology was not possible until you began to link together the different disciplines. I think this will accelerate learning. I think the linkage between math and biology is absolutely crucial. Once we link those we will get a much clearer description of biology. Models and simulations will be absolutely critical to make these descriptions feasible.
>
> Wayne Carter, D.V.M., Ph.D., DACVIM
> Senior Director for Clinical Technology
> Pfizer Global Research and Development

Open source research is a concept that envisions a collaborative, open process that results in the creation of a product. Not a new concept, open source has long been used in the computer community. Somewhat similarly, this type of collaborative effort also accelerated the human genome project. Many individual laboratories worked together and the results were released in the public domain. Those involved with the human genome project investigated the possibility of making the project fully open source by using an open-source licensing agreement. Subsequently, the SNP Consortium brought together private and public resources with a commitment to creating a rich public domain of new knowledge. Another successor project, the International HapMap Project, which is mapping the common patterns of variations in the genome, also places the completed data in the public domain and allows subsequent patents on discoveries derived from that data.

In the next few years, a number of promising open source projects will have a significant impact on developing a fully formed open source research system. One of the most forward thinking biotechnology projects under way is the Biological Innovation for Open Society (BIOS). The project will develop molecular biological Open Access Technologies (OATs) that will be released in the public domain under BIOS licenses. The BIOS licenses are designed to create protected commons around technologies by using licensing agreements that ensure that any and all technology improvements and data gained by the licensee is available to others.[60] The Tropical Disease Initiative is another recent project designed to use open source methods to power the drug discovery process for neglected diseases. The project hopes to leverage the similarities between open source software development and computational drug discovery to create new drug candidates for tropical diseases.[61]

"New ideas need new organizational structures," Leroy Hood argues.[62] The possibility that networks of scientists working across disciplines could speed discovery leads some close observers to anticipate that large corporations may outsource research to biotech companies, and perhaps networks of scientists. Some think that the financial incentive conferred by intellectual property rules means that it will take companies, small and large to harness science. Over the next 25 years, the biomedical research community could see collaborations of smaller institutions, including non-profit and patient advocacy organizations take a dominant role over large institutions. In the next five to ten years, collaboration between individual researchers in grid communities could become the new hubs of innovation and in the long-term patients will join with researchers as full-fledged participants in the research process.

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[60] The BIOS project is being developed by the Center for the Application of Molecular Biology to International Agriculture (CAMBIA). The goal of BIOS is to "extend the metaphor and concepts of open source and distributive innovation to biotechnology and other forms of innovation in biology." The two current projects are focused on agricultural biotechnologies, but future projects may be aimed at pharmaceutical screening and production technologies and vaccine development and delivery technologies.
Biological Innovation for Open Society (BIOS). (2005). Accessed online at http://www.bios.net/daisy/bios/15

[61] Stephen Maurer, Arti Rai and Andrej Sali. (2004). Finding Cures for Tropical Diseases: is Opens Source an Answer? Overview Paper. Retrieved Online at http://salilab.org/pdf/136_MaurerBIOESSAYS2004.pdf

[62] Leroy Hood. "Systems Biology: Changing Biology, Medicine, and Society." Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.

In the next few years, open-source research is most likely to play a role in non-patentable compounds, drugs whose patents have expired, and diseases that affect small numbers of people or are found mainly in poor countries. A lack of market incentive makes it less attractive for large pharmaceutical firms to develop these areas, but an open-source framework that brings in non-profits, universities, and individual researchers can make a significant contribution. Developing countries, especially Eastern countries, could play a leading role in advancing open source research. They are the countries most affected by neglected diseases and they don't have the same level of institutional resistance to new ways of conducting research. Countries in the East, including China, India, and South Korea, have expertise in biotechnology, more open intellectual property systems, and a community oriented approach to solving problems. They could become the leaders in open source research.

In the most probable scenario, open source research will play a role in developing tools and databases for basic research and in the drug discovery of neglected and tropical diseases. Major institutional players—both industry and government—will see it in their best interests to support open source research in these areas because they will see little conflict with their own work. However, institutional resistance to change is likely to be strong when developing open source research into more profitable diseases and for clinical research. The pharmaceutical and biotechnology industries, which rely heavily on intellectual property protection, are likely to resist the changes of open source research into more profitable diseases since it would force them to dramatically alter their business models. Government would also have to fundamentally change drug approval processes and clinical research to accommodate open source research in clinical trials. This is likely to generate institutional resistance in the name of patient safety and efficacy.

However, open source research is necessary to achieve many benefits discussed in this report. Advances in understanding personalized risk and developing personalized therapy will

require a more open system of research and intellectual property. There are two ways institutional resistance to open source research could be overcome in the future.

The first way this resistance could be overcome is evolutionary in nature. As researchers find it easier to collaborate together in grid communities devoted to open source research, solutions for neglected and tropical diseases could result. Success in smaller markets for neglected and tropical diseases will show the benefits of open source research. Sensing an opportunity, a large institutional player, either from outside or inside the industry, enters the pharmaceutical industry with a business model that is designed to leverage the advantages of open source research. This pioneer would succeed by breaking down barriers to innovation across multiple organizations and creating a network of dedicated researchers with expertise in a wide range of disciplines to create open source therapies. This open source company would make revenue not on the therapies themselves, but on selling the platforms that identify health risk and personalized open source therapies. Sensing the success of this business model, other organizations would change their methods and bring the regulatory agencies along with them.

The second way this institutional resistance could be overcome is more revolutionary in nature. A developing country, with little institutional resistance to change, could structure their national innovation system[63] to capitalize on open source research. This country gains an economic advantage over other countries by building a stronger research system and a healthier population. Other countries, seeing that their research and health systems are falling behind, adopt an open source system of innovation. This country could also claim to have a more ethical system of innovation because it would diffuse the benefits of research to poor populations faster than the current model.

[63] A national innovation system is a term that refers to the many aspects of a country that either encourage or discourage innovation. This includes such things as research capacity, regulatory frameworks, intellectual property protection, and social systems.

Biomonitors

> The health management approach needs cheap biomarkers. As you go into clinical trials and disease states then the need for free or cheap biomarkers diminishes and you can go to lower throughput, more expensive measures. In clinical trials there will be very powerful measurements. By 2029 maybe the need for imaging will be a lot less. We like to see the appearance of things, but by 2029, the images will have validated other things like proteomics. They are steps along toward validating the molecular markers that will be biochemical or proteomic.
>
> Stephen Williams, M.D., Ph.D.
> V.P. Worldwide Head of Clinical Technology
> Pfizer Global Research and Development

Advances in knowledge technologies, including smaller, faster processors, and wireless broadband connectivity, will make it cheaper and easy to monitor health at home on a continuing basis. Mattresses that monitor early health problems and smart toilets that perform instant urinalysis already exist.[64] Advances in Micro-electromechanical systems, nanotechnology, and network connectivity will create network-centric physiological monitors that can measure body temperature, hydration levels, chemical toxicity, and other biomarkers. Performance Software Corporation is already awaiting grant funding on just such a system and hopes to have a prototype ready by 2006.[65]

Biomonitors will provide a flood of new information for biomedical researchers and patients. The true challenge will be to design software systems that can take this information and turn it into usable knowledge and wisdom about a patient's health risk. Tying these biomonitors into a networked system that contains genotypic and phenotypic profiles, as well as patient medical history will enable many patients to lower their health risk, detect and treat pre-disease states,

[64] Kelly Greene. (February 23, 2004). Inside the Home of the Future. The Wall Street Journal: The Journal Report. R1-6.
[65] Lucas Conley. (July, 2004). A Pill With Brains. Fast Company, p. 34.

and maintain their health. The Health Advocate Avatar is one platform that could help turn the information gained from biomonitors into usable knowledge and wisdom about health.

Developing "N of 1" Clinical Trials

Health-care delivery in the future will be an integrated process, seamlessly linking discovery and development with health care services, and providing a rich source for examining the practical impact of innovative technologies. Early clinical development programs will acknowledge downstream healthcare implications, and every patient- physician transaction will be regarded as an opportunity for additional research. Electronic patient registries already provide a data platform for hypothesis generation, and ultimately may lead to a national health-care database within the United States. In that environment, sophisticated signal detection algorithms will be dominant for drug associated adverse events or to define and understand regional differences in health-care utilization, perhaps facilitated by health-care plans in partnership with the pharmaceutical industry, and data mining activities of claims information as well as observational research will be even further emphasized. Both psychosocial and biological hypotheses will be examined in prospective studies that define the experimental unit as the doctor/patient dyad. This approach has been implemented for randomized studies of educational programs in diabetes, and could be extended across disease states in controlled investigations with universally adopted information technologies.

Michael Murphy, MD, PhD
Chief Medical Officer and Senior Vice President for Drug Development
TorreyPines Therapeutics

Advances in nanotechnology, discussed further below, will create new scaffolds for tissue engineering. This will make development of new tissue for implantation or research easier and cheaper. Advances in therapeutic cloning will enable tissues grown on these scaffolds to have

the same genetic composition as the patient.[66] This will lower the risk of tissue rejection, but it will also enable researchers to test the toxicity of drugs *with tissue identical to the patient's.* These tissues will be combined with models and simulations to create better toxicity and efficacy studies. This will allow clinical trials with only one patient to determine the safety and efficacy of drugs. These "N of 1" clinical trials will, at first, involve only drugs that have been approved using extensive clinical trials. They will, however, enable doctors to combine different therapies and test them for efficacy and toxicity. As these "N of 1" clinical trials improve, doctors will be able to combine an increasing number of different compounds in very low doses to achieve the best therapeutic effect for their patients. The value added in pharmaceuticals, especially small molecule pharmaceuticals, will shift from those that discover new compounds to those that provide the platforms for testing and combining different therapies.

Looking at Potential Breakthroughs

Advances in new therapies involving stem cells, gene therapy, and implants will create new hope for thousands of patients, but will also place new pressures on healthcare systems. Eastern scientists are becoming vital to the basic and advanced research conducted in these new therapies. Some of these therapies will push past disease into health potential and even health enhancement. Developing an assessment mechanism for health risk that is formed around ethical agreements will be necessary in the long term.

Stem Cells

"I think stem cells are the penicillin of the 21st century," Leroy Hood has remarked.[67] The potential of stem cells are huge. Applications include repairing damaged heart tissue with

[66] For more information on this technology and its application, please read the Draper Labs report in Appendix B.
[67] Leroy Hood. "Systems Biology: Changing Biology, Medicine, and Society." Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.

cardiomyocytes grown from stem cells, implanting islet cells into the pancreases of diabetic patients, and developing dopaminergic neurons in laboratories for patients with Parkinson's disease. Stem cells could also provide new ways to target old diseases. For example, research is showing that cancer stem cells play a large role in the malignancy of cancer.[68] Understanding how these cells operate and where they reside in a tumor could lead to new ways of targeting and destroying tumors.[69] Although research into stem cells is still at an early stage, and is under significant political pressure in certain countries, the kinds of advances mentioned above are entirely possible in the next five to ten years.[70]

Although adult stem cells cannot turn into as many types of cells as embryonic stem cells, they may be usable in the regeneration process across an array of organs. For example, bone marrow stem cells may become both red blood cells and also liver cells if transplanted into the liver.[71] Also, research projects that use adult stem cells for organ repair are in a more advanced stage relative to embryonic stem cell research, although obtaining, processing, and preserving adult stem cells in large numbers could be a major stumbling block.[72] However, the primary advantage of adult stem cells over embryonic stem cells is they prompt fewer religious objections and suffer fewer immunological problems if certain stem cells from the patient are used.

Embryonic stem cells remain the most promising source of stem cells for research.[73] They have the promise of being able to be differentiated into a large number of different cell types

[68] Gareth Cook. (December 27, 2004). Are Stem Cells a Key to Growth of Tumors? The Boston Globe. Retrieved 6/20/2005 at http://www.iht.com/articles/2004/12/26/news/stem.html
[69] Lee Hartwell. (February 28, 2005). Telephone interview.
[70] Institute for the Future (2003). Healthcare 2010-The Forecast, The Challenge. Second Edition. Retrieved 2/2005 at http://www.iftf.org/docs/SR-794_Health_&_Health_Care_2010.pdf on p. 132.
[71] National Institute of Science and Technology Policy (Japan). The Seventh Technology Foresight-Future Technology in Japan to the year 2030-Survey Results-Health and Medical Care. Retrieved Online 2/2005 at http://www.nistep.go.jp/index-e.html on page 230.
[72] Mary Carmichael (Summer 2005) Organs Under Construction. Newsweek, 46-48.
[73] Embryonic Stem Cells are derived from the inner cell mass of an early embryo. Embryonic Germ Cells are derived from the primordial germ cells of a fetus. Both have a high capacity for self-renewal and differentiation compared to Adult Stem Cells.

for possible cell therapies. Early research has shown that embryonic stem cells can differentiate into a number of cell lineages, although not all of the results have been reproducible in other labs.[74] Optimism for embryonic stem cells remains high, although political opposition to stem cells due to religious objections has limited federal research funding in the United States. Some states are looking to fill the funding gap. In 2004, California passed a proposition to spend $10 billion in state funds over three years on stem cell research and other states are expected to follow California's lead.[75]

Large private companies both inside and outside the United States may be quietly initiating stem cell research programs. The Wall Street Journal conducted a survey of 12 of the world's largest drug firms by sales, as well as leading U.S. biotechnology concerns and medical-device makers. The journal found several previously undisclosed research programs involving human embryonic stem cells.[76]

In the meantime other countries are pushing ahead with stem cell research. China, South Korea, Singapore and the United Kingdom are all investing heavily in stem cell research and attracting talented research scientists from the United States. South Korea has made large strides in stem cell research after launching an ambitious plan launched in 1994 to become one of the world's top seven biotechnology producing countries by 2010. South Korea stepped onto the world stage in stem cell research when a researcher professor became the first to extract stem cells from a cloned human embryo.[77]

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[74] The President's Council on Bioethics. (2004). Monitoring Stem Cell Research. Retrieved Online 1/2005 at http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf on page 127.
[75] Constance Holden. (12 November 2004). California's Proposition 71 Launches Stem Cell Gold Rush. Science, 306: 1111.
[76] Some of the companies quietly initiating research programs include Johnson & Johnson, General Electric, Becton, Dickson, and company, Invitrogen and the U.S.-based research unit of Novartis.
Antonia Regalado. (April 12, 2005). Big Companies Quietly Pursue Research on Embryonic Stem Cells. Wall Street Journal, Page A1.
[77] J. Wong, U. Quach, H. Thorsteinsdottir, P.A. Singer, and A.S. Daar. (2004). South Korean Biotechnology-A Rising Industrial and Scientific Powerhouse. Nature Biotechnology Supplement, 22, pg. DC42.

China is also conducting pioneering research on both adult and embryonic stem cells. One of China's biggest advantages is its large and relatively cheap research force. It costs one fifth to one tenth the cost to employ biotechnology research scientists in China compared to American talent, and many of these researchers have U.S. training.[78] China's combination of liberal research environment and robust supply of researchers and stem cell banks will make China an important future player in stem cells over the next five to ten years.[79]

In the Christian West, many Churches teach that life begins at the moment of conception, which leads many conservative Christian churches to oppose embryonic stem cell research. In Europe, there is also opposition from social justice and environmental movements, which view stem cell research as irresponsible, even comparing it to fascist eugenics studies.[80]

In general, Asian scientists studying stem cells do not experience as much ethical resistance to their work as their colleagues in the West. Buddhism and Hinduism focus on the cycle of reincarnation while the Confucian tradition places the defining moment of life at birth, not conception. By the same measure, criticism from the left in Asia has been limited, although international scrutiny has causes South Korea to tighten up its oversight of stem cell research laboratories.[81]

The main challenge for Asia in stem cell research involves building up their scientific capacity and venture capital markets. Strong government support for biotechnology combined with the continual expansion of capital markets throughout the region indicates that these two challenges are not insurmountable.

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[78] Robert L. Paarlberg. (May/June 2005) The Great Stem Cell Race. Foreign Policy. Retrieved 6/20/2005 at http://www.foreignpolicy.com/story/cms.php?story_id=2831&page=0

[79] L. Zhenzhen, A. Jiuchun, W. Ke, H. Thorsteindsdottir, U. Quach, P.A. Singer and A.S. Daar. (2004). Health Biotechnology in China-Reawakening of a Giant. Nature Biotechnology Supplement, 22, pg. DC13.

[80] Robert L. Paarlberg. (May/June 2005) The Great Stem Cell Race. Foreign Policy. Retrieved 6/20/2005 at http://www.foreignpolicy.com/story/cms.php?story_id=2831&page=0

[81] Robert L. Paarlberg. (May/June 2005) The Great Stem Cell Race. Foreign Policy. Retrieved 6/20/2005 at http://www.foreignpolicy.com/story/cms.php?story_id=2831&page=0

Gene Therapy/Silencing

Gene therapy is a promising therapeutic treatment that involves altering the genetic composition of cells to prevent or treat disease. This can cause the cell to produce therapeutic proteins that it would not otherwise produce or to suppress an acquired disease like cancer. Despite considerable success in the laboratory and the movement of some gene therapies into clinical trials there remains many basic research challenges for gene therapy and gene silencing. Basic research needs to be fleshed out in the following areas:

- Better delivery technologies to carry corrective genes into target cells
- Better targeting of genes to specific sites and tissues
- Enhancement of gene expression of altered genes[82]

Gene therapy research is expanding in all three areas, but significant challenges still remain. Part of the problem with developing gene therapy and gene silencing therapies is the complexity not only of the genome, but the entire cellular system. Complexity not only makes it difficult to deliver and target the gene therapy, but to predict and prevent the therapy from having unintended effects on the system. In the next five to ten years, advances in systems biology will develop better models and simulations of the cell, and many of the remaining challenges in basic research of gene therapy could be overcome.

Gene therapy research has slowed down in the United States, the world leader in gene therapy and gene silencing research, due to safety questions and research setbacks. However, Eastern countries are moving forward with research into gene therapy. China has reached world standards in gene sequencing and other genomic technologies and is looking to apply that expertise to gene therapies. Currently there are five gene therapies being tested in

[82] Institute for the Future. (2003). Healthcare 2010-The Forecast, The Challenge. Second Edition. Retrieved 2/2005 at http://www.iftf.org/docs/SR-794_Health_&_Health_Care_2010.pdf

China and one approved therapy on the market.[83] In January of 2004, Shenzhen SiBiono GeneTech made history by becoming the first company to sell a gene therapy medication commercially. Sold under the brand name of Gendicine, the therapy treats head and neck squamous cell carcinoma (HNSC), a cancer that accounts for 300,000 new cancer patients a year in China. The treatment costs $360 dollars and can be administered by a regular doctor. Sixty-four percent of HNSC late stage tumors experience a regression after eight weeks of treatment using radiotherapy and weekly gene therapy injections. The only side effect, seen in 30 percent of patients, is a fever.[84]

Another therapy that focuses on the gene is gene silencing. Using RNA to interfere with gene expressions, often referred to as RNAi, has been very useful in validating drug targets in pharmaceutical research. Research in gene silencing is also focused on interfering with cell surface receptors to make a patient more resistant to viral infections like influenza and HIV. There has also been research in using gene silencing to develop therapies to silence overactive genes that cause disease in patients. This could lead to new therapies for diseases such as some cases of Lou Gehrig's disease,[85] macular degeneration, and even lowering cholesterol.[86]

Research into gene silencing is shifting toward applied research and medical applications using animal models for human disease.[87] Many of the same basic and applied research

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[83] L. Zhenzhen, A. Jiuchun, W. Ke, H. Thorsteindsdottir, U. Quach, P.A. Singer and A.S. Daar. (2004). Health Biotechnology in China-Reawakening of a Giant. Nature Biotechnology Supplement, 22, pg. DC13.

[84] S. Pearson, H. Jia, and K. Kandachi. (2004). China approves first gene therapy. Nature: Biotechnology 22(1): 3-4.
Bioscience News & Information. (2005). China approves first cancer gene therapy. Retrieved online 3/2005 at http://www.lifesciencesnetwork.com/files/news-detail.asp?NewsID=6090

[85] Some cases of amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease are caused by a mutated gene. In mice, researchers were able to use RNAi to delay the onset and progression of ALS.
Robert Preidt. (2005). Gene-Silencing Technique Could Fight ALS. Retrieved online 3/2005 at http://www.medicinenet.com/script/main/art.asp?articlekey=46242.

[86] Erika Check (2004). RNA treatment lowers cholesterol. News@Nature. Retrieved online 3/2005 at http://www.nature.com/news/2004/041108/pf/041108-11_pf.html.

[87] Yuko Ito. (October 2004). Trends in Gene Silencing Research. Science and Technology Trends: Quarterly Review, p. 32-43. National Institute of Science and Technology Policy (Japan).

problems that have hindered gene therapy research apply to gene silencing as well. In particular, gene delivery and the complexity of the cellular system are areas where basic research is still needed. While some early stage clinical trials using gene silencing to treat macular degeneration are ongoing, it could be years before an RNAi drug is approved.[88]

Nanomedicine

> The multitude of proteomic signals that could be picked up and interpreted so they can be followed over time will prove to be a revolution if it can be figured out. The proteomic profiles that include receptors on the tumor will be the prescription for nanotech. It has to be small, quick, cheap and multiplex. This will be the breakthrough—identifying the markers for personalized therapy.
>
> Mauro Ferrari, Ph.D.
> Special Expert in Nanotechnology, National Cancer Institute, and
> Professor of Hematology & Oncology, Ohio State University School of Medicine & Public Health

Nanomedicine is beginning to emerge from research in nanotechnology. There are already more than 60 drugs and drug delivery systems based on nanotechnology as well as more than 90 medical devices or diagnostic tests.[89] Nanotechnologies have features on the scale of nanometers or billionths of a meter. In biology the scale of a single human hair is about 80,000 nanometers wide and a red blood cell is about 7,000 nanometers wide. Materials can be produced that are nanoscale in one dimension (such as ultra-thin surface coatings), in two dimensions (for example, nanotubes and nanowires), or in all three dimensions (nanoparticles

[88] New Zealand Ministry of Science and Technology. (2005). Futurewatch: Biotechnology to 2025. Retrieved online 2/23/2005 at http://www.morst.govt.nz/uploadedfiles/Biotechnology/FutureWatchBookFull.pdf on page 34-5.
[89] Numbers are from Nanobiotech News, a weekly trade publication for the industry.
Rick Weiss (January 31, 2005). Nanomedicine's promise anything but tiny. Washington Post, pg. A8.

and Buckyballs).[90] Nanoscale materials often have novel properties related to their high ratio of surface area and quantum effects.

Nanomedicine has a limited number of current applications.[91] But research is continuing both in academia and in industry. For example, Wyeth and Merck utilize nanocrystal technology in drug formulation research, and Pfizer, GSK, Astra Zeneca and Genentech use quantum dot particles to perform drug screening analysis.[92] Academic centers including Cal Tech and Harvard are using nanowires to create biosensors capable of identifying proteins in cells as well as viruses in the hopes of developing a new generation of diagnostics.[93] The National Cancer Institute is supporting an ambitious research program spelled out in its cancer nanotechnology plan.[94] Along with developments in implants, which are described more fully below, current research and development efforts, are concentrated in the following areas:

- **Antimicrobial Properties:** Research efforts are focused on investigating nanomaterials with strong antimicrobial properties. Nanocrystalline silver, for example, is already being used for wound treatment.
- **Biopharmaceutics:** Efforts are focused on drug delivery applications using nanomaterial coatings to encapsulate drugs and to serve as functional carriers. Nanomaterial encapsulation could improve the diffusion, degradation, and targeting of a drug. Furthermore, nanomaterials could serve as camouflage to avoid immune responses, or as agents which could catalyze or respond to certain molecules or chemical events.
- **Nanomaterials:** Nanotechnology is being used to develop new materials that can be implanted in the body or used for tissue engineering. Nanomaterial implant coatings could increase the adhesion, durability, and lifespan of implants, and nanostructure scaffolds

[90] The Royal Society. (July, 2004) "Nanoscience and Nanotechnologies: Opportunities and Uncertainties." Accessed online at: http://www.royalsoc.ac.uk
[91] (2005) "Applications/Products" National Nanotechnology Initiative. Accessed online at http://www.nano.gov/html/facts/appsprod.html
[92] (July 19, 2004) "Nanotechnology – Product News." Country Doctor. Accessed online at http://www.countrydoctor.co.uk/education/education%20-%20Nanotechnology.htm
[93] See http://www.systemsbiology.org/extra/PressRelease_102204.html and also http://cmliris.harvard.edu/research/devices/index.php.
[94] See http://www.nano.cancer.gov (2004).

could provide a framework for improved tissue regeneration. Moreover, nanomaterial implants could be engineered for biocompatibility with the host environment to minimize side effects and the risk of rejection. In the long term, smart nanomaterials could detect and respond to environmental conditions and chemical reactions.

- **Diagnostic Tools:** Efforts are directed at utilizing lab-on-a-chip devices to perform DNA analysis and drug discovery research by reducing the required sample sizes and accelerating the chemical reaction process.[95] Moreover, imaging technologies such as nanoparticle probes and miniature imaging devices could promote early detection and diagnosis of disease.
- **Understanding Basic Life Processes:** Efforts are focused on using nanoscale devices and materials to learn more about how biological systems self-assemble, self-regulate, and self-destroy at the molecular level. Insights into basic life processes will overlap multiple disciplines and could yield scientific breakthroughs.

In the short term, most experts anticipate a valuable set of research tools and clinically helpful devices will emerge. The Asia-Pacific Economic Cooperation (APEC) Center for Technology Foresight predicts the development of selective nanosensors and drug delivery systems over the next three years, and the application of advanced medical diagnostics and the ability to target human cells for organ repair by 2013.[96] The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry in the next two to five years to include "advanced drug delivery systems, including implantable devices that automatically administer drugs and sense drug levels, and medical diagnostic tools, such as cancer tagging mechanisms."[97] Leroy Hood predicts it will take five to eight years to develop the microfluidic

[95] Nanotechnology Enabling Lab-on-a-Chip Devices. Institute of Nanotechnology. Accessed online at http://www.azonano.com/details.asp?ArticleID=886

[96] Greg Tegart. "Nanotechnology: The Technology for the 21st Century." The APEC Center for Technology Foresight. Bangkok, Thailand. Presented at The Second International Conference on Technology Foresight, Tokyo, Feb. 27-28, 2003.

[97] Applications/Products. National Nanotechnology Initiative. Accessed online at http://www.nano.gov/html/facts/faqs.html

nanolabs that will be capable of measuring key interactions within individual cells and aggregating those measurements for hundreds of thousands of cells.[98]

The range of long-term expectations in nanomedicine expands from more cautious forecasts into a realm some scientists view as science fiction. If the wild card breakthrough occurs in the more radical micro-machine form of nanotechnology, it would arguably be the largest single development in the history of technology. However, many prominent researchers in the field feel that this development is extremely unlikely. Developing techniques to manipulate atoms into molecular machines, enabling the machines to withstand the forces inside the body, and controlling those machines could be insurmountable challenges to developing nanomachines.

Speculations about the medical devices that might become possible range from cell herding machines that could supplement the body's own tissue repair mechanisms, to cell repair machines that could kill viruses that attach to genetic material within cells and repair cellular damage caused by disease, chemicals or radiation. Genetic surgery might become a simple procedure done by swallowing a tiny pill filled with nanorobots.[99] Ultimately, we might be able to counter or repair many of the effects of aging. While possibilities like these are highly controversial and uncertain, they suggest that nanomedicine today is still in a primitive state compared to what could be possible over the next 25 years.[100]

Implants and Drug Delivery

New advances in microelectromechanical systems (MEMS), nanotechnology, and other technologies will provide new implants and more ways of delivering drugs. MEMS systems are

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[98] Leroy Hood. "Systems Biology: Changing Biology, Medicine, and Society." Carnegie Institution New Horizons for Science. Capital Science Evenings: Fifteenth Season. Washington D.C. January 6, 2005.
[99] Robert A. Freitas Jr. (January 19, 2005) Telephone interview.
[100] Readers interested in the long-range uses of nanomachines in nanomedicine should read Robert A. Freitas Jr's Nanomedicine series. The volumes I and IIA are available online at http://www.nanomedicine.com. Robert A. Freitas Jr., Nanomedicine, Landes Bioscience, Georgetown, TX, Vol. I: Basic Capabilities (1999) and Vol. IIA: Biocompatibility (2003).

becoming more robust and better able to deliver drugs to patients. Developments in nanotechnology will enable better coatings for drugs and smaller implants for drug delivery.

In November 2004, the IAF 2029 team held a workshop at the Draper Laboratory. Draper scientists foresee the development of very small MEMS and nanotechnology devices for drug delivery, micro-sensors to monitor patients, and microdevices for drug development (A full report from this meeting is found in Appendix B). Advances in MEMS technology will make implantable devices that can monitor and adjust the concentrations of drugs in the body feasible in five to ten years. And by 2029, there may be biological systems that can recharge implanted devices using the body's own organic chemistry. More information on these and other forecasts from the Draper Laboratory workshop is included in the appendix section. These advances will improve patient care and allow patients to be more mobile.

Section 5: The Evolution of Ethics and Healthcare

Increases in the science and technology of healthcare will bring new ethical challenges. In the presence of global information transfer, I believe Darwinian selection pressures will drive societies to adopt new ethical frameworks that will benefit the greatest number of people in those societies. These utilitarian ethical mores will increase the fitness and ultimately the economic and political survival of societies that embrace them. I believe the world is moving to a new ground between purely maximizing personal health and well being and the alternative of normalizing everyone's health status through some form of national healthcare, which is suboptimal for many. This new ground will come about through advances in knowledge, driven by information analysis, which will show what each member of society needs for their health and how the healthcare of the whole society improves by providing it. This insight will drive a new system of ethics that will unite societies in their appreciation and implementation of the science and technology of healthcare.

Ian Williams, Ph.D.
Principle, Ian, Inc.

Ethics is the study of morals, the voluntary action to choose between right and wrong. An ethical system prescribes how our beliefs guide our thinking and actions. While morality has a timeless quality evident through the ages, ethics develop and evolve. Over the next twenty five years a global ethic will evolve that expands concern for life worldwide. The population supporting this ethic will grow stronger, particularly in Europe and the United States.[101] Natural selection works with cultural as well as biological evolution to favor ethical positions that provide advantages to communities and societies. Those that adopt an ethic based on knowledge of and concern for global cultures and circumstances will gain political and

[101] See P. Ray and S.R. Anderson The Cultural Creatives for empirical research grounding this forecast. The Cultural Creatives website is available at http://www.culturalcreatives.org
Paul H. Ray and Sherry R. Anderson (2000) The Cultural Creatives—How 50 Million People Are Changing The World. Three Rivers Press. New York: New York.

economic advantages over time as globalization links more people on the planet. This ethical position will reshape not only the global political economy, but also healthcare by 2029.

Different ethical positions reflect evolutionary stages of cultural development. A legitimate ethical position for an individual or society at one stage of development will be different than what is ethical for a larger social unit at a different stage of development. Just as an infant's concerns are different from an adult's, so too the ethical concerns of a tribal society are unlike those of a globally networked society. Neither society is better in a moral sense. However, ethical issues and expectations do change as societies develop. The most advanced societies will grow older and richer over the next twenty-five years, and they will also gain a remarkable increase in access to knowledge. More people will realize that global health demands a new level of cooperation and that wealth is supported by health. This realization will lead wealthy societies to recognize the ethical imperative to care for the poor on a worldwide basis.

> Healthy societies will be those that offer equitable access to those resources that promote health. Appropriate health measures are where equity is most important. The growing gulf between rich and poor is a concern. Healthy societies are going to depend on governmental units losing the fear of tackling difficult issues now rather than passing them on to the next generation, next congress or next meeting. Doing the hardest things will be the most important thing for healthy societies to tackle.
>
> Donald Bone, Ph.D.
> Corporate Director for Science and Technology, Johnson & Johnson

The 2029 thesis holds that human systems, like nature's, are organized as a hierarchy of systems nested within more complex systems—called a holarchy.[102] Thus healthcare is a

[102] Ken Wilber defines "a holarchy: a series of concentric circles or nests, with each senior level transcending but including its juniors." (32)He further notes that the word "holons…indicate *wholes* that are simultaneously *parts* of other wholes: a whole quark is part of a whole atom; a whole atom is part of a whole molecule; a whole molecule is part of a whole cell; a whole cell is part of a whole organism…and so on." (99).
Ken Wilber. (1997) The Eye of Spirit. Shambhala Publications, Inc. Boston: Massachusetts.

whole system that is part of a political economy, which is nested in an ethical system. Each level has its own rules and each system creates selection pressures that drive evolution at that level. In healthcare the pressure pushes toward quality outcomes that create health for both individuals and societies. When healthcare creates health, it creates economic and political advantages that foster evolution of our political economy. In politics and economics, the evolutionary pressure is toward higher global value propositions. The more advanced societies become economically and politically, the more their populations will adopt the global concerns we forecast will be the highest level of ethical development in 2029.[103]

At each level of this holarchy, values change to reflect different beliefs in what is important. At the level of individuals, ethics are often virtue based, i.e., concerned with the development of "good" character. However, each individual understanding of "good" character is different depending upon the larger social unit that creates the cultural context. Therefore, the higher-up the holarchy we go, the more ethical systems rely on the utilitarian-based ethics of providing the greatest good for the greatest number.

Our forecast is that today's ethical systems will evolve in order for science to enable health for a growing global population over the next decades. Science challenges our ethical systems and our ethical systems direct science. The more highly evolved ethical systems will direct new technologies such as stem cells, neuroscience, and gene therapy, among others toward global health improvements. These advances force us to make tough ethical decisions between what may be morally repugnant for many individuals and what may be in the greatest good for society. These decisions shape public support for basic research into these advances. Some societies will delay or derail a scientific enterprise based on the concern over

[103] This forecast assumes the hierarchy of needs described by Abraham Maslow. The 2029 thesis is that the hierarchy described in individuals can also be seen in cultures and societies that evolve from lower levels to higher levels as described by Don Beck and Christopher Cowan in Spiral Dynamics: Mastering Values, Leadership and Change.
Abraham H. Maslow. (1968) Toward a Psychology of Being. John Wiley & Sons. New York: New York.
Don E. Beck and Christopher C. Cowan. (1995) Spiral Dynamics: Mastering Values, Leadership and Change. Blackwell Publishers, Ltd. Oxford: U.K.

the individual. These societies will be placed at a disadvantage as the global economy rewards those who create the greatest good for the greatest number. Science that contributes to health creates economic wealth and quality of life. The wealthy, healthy societies that link people to knowledge will expand their ethical concern for the large number of people not served by the global economy.

Ethics and Technology in a Global Context

Schumpeter demonstrated some years ago that the cycle time of new technologies is shrinking.[104] New technologies are not only being developed faster than ever before, they are also being diffused around the globe faster. Once the Pandora's box of technological innovation is opened it is almost impossible to shut the lid again because other units in the global community will rush to occupy the vacant niche. Stem cell research is a good example. Some countries have limited the use of national monies to fund this research, while other countries are forging ahead, even though these countries may not have such a traditionally strong science and technology culture. The ability to communicate complex scientific ideas and thus shrink the technology cycle time ensures that those inhibited by a concern with the smallest social unit (e.g., embryo) will lose out to those seeking a larger social good.

The end result is that the development of morally questionable technologies will only be slowed down when there is global agreement to stop the development of these technologies and a global enforcement regime to ensure the agreement is enacted. The example of nuclear weapons shows that developing and maintaining these international institutions is extremely difficult at this point in history. Any such institutions designed to slow the spread of health technologies, such as embryonic research or therapeutic cloning, will be much more difficult to establish and maintain. This is because, unlike nuclear weapons, these technologies have the potential to provide for the greatest good.

[104] Joseph A. Schumpeter. (1983) The Theory of Economic Development. Transaction Publishers. New Brunswick: New Jersey.

Evolution of a Healthcare Holarchy

Darwinism proposes that in a changing system those entities best suited for the new system will survive and reproduce. The changes can be external like a meteorite hitting the earth or internal like an animal's own germ line DNA undergoing constant mutation to confer an advantage on a progeny. This principle of Darwinism holds true for other entities. Processes, institutions, and ethical paradigms are all subject to evolutionary pressures.

To understand how healthcare will evolve, we need to see it as a holarchy, or an overarching system composed of smaller systems similar to a Russian nesting doll. Each level informs and is informed by the systems above and below it. Healthcare processes and institutions are undergoing evolutionary change at all these levels. Individuals have more access to health information. At the level of healthcare systems, the relationships between patients, providers and payers is shifting as information becomes transparent and knowledge grows. At the level of political economy, globalization is changing how nations and companies compete. Increasingly, healthcare systems are viewed as either a hindrance or an advantage in the economic competition between nations and companies. This pressures healthcare systems to evolve. The changes at one level of the holarchy change the dynamics of systems at other levels.

Natural selection works differently at different levels of the holarchy. For example, at lower levels competition confers an evolutionary advantage while at higher levels cooperation is more successful. Computer simulations show that at the level of individuals within a community selfishness confers advantage, but at the transcending level of communities within larger boundaries altruism confers advantage.[105] Natural selection thus keeps both competition and cooperation in a dynamic balance, but the rules change at different levels of

[105] Elliott Sober and David S. Wilson. (1998) Unto Others: The Evolution and Psychology of Unselfish Behavior. Harvard University Press. Boston: Massachusetts.

the holarchy. At the individual level, those who compete more aggressively gain advantage. Shift up a level of the holarchy and the communities that behave more altruistically are naturally selected to thrive because they gain economic advantage. When looking globally, cooperation among communities creates the highest level of health for all, which confers economic advantage. Thus, the ethic of altruism becomes an underpinning for the economic and political success at the very highest level of globalization.

The Universal Declaration of Human Rights created a dynamic ethical position that shapes both global politics and economics. The continuing evolution of ethics will foster higher levels of cooperation, which in turn will change the rules both for economics and healthcare. By 2029 competition will continue to create innovation while cooperation will grow to improve dissemination. The ethical evolution will be evident with faster dissemination of innovation to the world's poor. This ethical evolution is already somewhat evident in corporate social responsibility.

The Health Advocate Avatar can help negotiate this dynamic between competition and cooperation to support the evolution of ethics. The Avatar can help guide economic and political agreements in an ethical framework that will lead biomedical R&D to most effectively improve health for all. Advances in biomedical research and development will increase the knowledge and wisdom accrued from individual healthcare experiences. The Avatar can combine this knowledge and wisdom with a statistical view of the whole social unit that will clarify the mutual benefit to both the individual and the community. This Avatar will provide a compelling case that the evolution of healthcare will involve both a focus on the individual and the community.

The ability to gain and transfer information and knowledge between social units will create a higher order healthcare system. The benefits from treating an individual will go not only to that individual, but to the whole social unit. The knowledge and wisdom will flow between the various levels of the holarchy (i.e. the individual, the social unit, the community, and the

nation). If economic disadvantage and the ethic of the greatest good for the greatest number preclude a particular service being offered then the rationale for the decision will be transparent. Even when individuals and families do not agree with the rationale that restricts their healthcare, they will understand it is ethical.

Evolution of Global Ethical and Health Standards

We forecast more and more examples will show how the evolution of healthcare, politics and economics are guided by an evolving ethic based upon global concerns. In the short-term, self-interested policies that advantage smaller social units may prevail with destructive global results. However, in the long-run, the close interconnection of economic and political systems in a transparent environment of knowledge exchanges will encourage the development of a global ethic of care.

Three developments will provide evidence that the ethical evolution is proceeding as forecast.

1. Natural selection will favor those societies that determine how to use healthcare and education investments to support national economies and altruistic policies toward the developing world where new markets can grow at "the bottom of the pyramid."[106]
2. A global ethic will affirm the need to define a balance between the creation and diffusion of technology. Profit on technologies designed to treat suffering is needed to invest in future innovation, but it is also important to place limits on how long high margins can be maintained. It is that balance between dissemination and innovation where a higher global ethic is needed.
3. Experience will reinforce the principle that a rigorous ethical position needs to precede technological innovation to ensure both that it takes place and is optimally deployed.

[106] C.K. Prahalad. (2005) The Fortune at the Bottom of the Pyramid. Wharton School Publishing. Upper Saddle River: New Jersey.

This will also modulate the current trend to seek technological (rather than social or environmental) remedies to many acknowledged problems.

As global access to knowledge grows in the next two decades, it will start to compel global health standards as an economic good and an ethical imperative. The standards may start with a basic nutrient requirement outlining calories, vitamins, and percentages of protein and fat. Successful economic outcomes will then support vaccines for diseases and widespread access to generic drugs. Eventually, as global economic wealth increases the standards will rise to include prevention of major early killers such heart disease and eradication of infectious diseases.

Ethics and Risk Assessment

New prevention technologies will enable fundamentally new ways of assessing risk. These new technologies will also create a new way of understanding the ethics of healthcare. For the last fifty years, the ethical debate in healthcare has been focused on what role the social unit should play in the financing and delivery of healthcare. In Europe, a single payer system developed to spread health risk across the nation. In the United States, the health insurance industry evolved to spread health risk among a specific social unit: the corporation.

These systems made sense when the focus was disease and the ability to predict an individual's susceptibility to disease was not well developed. As we shift from a disease model to one focused on health and health potential, both the system of distributing risk and the ethical obligations of the individual to the larger social unit will change. For both systems to work there needs to be an ethical agreement between the individual and the social unit. For those health risks (i.e. lifestyle factors) that individuals have control over, they will have a positive moral obligation to maintain their own health and prevent disease. For those health risks (i.e. genetics) that the individual has no control over, the social unit will have a moral obligation to provide care. Without such an agreement, the healthcare system will naturally

shift back to a private care model because their will be no benefit, either moral or economic, for pooling risk.

Evolution of Social Unit Health Standards

The health plans of large U.S. corporations are a forerunner of an anticipated evolution in social unit health standards. For example, G.M. spends nearly $6 billion a year on healthcare, mostly for retirees and their dependents. The unions are fighting to keep the standard of care. Financial analysts project that unless GM shrinks its size and reduces the percentage of its revenue expended on healthcare it will become bankrupt. GM's system was set up on an economic basis and there was no commitment by the workers to look after themselves as part of an ethical agreement with GM. GM ended up paying too much for the wrong things. Too many workers were free to pursue lifestyles destined to lead to enormous health bills for retirees that now threaten all the workers' very future.[107]

Most corporate health plans made healthcare a benefit without assuring it also creates an economic good. A more ethical approach to healthcare will recognize the economic benefit for larger social units. The success of the American economy will thus become more important than the desires of a given company's workforce. Ultimately, the economics of globalization will elevate the ethical imperative for healthcare provision to provide advantages to nations as well as companies, and the care will have to be higher in quality and lower in cost than it is today.

[107] L. Hawkins (April 7, 2005) "As GM Battles Surging Costs, Workers' Health Becomes Issue", The Wall Street Journal.

The Ethics of Health Enhancement

New health technologies will enable us to cure disease, but it will also enable us to enhance our health. Health enhancement raises a number of ethical issues. If it is technologically possible to improve someone's cognition, then to whom should that enhancement go? If it goes only to those who can pay for it then we widen the divide between those that have and those that do not. The technology could also be banned, but what would be the effects on civil liberties? These questions are not new, but the range of new technologies that will be available by 2029 will make them a more pressing concern. The best way to answer these questions will be to orient individual choices within the social unit. When considered from this ethical perspective, the answers will be more firmly seated in an acceptable rationale that all social unit members can accept.

East Meets West

Eastern medicine has had a steadily increasing influence in the West. This is seen in a variety of alternative practices such as acupuncture. As the West has adopted these practices it has also sought their philosophical and ethical underpinnings. This is leading to an increased awareness of the importance of treating the whole body, the physical and spiritual self. The priority is shifting from treating disease towards maintaining health. Large Pharma companies today are already re-writing their missions to cast themselves as healthcare companies as opposed to pharmaceutical companies.

Eastern ethical principles promote the well being of the social unit as the desired goal. Interestingly, Buddhism tends to deemphasize the idea of self as permanent physical entity and Shintoism emphasizes the interrelatedness of humans and nature – a theme we see emerging worldwide by 2029.

Well before 2029 we can anticipate the emergence of a new view on health that has its roots in both traditional western and eastern practices, but transcends both. The goal of this new practice will be to maximize both individual potential and its contribution to collective health.

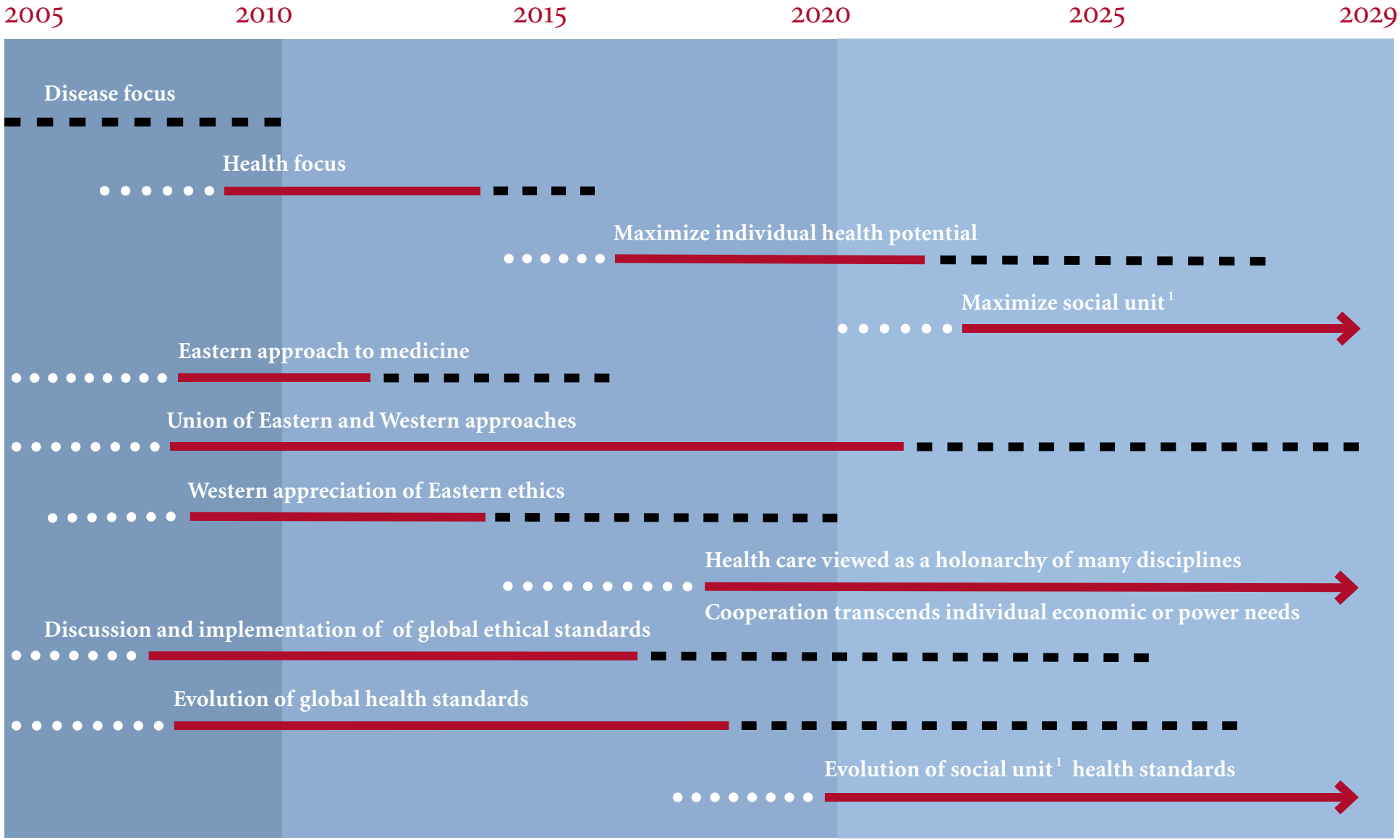
What Will the "New Ethics" of 2029 Look Like?

The current and future diversity of social, religious and political systems in the world ensures that all scientific and technological developments will find some place where they can be developed and exploited. These will in turn confer advantage on that social unit that exploits them and this in turn will put pressure on other social groups to adopt them. In 2005, there are still many areas where the dominant virtue-based ethical system inhibits such developments, for example with stem cell research. Others who are not inhibited will move forward and gain the economic advantages as well as the health gains in their populations.

The ethical imperative is coming more to the fore in healthcare, business and politics. The number of committees and working groups set up by international and national organizations supports this idea that we need a new ethic to deal with increased knowledge and received wisdom. This new ethical system will focus on the wellbeing of social units against an ever-increasing global ethical standard. Increases in the economic wellbeing of developing population centers such as India and China will help fuel this evolution. By 2029, well established ethical conventions will direct law and economics as never before. With this alignment, science and technology can fulfill its promise to deliver global health.

ETHICAL AGREEMENTS

Huge increases in knowledge will cause us to think about health in new ways. Our ethics will then evolve to allow new mores for health responsibilities, much as the evolution of quantum mechanics allows us to understand the complexities of the physical universe.



1 Social unit could be extended family (gene pool), gated community; geographical unit; racial/ethnic/religious unit; nation, global society etc.

Section 6: Seven Recommendations

IAF has developed the following set of recommendations intended to promote biomedical R&D, expand the knowledge of health and disease, and improve health for everyone.

1. Set a goal for U.N. adoption of a minimum global health standard for all. This goal is both an ethical position and a strategy for global political and economic development.

   By 2029 there will be tremendous advances in the capacity to improve health, which will strengthen economies and elevate the ethical concern for those who do not benefit from globalization. By boldly proclaiming a goal that symbolizes the concern that wealthy and powerful people share for the poor and disadvantaged, we invite the evolution of an ethic to guide globalization. Our research shows scientists have a deep interest in serving humanity. A clear, compelling goal such as this can incite the creativity and commitment that is necessary for science to make its greatest contribution to health in the years ahead.

2. Create personalized risk profiles that integrate the collective understanding of health and disease in order to improve health for individuals who can contribute their records to build a knowledge base supporting health for all. Individuals and society should use these profiles to encourage individual responsibility for health and collective agreements about resource limits on healthcare.

   The knowledge revolution has just begun to show that information technologies can shift the center of learning from population norms to individual variations from the norm.[108] By surrounding each individual with fields of personal information and accessing collective knowledge, healthcare can create scientific risk assessments based on an integrated suite

[108] For an example of the different risks individuals may face in taking the same dose of Warfarin, see Rieder, M, et al. “Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose” (June 2, 2005), The New England Journal of Medicine.

of research methods. The resulting personalized risk assessments will provide far better guidance for individual decision making as well as communal resource allocation. Not everyone will have the same risks and opportunities. So the ability to address personalized risk profiles promises large improvements in quality as well as economic savings that are ethical.

3. Initiate a global discussion of ethical positions for intellectual property that inform policies that foster business models for both innovation and diffusion of technologies contributing to health.

   Innovation typically meets the needs of the wealthy first and later offers access to the poor. Ethical policies can be engineered for greater speed of diffusion while prompting innovation. Intellectual property must work so that innovation offers promise to both the rich and the poor. Successful policies, such as the Hatch-Waxman Act, have demonstrated that innovation and diffusion can create wins for all. Global policies should do the same.

4. Move from healthcare focused on treating disease to knowledgeably promoting health.

   As our knowledge and wisdom of health progresses, the greatest gains to be made in healthcare will be in predicting and preventing disease as a step toward promoting health. Biomedical research has a large role to play in this shift. Systems biology can bring a new understanding about signals from biomarkers showing risk of disease. This knowledge needs to be accompanied by a new understanding of why people choose behaviors that are healthy. Scientific research must build on success at the molecular and cellular levels to create knowledge all the way up the holarchy to global health. Lifestyle, mental states and environment have to be recognized as integral to health.

5. Change healthcare regulations to promote information sharing and new methods beyond traditional clinical trials.

The coming era of personalized treatment and prevention needs new research methods that regulations must foster rather than impede. A partnership between research subjects and the biomedical research community should form around new methods that serve individual as well as collective interests. Adaptive clinical trials provide one such method because research subjects are directed toward experimental therapies that are demonstrating benefit. This approach is preferable to blindly placing subjects in a study arm that will prove disadvantageous to them if the study succeeds. Other study designs that take advantage of the growing information infrastructure (e.g., electronic medical records) should become part of ongoing regulatory reviews. The lead regulatory agencies should be given budgets to conduct their own R&D that encourages innovation in areas such as modeling and simulation that can lead to faster, better regulatory decisions over safety and efficacy.

6. Foster an open-source system for health research, including drug discovery.

   Treating complex diseases requires more support and communication between biomedical researchers. An open source system for health research can break down the barriers between organizations and scientific disciplines to create higher quality drug candidates. Patients, and their valuable insights, should also be considered partners in open source research. Both the public and private sectors need to negotiate how intellectual property policy and business models can better serve public and private interests by taking advantage of open source science.

7. Create a collaboration of stakeholders to pursue the design and development of the Health Advocate Avatar as a central tool and capacity for integrating the learning about and for each individual as well as the effective aggregation of individual and environmental knowledge to understand, explain, forecast and enhance health.

As this report demonstrates, the early components of the Health Advocate Avatar are available today. No one has brought together the people and resources needed to integrate capabilities around this Avatar vision. The Avatar represents an incredible leap beyond existing strategies to empower patients, transform research and development and promote an ethical system of healthcare. The Health Advocate Avatar can focus the tremendous potential of biomedical R&D on the health of the individual and social units up to the highest level of global health.

Section 7: Conclusion

The future for biomedical research and development promises to contribute more to global health than we could believe if we only based our view on history. By looking more deeply and understanding that evolution operates at all levels of life, all the way up through our ethical systems, we can see a far better future. In 2029, we can imagine a world in which the poorest person in Africa, Asia or anywhere else knows that science offers the hope for a healthier life. We can imagine that the wealthiest people in the world also know that the benefits they gain from scientific innovation will extend worldwide.

Clearly science is bringing us remarkable technologies, from new applications of nanomedicine to the promise of stem cells. This science can improve the health of billions of people around the world. There will be new ways of organizing research based on advances in knowledge technology and open source research. Our knowledge of health and disease will increase dramatically due to advances in imaging, the –omic sciences, and systems biology. These advances will fundamentally affect how biomedical research is performed and healthcare is delivered, creating new ethical agreements about the value of health.

The deeper question is how do we make sure that the full potential of science is unlocked? Perhaps surprisingly, the key turns out to be the evolution of our ethical positions. Natural selection will favor those who assure that the knowledge revolution serves the larger commitment to global health. The economic good that health provides confers advantage to whole societies.

This advantage can grow if we deploy the Health Advocate Avatar in order to improve individual and global health in tandem. The challenge to develop this Avatar is an exciting way to tie the evolution of healthcare, economics and ethics together. The 2029 Project began as an exploration of many different paths into the future. The Project concludes as a loud call

back to the present—we've found a path that will take us to a surprisingly visionary future. In 2029, we can distribute the benefits of biomedical research more equitably than our current capabilities and ethics would let us see. That is the ethical path for science.

Appendix A: Experts and Meeting Attendees

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Draper Laboratory

Paul R. Blasche, PhD
Principle Director
Draper Laboratory

Donald Bone, PhD
Corporate Director for Science and Technology
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Jeffery T. Borenstein, PhD
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Ed Carlen
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Wayne O. Carter, DVM, PhD, DACVIM
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Heather Clark, PhD
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Cristina Davis, PhD
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Amy Duwel, PhD
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Martin L. Ferguson, PhD
Founder and Senior Vice President
Ardais Corporation

Mauro Ferrari, Ph.D.
Professor of Hemotology & Oncology
Special Expert in Nanotechnology
Ohio State University

Timothy Ferris, MD, MPH
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Jason Fiering, Ph.D.
Draper Laboratory

Richard A. Frank, MD, PhD, FFPM
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GE Healthcare

Robert A. Freitas Jr., JD
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Gary Gordon, MD, PhD
Division Vice President
Global Oncology

Jeffrey A. Gelfand, MD
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Leland H. Hartwell, PhD
President and Director
Fred Hutchinson Cancer Research Center

Leroy Hood, Ph.D.
President
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James Mayne, PhD, DABT
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Wayne B. Jonas, MD
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Mark Keegan, PhD
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Brian Lovatt, M.D.
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John C. Marlow, MD
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Mark Mescher, PhD
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Michael Murphy, MD, PhD
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Robert Temple, M.D.
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Sheryl Torr-Brown, PhD
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Mindy Tupper, PhD
Draper Laboratory

Ralph Weissleder, MD, PhD
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Ian, Inc.

Mark Williams, PhD
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Eastport Analytics

Steven A. Williams, MD, PhD
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Angela Zapata, PhD
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Appendix B: The Draper Laboratory Report

Introduction

The Institute for Alternative Futures (IAF) and the Draper Laboratory held a workshop on the 15th of November 2004 in Cambridge, Massachusetts on the Future of Biomedical R&D in 2029. They recognized that the future of biomedical R&D is actually small, very small. The session forecast that a new tool kit of very small technologies is feasible, including micro-systems for drug delivery, micro-sensors to monitor patients, and micro-trials for drug development. Advances in imaging, biomarkers, organoids, systems biology, and multi-disciplinary collaboration will also accelerate advances in biomedical technologies, drug development, and healthcare.

Draper Lab Principal Director Paul Blasche welcomed participants, and expressed his desire to see some innovative ideas developed during the workshop. IAF President Clem Bezold facilitated the workshop with help from Jonathan Peck and Craig Bettles. Draper research scientists in the areas of biomedical engineering, microelectromechanical systems (MEMs), bio-informatics and other technologies shared their insights on the future. Outside experts from Center for the Integration of Medicine and Innovative Technology (CIMIT), the Massachusetts Institute of Technology (MIT), Harvard University, and Massachusetts General Hospital also attended.

Workshop Objectives

The workshop participants were provided with a range of initial "provocative forecasts" developed by IAF. At the workshop these were explored, critiqued and refined and additional forecasts were added. Key forecasts were evaluated for their likelihood. Critical steps necessary for the development of the forecast were also identified.

The discussions considered:

- The general environment for innovation in biomedical technologies.
- Business models for future innovations.
- Changes in the regulatory environment for biomedical technology.
- Possible funding sources for future R&D.

Forecasts for 2029

There were six main groups of forecasts discussed during the workshop. The first two forecasts presented below were developed by Draper research scientists. The last four were developed by the IAF team for the 2029 project.

Organoids Developed for Drug R&D

The distinction between in-vivo (living) and non-living systems for the discovery of biological phenomena, understanding disease processes and discovery of new drug compounds has vanished by 2029. The systems will be very complex systems of living & non-living systems called organoids.

Parallel thrusts in the development of nanoscale devices and the generation of in vitro biological systems have merged. Tools for identifying subpopulations on the basis of genetics and environmental exposures are available and help in targeting for the discovery of new compounds.

Organoids – replicas of human organs or components of them- will be developed and used to test the toxicity and efficacy of compounds outside the body. These will significantly lower the time and costs associated with the development of new drugs, particularly by discovering the toxicity of compounds earlier in the process, leading to drugs being discarded earlier in the process, or developed only for relevant subpopulations. Most animal testing will be eliminated because organoids will allow a more complete picture of the compound's effects on humans. The overall effect will be to drive price and spur the advance of personalized medicine.

Insights from advancing revolutions in systems biology and bioinformatics enable the replication of biological systems in the laboratory. Drugs are tested on organoids with the results uploaded into in-silico models to create a better understanding of the drugs properties. These capabilities accelerate the understanding of the full life cycle of interactions and effects of new compounds.

Personalized medicine will require tens of millions of human trials focused on the individual patient (trials with an "N of 1"). This will require major revolutions in our current approach to drug development and approval. Better models and understanding of why individual subpopulations react differently to different compounds will require better regulatory and health care information systems to ensure that this vital information is used properly and that patient privacy is respected.
Ex-vivo tissue models will be an important intermediate step to creating the full fledged organoids needed for successful "N of 1" trials. In ten years, doctors will be able to perform very small out-patient biopsies to collect tissue for testing personalized medicines. The biopsies will allow tissue to be engineered with the patient's own DNA profile.

To a certain extent, biomedical engineering is experiencing a paradigm shift from the development of tissue replacements to an in-vitro model for drug discovery. One of the key technological problems is developing three dimension matrixes of cells for replication. One solution may be the development of better nano-devices for fields other than medicine that can then be readapted by biomedical engineers to allow the precise movement of individual cells.

The development of organoids for the research and development of drugs outside of the body is likely to take between 10 and 15 years. The first applications during that time period would involve cell death forecasts for compounds. This will allow researchers to better understand the toxicity of

compounds on a cellular level. In 10 to 15 years, researchers will be able to do comprehensive efficacy tests on compounds in organoids before clinical trials in humans.

In the next ten years there will be better methods for using stem cells to create differentiated tissue types. The advances could be in either embryonic or adult stems cells, but the ability to create differentiated tissue from adult stem cells will be a key breakthrough for creating organoids with the same genetic pattern as individual patients. The use of animal stem cells to create differentiated tissue will also be important for using fewer animals in research and development.

The ability to create readouts for individual genomes will also be required. The readout would be a chart of the patient's genetic information. The workshop participants estimated that a full individual genomic readout would be available in five years, but that the computational power and sophistication needed to create models to understand and effectively use these readouts could take between 15 and 25 years.

Implantable Drug Delivery

Drug discovery and drug delivery are going to be strongly coupled in the future through implantable drug delivery devices. **By 2029, there will be a prototype engineered biological system, operating inside the body, which senses disease, and then synthesizes and delivers therapeutic compounds in-situ.**

There are currently implantable drug devices with no feedback loops that use advanced materials to slowly diffuse drugs into the patient's system. Drug eluting stents and controlled release polymers are good examples of current drug delivery devices. Currently, there are also MEMs systems with one feedback loop containing a flow sensor to monitor and adjust the flow of drugs into the body.

Two loop systems with a sensor to monitor and adjust the concentration of drugs into the body could be viable within 5 to 10 years. Patients and doctors could also adjust their medication through outside systems. Both one and two loop systems would still be open systems requiring monitoring by doctors to prevent adverse reactions and adjust dosages.

Three loop systems incorporate a sensor to monitor patient response to the therapy and adjust drug flow and concentration. These systems could either be completely closed loop where a doctor would not need to monitor the patient or hybrid systems where a doctor or patient would electronically "authorize" any changes in drug flow or concentration. These systems will be technologically feasible in 15 to 20 years.

The use of implantable drug delivery systems will be delayed without a more viable business model and changes in the regulatory structure. Under current regulations, each dosage level and delivery method must pass separate clinical trials even if the drug being delivered has already been approved. Clinical trials for implantable drug delivery systems are also extremely expensive since the subjects have to undergo surgery.

A viable business model also needs to be developed. Possible new areas to explore are adjustable insulin MEMs that allow diabetics to monitor their blood sugar levels and add more insulin before meals, MEMs that deliver a continuous stream of medication for patients with cancer and other chronic diseases and will allow patients more mobility, anti-inflammatory drugs delivered directly to joints, generic drug combinations for chronic diseases and for expensive biologics where smaller targeted doses might be cheaper and more effective than larger less frequent doses.

There are two main technological stumbling blocks to these systems. The first involves the power supply. Improvements in battery technology will allow smaller MEMs with more functionality. **In 25 years there may be biological systems that recharge implantable devices using the body's own organic chemistry.**

The second stumbling block involves drug stability and volume. The drug must be stable, able to be preserved for a long period of time, and effective in small doses. Drugs that do not last long or require large doses are not ideal for a MEMs system. **By 2029 many drug companies will develop new drugs, combinations of generic and non-generic drugs, and drugs that might be safe in small continuous doses, but toxic at larger doses, specifically for implantable drug delivery systems.**

Imaging and Biomarkers

Twenty-five years from now imaging and biomarker advances (libraries in the 1,000s) will expand the notions of disease to pre-disease and develop new business models. The concept of disease will shift so that prevention and early stage treatment becomes the new paradigm.

Three quarters of private insurance and two thirds of Medicare is spent on people with five or more chronic conditions. The expense of patients with multiple chronic diseases will continue to grow as the population ages. The most effective way to fight these chronic diseases is through prevention.

Using better imaging technologies, such as functional MRI, along with biomarkers will make prevention the best way to fight chronic disease. Biomedical researchers will compile extensive libraries of pre-disease states. Advances in imaging and biomarkers will help doctors diagnose pre-disease and help patients monitor their health.

Improvements in imaging and biomarkers will also help accelerate the forecasts above. Better bio-markers will make personalized medicine cheaper while advances in imaging will accelerate the development of computational models.

Miniaturized Research Infrastructure

By 2029, bio-chips and nano-labs will proliferate, allowing research to operate at various scales from molecular to global. Interconnected sensors communicate through a network that links trillions of information sources and a large human population, who contribute data directly through bio-monitors in the form of implants and wearables.

The development of a miniaturized research infrastructure will improve health by making it easier for researchers to monitor the effects of the environment (pollution, stress, ect.) on health. It will also allow for distributed phase four trials where the side effects and safety of drugs can be more effectively monitored.

- There are two main business models in development for distributed monitoring of health. The first model focuses on very sick, high risk patients where appropriate, timely intervention can prevent costly hospital stays and even death. Insurance companies would provide most of the funding in this model, but since this kind of intervention is very expensive, it becomes very important to narrow down the patients most likely to benefit. Chronic diseases with a clear path of progression, such as heart disease, are the likely targets for this kind of intervention.

- The second is consumer focused. In this model, consumers would pay to monitor their own health and preserve their independence. Elderly patients wanting to preserve their mobility and independence would be the largest market for this kind of technology.

Some of the main barriers to this forecast are getting the cost of sensors and computation down to the levels to make widespread deployment economically viable. Decreasing the size and increasing the stylishness of designs for these devices will also be important for opening up the market.

Evolution of Systems Biology

Biology becomes the preeminent science of the 21st century. Predictive models of biological processes are reliable for most molecular processes including many key cellular pathways and a number of key organ systems. By the 2020s there are predictive models for ecological, national, community and family health, but their reliability is not very high.

The workshop participants agreed this was one of the most difficult forecasts to achieve by 2029. Building models for complex biological systems will require large advances both the understanding of systems biology and in-silico biology. The challenges are particularly high for in-silico biology since biology has many non-linear systems that are difficult to replicate in-silico.

Well developed virtual organs, such as the virtual heart, will be common, but other virtual biological systems will be rare. It will be possible, but not likely, to have virtual models for cells and proteins in 25 years. Integration of these in-silico systems into a virtual patient able to advance biomedical R&D might be beyond the 25 year timeframe.

Merger of Disciplines

Education in 2029 integrates brain research into the traditional curriculum, typically offering a lifelong trajectory of cross disciplinary expeditions undertaken with teams of people who work in various modes (face-to-face, virtual teams, and in isolation) for different periods.

The workshop participants agreed there is an ongoing trend for more multi-disciplinary work among the hard sciences, and that trend is likely to grow stronger over time. Many also agreed that more multi-disciplinary work between hard scientists and social scientists (as well as ethicists) is also a future trend and that the exposure of scientists to these studies during graduate school is likely to grow.

However, they disagreed that there would be any merger of disciplines between hard science and the humanities, especially religious studies. They felt that there were many things that science could learn about religion, especially meditation, but that there was little that science could learn from religion. They were extremely skeptical about the value of having religious figures as collaborators in multi-disciplinary research.