PACIFIC HEALTH SUMMIT
SEATTLE 2005

Summit Challenge

THE NATIONAL BUREAU *of* ASIAN RESEARCH

Published in the United States of America by
The National Bureau of Asian Research
4518 University Way NE, Suite 300
Seattle, Washington 98105
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http://www.nbr.org

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Printed in the United States of America

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The Pacific Health Summit

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The Summit of Everest

In 1924 George Leigh Mallory and his climbing companion froze to death just 240 meters from the summit of the world's tallest mountain. Mt. Everest may never yield the secret of whether Mallory realized his dream and perished on the descent or whether he died only meters short of the pinnacle. Yet we do know for certain that on May 29, 1953 Edmund Hillary and Tenzing Norgay made the dangerous climb and finally stood atop Everest's 8,848-meter crown. Since that triumphant day half a century ago, one thousand men and women from over twenty countries have followed in the footsteps of Hillary and Norgay to climb to the top of the world. In fact, on one day alone in May 2002, fifty climbers reached the summit.

Due to huge strides in technology, climbing Mt. Everest today has become a matter of regular, if not predictable, success. Compared to the technology available to Mallory and his companion in 1924, climbers today have access to a phenomenal range of high-tech clothing and equipment which make the climb safer, faster, and easier. When Mallory's body was discovered in 1999, perfectly preserved by Everest's thin air and frigid temperatures, photos of his woolen clothing and leather and metal equipment stand testimony to just how far technology has developed in the past century. As every climber to take the first step onto Mt. Everest knows, however, any ascent can be unpredictable and dangerous. A thousand men and women have met the challenge and reached the summit, but more than one hundred and fifty have perished on those same slopes. The chilling fact remains that about one in six climbers who attempt to scale this mountain will die.

Advance preparation and teamwork can make the difference between life and death. Today's climbs are launched after years of preparation and include sup-

port teams numbering in the hundreds both at base camp and back home. Climbers now benefit at every step of the way from the hard and dangerous labors of their predecessors. In places that have claimed the lives of many climbers, there are now fixed ropes and ladders. Dangerous descents from the top of Everest are now measured in hours, not days. Whether the ascent is attempted by an individual or by a team of ten, success is the result of training, careful preparation, and the unsung teamwork of hundreds who help a handful achieve the glory of the summit.

The Summit of Pacific Health

Much like those who aspire to climb the world's tallest mountain, we have our own extraordinary and demanding challenge before us. Our summit is to make the future healthier than the past—to prevent and detect disease early enough to save lives at a much lower cost in terms of both suffering and money. Reaching this summit is a matter of extraordinary importance to us all, as the indiscriminating transmission of disease makes every person a member of the global health community.

We believe that there are several reasons to face this challenge now. In a world divided by language, we have a chance to make "health" into the *lingua franca* of the 21st century—a language spoken and understood by all of us. Scientific advances have already given us a common "alphabet" for the language of health with the four base pairs of C, G, A, and T. Despite the infinite combinations of DNA, the mapping of the human genome has shown us just how much we as human beings share in common.

This new language of health is being translated into huge investments in both the life sciences and applied technologies around the Pacific Rim. Not so long ago, the United States was the primary producer and consumer of science and technology in the Pacific Rim. But today a growing number of Asia-Pacific economies are investing their hard-earned affluence into life sciences, biotechnology, and bioventures. This shift began in post-World War II Japan, and has now spread to Australia, South Korea, Singapore, Taiwan, Malaysia, Thailand, and China. One

very important trend is that Asian scientists who journey to the West for training are increasingly returning to their home countries to launch world-class research and development activities. As a result, we now share a common scientific and technological foundation that will enable us to collaborate and build a healthier future together.

Unfortunately, we also share an increasingly common experience of disease, particularly infectious disease. The global HIV/AIDS crisis and the resurgence of a resistant tuberculosis and malaria have shown us how vulnerable we continue to be. The SARS crisis has demonstrated how a problem in one region can become a global problem in mere days. With the avian flu, we may now be witnessing an even more disturbing example of high velocity transmission, as this emerging infection threatens to make the quick and catastrophic jump from one species, birds, to another species, humans.

More surprisingly, we now also share the chronic diseases associated with affluence, aging, and dangerous lifestyle choices. An editorial in the January 21, 2005 issue of *Science* magazine noted that chronic diseases such as cancer, diabetes, and cardiovascular disease account for more than 50% of all deaths worldwide. Chronic diseases already take a significant toll on the health and economies of developing countries. As the editorial noted, efforts in chronic disease prevention can often take decades to yield benefits, a time lag which often leaves both developed and developing countries to face a combined medical and economic catastrophe.

In East Asia, as with Western countries, a "health explosion" marked by plummeting birth rates and rapidly aging societies has resulted in a profound demographic transformation. Japan now boasts the world's longest average life expectancy of 81.6 years. But other societies are not far behind. In the second half of the twentieth century, China added over 20 years to the average life expectancy for its 1.2 billion citizens, and the average Chinese now enjoys a life span of 71 years. Dramatic decreases in total fertility rates have paralleled the rapid aging of East Asian societies; Japan's birthrate of 1.32 again tops the list while China's birthrate has dropped to 1.8—both below the replacement level of 2.2.

In conjunction with these demographic trends, chronic diseases (such as cancer) have become a looming shadow over the development of all Pacific Rim societies. Cancer is now the leading cause of death in Japan; other societies have seen a similar spike in diseases associated with a rapidly aging society. China—with a total population of 1.2 billion, an average life expectancy over 70 years, a caregiver population hard-hit by the "one-child" policy and sex selection, and growing environmental pathogens resulting from rapid economic growth—faces a daunting series of public health challenges over the next few decades. In the United States, the inexorable march toward retirement and beyond for the 75 million members of the postwar "baby boom" generation may traumatize the entire American healthcare system. The economic and social reverberations stemming from these enormous demographic changes have already begun to echo through our Pacific Rim societies.

The Pacific Health Summit

To prepare for the challenge of scaling the summit of health in the Asia-Pacific, we have invited to Seattle the world's best minds in science, policy, industry, medical practice, and public health for the June 2005 inaugural meeting of the Pacific Health Summit. By building lasting partnerships, we hope that the Pacific Health Summit will become the base camp where we assemble powerful teams of climbers and then equip them with the scientific and innovative technologies to enable a successful summit ascent.

The character chosen to represent the Pacific Health Summit in our logo, pronounced *sheng* in Chinese and *ikiru* in Japanese, means "life" or "to live." The character is simple, clean in meaning, and powerful in scope. In the same way that this character for "life" also combines easily with other characters to build hopeful and strong compounds, we too hope the Pacific Health Summit will become a cornerstone upon which to build partnerships and collaborations. While scientific collaborations are among the first steps to be taken, we also seek to form partnerships around policy, medical practice, technology, and public health initiatives.

In order to reach this summit, we will have to create fundamentally new levels of organization, collaboration, and teamwork. Reaching our common summit of health cannot be done in isolation. Our Summit poster shows that teamwork is the only way to achieve our goals. Such teamwork must cut across wealth and poverty lines, cultural and national boundaries, and—perhaps just as important—the "silos" that vertically divide each healthcare system. This is also true for the global medical industry, which suffers from an unfortunate mindset and organizational structure that segregates pharmaceuticals, diagnostics, devices, and services from one another. To bridge these gaps, we have invited a broad cross section of leaders from the various health constituencies—science, policy, medical practice, healthcare administration, industry, and media—to join us in Seattle for this inaugural Pacific Health Summit.

The 2005 Summit is titled "Science, Innovation, and the Future of Health." The focus of our efforts is on how to transform healthcare by applying emerging scientific and technological advances to the prevention, early detection, and treatment of disease. We have organized the 2005 Summit into four plenary segments as follows:

1. The promise of science
2. The impact on public health
3. The impact on health systems and personal health
4. Science, health, and economic growth

This Summit Challenge document is a call to action. Our authors—William Castell, William Clarke, Lee Hartwell, and Richard Klausner—ask that you consider the challenges facing our global community, and then join us in the demanding global team effort to climb this summit.

Are We on the Verge of a New and Better Model for Healthcare?

W.M. Castell
President and CEO, GE Healthcare

During the second half of the 20th century, the developed world achieved colossal advances in medical innovation. These advances—in scientific innovation, industrial development, and service delivery—have saved and improved the lives of hundreds of millions of people. These innovations together constitute one of the great achievements of the century—alongside such other achievements as improved education and living conditions. The only danger is that their success locks us into thinking that the same model will automatically serve us as well in the future. We should therefore be prepared to think critically. Can we create and expect more from healthcare in the 21st century? When we ask ourselves this question, we unveil probably the most exciting set of opportunities to confront mankind since the fusion of three elemental resources—coal, water, and iron—created a new world order almost three centuries ago. This essay seeks to offer a preliminary agenda of action to take advantage of these very opportunities.

Health Care Advances in the 20th Century

The colossal advances in medical innovation achieved during the second half of the 20th century sprung from two distinct science streams. Medicinal chemistry and related disciplines spawned important new therapeutics that were then developed globally by a high-performing pharmaceutical industry. Separately, precision engineering and material sciences allowed for great advances in medical devices and instrumentation. Taken together, these innovations saved the lives of and provided a higher quality of health care for millions of people.

Despite these successes, the most frequently cited limitation of 20th century healthcare has been that it was developed to meet the needs of first-world markets and diseases. During the past two decades the industrial model has narrowed still

further, with the United States (which constitutes over 50% of the world market by value but only 4% by population) taking a pivotal role in determining the prioritization of pharmaceutical R&D portfolios. Mass tropical and niche orphan diseases were equally neglected. I highlight this not in order to join the fashionable ranks of those criticizing the pharmaceutical industry—on the contrary I believe that this industry delivers very successfully exactly what its customers demand of it—but to question whether these very real shortcomings are actually indicative of an incomplete and immature model.

True, infection and occupational illness have declined in the West, and impressive progress has been made in improving life expectancy in the face of cardiovascular disease and some cancers. Nevertheless, changes in aging patterns, environment, and lifestyle all pose challenges to human health and well-being. A new equation has arisen at the end of the 20th century:

longer life ***x*** multiple chronic co-morbidities ***x*** increased expectations =
great pressure on healthcare resources

These three new factors have also now led to the perception in the minds of major funders that healthcare, rather than rightfully being one of our greatest assets, is instead one of society's greatest liabilities.

Today, almost all of our healthcare resources are focused on the treatment of post-symptomatic illnesses. We need to question whether this narrow focus on "late disease" makes the best use of our technological potential, and whether this approach is the best way to help people maintain their own health. I believe that we as a global society can—and must—do better.

Toward Health Care in the 21st Century

The question now facing us is how to create an improved model for the 21st century. First, we must move to a much more geographically and socially inclusive healthcare universe. Our highest priority should be to address the colossal waste

of both life and potential that is epitomized by sub-Saharan Africa. Meeting this priority requires far more than medicine. Our failure to support and guide these countries toward greater participation in the responsibilities and benefits of modern civilization lessens our collective humanity. I applaud the apparent new determination of the G7 governments to address this issue more seriously.

From a global perspective, we must find a means of directing our long-term resources toward higher and more ambitious healthcare goals by utilizing the combined mechanisms of dynamic markets, innovative investment policies, and proactive regulations.

A combination of technology, education, and socio-economic change drove improvements in therapeutics and public health in the 20th century. The same forces apply today, but the key now lies in the transformational nature of the range of technologies presently becoming available.

The Revolutionary Opportunities of Information

Our main challenge is to recognize the true scope of the opportunity that lies before us, opportunities that have the potential to allow for a more connected and inclusive 21st century society. Previous industrial revolutions, all triggered by step-changes in science, have required long periods of "blood, sweat, and tears"—immense physical labor, massive migration, and negative environmental impacts.

The potential joy of the 21st century healthcare revolution—a revolution so new that it does not yet have a name—is that it can be achieved without any of the physical traumas of previous social advancements. This revolution will be led by information, that most mobile and educative of technologies. With the consent and support of the peoples we serve, we need to turn a deluge of raw and turbulent information streams into much clearer fonts of decisional wisdom.

I suspect that even the attainment of an age of truly decisional information will be far less of a challenge than the reengineering of our healthcare systems that would be necessary to take advantage of such advances. The aim of this Summit is to provide material to help guide this broader thinking. In fact, the late-disease

model is now ever more firmly entrenched, both in our medical infrastructures and in the individual and collective behavioral patterns of modern society. Over 90% of our resources are currently directed at treating post-symptomatic illnesses. Is this a desirable balance? Can we afford—both in economic and moral terms—for millions of our citizens to develop multiple co-morbidities in their early fifties, and then spend thirty years palliating their symptoms as their quality of life (physical, social, and economic) declines prematurely? We have all seen the upward trends on the major chronic disease graphs. The projections for diabetes in particular are little short of horrifying. These are challenges not only to the "obesity belt" of the United States, but to all populations now adopting a modern, more urbanized lifestyle.

Regardless of whatever technological advances may come, we still need to shift our healthcare model. We must place greater emphasis on providing the practical tools to help and motivate the individual citizen to understand and maintain their own health. This should be done through re-prioritization—from today's 90:10 to a more respectable ratio—of the balance between expenditure on the liability of illness and investment in the asset of health. I would argue that the key is to adopt a *holistic* view of the individual's health and to act *early*, before symptomatic disease—or the factors which provoke it—are allowed to gain the upper hand.

This may sound surprising, coming from an avowed advocate of global biomedical capitalism, but I genuinely believe that the industrial, scientific, and medical communities can now set themselves on a path of convergence. This new "early health" model is a tremendous opportunity for all contributors to the healthcare value chain to unite in the design and collaborative delivery of vital new programs. We have common values and thus can set common goals to respect and encourage the complementary reward mechanisms through which we operate.

The Power of Technological Tools

The principles of early health are therefore an unremitting drive to discover and address the *causes* of ill-health—environmental, lifestyle, or genetic—and to address these causes at the level of the individual before they become debilitating and expensive.

Whether we are engaged in policy, funding, innovation, or delivery, few could disagree with these broad precepts. Where these issues come alive, however, is when we consider the technological tools that are now appearing on the horizon. Let me stress that these tools are wholly and absolutely different, in terms of both nature and scope, from the levers that we had at our disposal even at the very end of the 20th century. Indeed, those countries now building their healthcare infrastructures may for the first time be at an advantage over more "advanced," mature economies, whose massive resources are locked into the major physical institutions and practices of the late-disease model. Our greatest planning tool may in fact be a very large, blank sheet of paper.

Let us (without arrogance) take for granted the panoply of technologies that drove 20th century clinical practice—including drugs, mechano-electrical instrumentation, physical devices, prospective-trial based clinical research, printed medical journals, and person-to-person communication by letter, phone, conference, and face-to-face, doctor-patient dialogue.

What are the new key drivers, and why do they have such power? In my view, there are at least five such tools and their exponential power lies in their combined use:

- genomics and its daughter sciences
- informatics—both genetic (micro) and epidemiological (macro)
- consumer connectivity, through telephony and demand
- nanotechnology
- bioengineering

The critical interplay lies among the first three, which together constitute the fundamental building-blocks of "biology, bytes, and broadband." Nanotechnology and bioengineering—from gene chips to stem cells—will help realize fundamental solutions.

This is transformational technology at its most powerful, equal in power to coal, iron, and water. As with the first industrial revolution, these elements are significant only when combined. DNA means little without massive analytical pro-

cessing, and raw SNP analyses only become capable of transforming clinical practice through the connectivity of epidemiological data and mass engagement with increasingly knowledgeable consumers.

Toward an Agenda for Action

Those societies which truly grasp the potential available here will become the leading contributors and beneficiaries in the 21st century. The biology, bytes, and broadband combination is at the heart not only of healthcare but also of the interlinked development of our overall "environment, economy, and education." These "Bs and Es" will be the true drivers in the coming decades.

The key challenge for us at this Summit—as laid out implicitly by the electorates, patients, and stakeholders we represent—is to grapple in practical terms with how we best integrate these opportunities into our healthcare systems. We cannot stand on the sidelines.

In my view, the technologies behind early health offer us yet another revolutionary opportunity—this time to act as a concerted world community, equally participating in innovation.

In the 20th century model, innovation spent years gestating in U.S. and European universities, followed by an agonizingly slow clinical and regulatory process which only the advanced Western economies could afford to fund. The seeds of innovation emerged from iconic institutions such as Harvard, Stanford, and Cambridge. The largest engine rooms of development were located in New Jersey, London, Basel, and Japan. Funded mostly—if not entirely—by first-world consumers, it is not surprising that this innovative cycle focused mostly on meeting first-world consumer priorities; other markets had neither the finance nor the infrastructure to participate in any manner other than as eventual passive consumers.

In the age of biology, bytes, and broadband, technology barriers are becoming less relevant. Every human being has a genome of equal value and interest to both themselves and to society. Even the most remote settlements are accessing satellite broadband, a $1 CD-ROM or $10 mobile phone contains more comput-

ing power than the first Apollo moonlander, and information transfer is global and instant. By the same token, the accessibility and power of the best diagnostic tools, critical to an early health strategy, have improved exponentially. We can now all have a stake in creating value from this opportunity.

The cost profile is also changing. An early-health model may actually be less expensive than building and maintaining a late-disease health system. Investment in excellent holistic primary-care—one that pays close attention to lifestyle, environment, early diagnosis, and intervention—stands the best chance of limiting the development of the expensive, debilitating late-stage diseases. We would thus make less investments in remote, tertiary hospital institutions and more in community-based patient-centric services. Such services would be based on integrated electronic healthcare records, remote real-time monitoring, and the best possible screening and early diagnostic programs—all tailored to the phenotype and genotype of the individual through well-validated epidemiological algorithms. The problem we should be addressing is how to take the best care to the individual, not how to bring the patient into an institution. In this environment, the streamlined, flexible, and in some cases virtual infrastructures required can serve not just for healthcare delivery but also for participation in global innovation and other economic activity.

Why, for example, should a primary care physician's office simply be a place that people visit when sick? An obvious step forward would be the creation of centers for health, fitness, and diagnostic resources. Could such centers not also become the focus of interaction for the broader community—such as for financial, agricultural, commercial, and other types of advice and social interaction? We have the opportunity to think very laterally here.

I see this summit as an invitation to join together to find new, closer partnership mechanisms that bind both countries and contributors to the healthcare value chain. Only by rolling up our shirtsleeves and working together on piloting and installing real applications can we develop a cadre of experience within our own

funding and delivery systems that are capable of judging how best to reengineer healthcare more broadly for the 21st century.

I can commit publicly that the organization I have the privilege to lead is realigning and reequipping itself to maximize the contributions that it can make in this field. To reach the main goals outlined above requires, however, resources of an infinitely greater scale. I would encourage all co-delegates to join together in communicating the strategic and human value of the opportunities that lie before us. We need to attract significant investment to the field of early health, which is distinct from the stretched financial burden of the late-disease model.

Healthcare needs to move from being our greatest modern cost to becoming our greatest modern asset. The investment required will offer rewards both to society as our ultimate funders and to ourselves as its protagonists.

Achieving Better-Informed Healthcare: Aspirations, Opportunities, and Challenges

Bill Clarke
Executive Vice President and Chief Technology and Medical Officer
GE Healthcare

When Does More Information Become Less Knowledge?

Geopolitics, environment, and socio-economic structures are all evolving at a pace with which communities across the world are becoming increasingly uncomfortable. Our traditional institutions are struggling to interpret and react to these challenges. There exists an increasing perception that change itself—particularly when driven by a combination of technology, mobility, depersonalization, and globalization—is a fundamentally negative phenomenon.

Information is the common driver of these accelerating dynamics. In many fields of human activity, information is arriving at such a bewildering speed that we are struggling, both individually and collectively, to weigh and form meaningful judgments. Differentiating between the fundamental and the ephemeral, and the vital and the trivial is becoming increasingly difficult. Paradoxically, the more information we have, the more we feel impelled to take instant action, yet the less confident we feel in the quality of the judgments we make, or that others make on our behalf.

Never has the challenge of translating data into wisdom been so great, and nowhere is the exponential growth in raw data more marked than in the field of healthcare. Yet, nowhere else is there a greater need for more useful decisional information that is applicable to, and actionable by, the individual to whom it relates.

To achieve a mature, fully personalized healthcare system will take many decades. Yet the first steps we take in this direction will define both long-term physical architectures and public attitudes—the fundamental twin contexts within which

all our development will take place. It is therefore vital that we actively plan to create a positive, durable role model that would allow us to see the benefits of an information-rich system. Such a model would not simply be a trigger for further self-justifying acceleration, but would rather be a stabilizing force, helping us to improve judgment, personalize our human environment, and increase the connective bonds of our social fabric.

In short, the world needs a sector which exemplifies a sustainable role model of the positive impact that more information and knowledge can have. The field of biomedicine is of a scale and importance to be able to provide this model. The key lies in the vision, determination, and skill with which we can develop, interpret, and integrate new types and volumes of information in partnership with the individual and collective humanity who are its true proprietors. So, where do we start?

The theme of the first Pacific Health Summit is "Science, Innovation, and the Future of Healthcare: Building Partnerships to Transform Healthcare." The plenary sessions on "Science," "Public Health," "Personal Health," and "Economic Growth" approach this transformational agenda from different aspects. In each plenary session there is, however, one theme which remains common: the huge—and rapidly growing—volume of raw clinical and biomedical data and information created daily throughout the world. To transform healthcare, this data and information must both be available to and be assimilated by healthcare professionals and healthcare systems in a manner transparently understood and supported by the global community.

Healthcare practitioners and healthcare systems rely on data, information, and knowledge—both explicit and implicit—to improve the health of individuals and populations. Yet the quality, availability, appropriateness, and utilization of this data varies vastly across practitioners and healthcare systems. Healthcare information can be as simple as an individual patient's medical history or an epidemiological identification of the most current influenza serotype. Increasingly, however, healthcare information is extremely complex—as found in the emerging ability to

"fingerprint" the RNA and proteins in a patient's tumor and then use the patterns to determine optimal, "personalized" therapy.

Today healthcare providers and systems struggle with processing and transmitting even the most simple data relating to an individual episode of treatment. While healthcare systems do a fairly poor job of turning today's healthcare data and information into knowledge, science, as we will learn at the Summit, promises to increase healthcare data and information on a vast scale. In other socio-economic systems, these deluges of data have tended to accelerate the pace of instantaneous decisionmaking, but have not always improved the quality of such decisions. We must avoid this trap.

It is an oft-repeated statement that data does not necessarily lead to information, information does not necessarily lead to knowledge, and knowledge by no means leads inevitably to wisdom. To this I would add that we must recognize that the attainment of wisdom is itself only a beginning. An optimized disease management paradigm is worthless unless that wisdom is generalized, socially accepted, and—above all—actioned. Such a goal requires a new focus on communication.

The challenge facing participants at the Summit is to engage in discussions on how to turn new data into practical, functional knowledge for patients, healthcare professionals, and healthcare systems. We must above all ensure that this translation occurs successfully across different cultures, countries, and contexts. We need consistency in our datasets and methodology, and localization in our application, communication, and delivery.

So, in short, how does more information lead to greater wisdom? Or in more practical terms, how can we use the Summit to help shape a medical future in which new clinical and biomedical information assists overburdened providers and systems in improving health, rather than drowning them in a flood of raw digits?

To stimulate discussion during the Summit, I will try to address each of these questions in the context of the Summit's plenary sessions in order to help spell out our common aspirations, challenges, and opportunities.

The Promise of Science

The *aspiration* in addressing the issues of information related to the first plenary session—"the promise of science"—is that clinical and biomedical research is rapidly expanding our understanding of the etiology of disease. This deep insight into the mechanisms of disease will allow an earlier and more precise selection of proper advice, lifestyle, environment, monitoring, and therapy—thereby collectively providing the best chance for improved overall health. The most fundamental aspiration is to transform today's pathology-based approach to healthcare (which often comes too late) into one that is a truly preventative and early intervention paradigm.

The *challenge* arises from the fact that the reality stands in stark contrast to this ideal. While biomedical research and publications grow at an increasing rate, the fraction of these that are applied to actual clinical practice remains small, and the time required for such application remains very long. The lead time from biomolecular discovery to routine application in a physician's office can easily take fifteen to twenty years. From the perspective of public health impact—especially in the context of the needs of countries whose health infrastructures are at widely different stages of development—one could thus argue that much of this scientific work is actually wasted effort. The *challenge* for the Summit is to find ways in which the tremendous wealth of emerging clinical and biomedical information can be applied more rapidly within the different contexts and environments represented by Summit attendees.

On the bright side, the *opportunities* are many. The Summit consists of representatives from many different disciplines and countries; as such, participants are uniquely able both to identify those scientific trends that may have a more immediate and/or tangible impact on healthcare and to recommend methods by which this science can be applied to healthcare. The diverse backgrounds of the Summit attendees offer the opportunity for this and subsequent Summits to serve as a structured basis through which young clinical and basic scientists from different countries are introduced both to each other and to critical issues of science, health, and

public policy. As an example, the Summit could sponsor "Pacific Healthcare Fellows" in science, health, and public policy. This year's summit offers an opportunity to structure these fellowships.

The Impact of Better Healthcare on Public Health

There are two main *aspirations* concerning the potential impact of better healthcare information on what is the theme of the second plenary session—public health. First, there is the very real hope that improved clinical and biomedical information can lead to better and earlier diagnosis, better and more tailored therapy, and better use of healthcare expenditures for other public health or social needs.

The second *aspiration* is that a better flow of information between healthcare systems and healthcare providers will lead to a more rapid adoption of improved healthcare paradigms in developing countries. As many Asian economies have greatly compressed the cycle of economic development, an improved quality and flow of clinical and biomedical information should allow these countries to compress the development of their healthcare systems and positively impact public health. Such a compression would involve not only an acceleration of timescales, but also the adoption of the correct physical, social, and virtual infrastructures necessary to achieve a viable 21st century healthcare model.

The *challenges* are also twofold. The first is whether there is a way to clarify where the dearth of information is most acute in public healthcare needs. The second occurs after that information becomes available, and centers on identifying the mechanisms by which this information can be distilled into a form that can be actively and effectively communicated so as to impact public health.

The *opportunities* here are significant. The breadth and depth of scientific healthcare and policy expertise represented at the Summit is unprecedented. While prioritization is always difficult, we should not shy away from selecting a very small number of areas where we believe that focused transnational and transdisciplinary efforts can generate new data, information, and knowledge capable of making a demonstrable impact upon public health in the near term. Scientists such as myself

disapprove of making *a priori* prioritizations, preferring to let investigations follow paths as they open. Yet, in the context of our mission in the Pacific Health Summit, I would argue that we do not have such a luxury. The flow of data inundating healthcare systems is too large to allow us to adopt a "wait and discover" attitude. Millions of people need better public healthcare. Healthcare information, knowledge, and wisdom are a critical means of delivering such care to these individuals.

The Impact of Information Upon Healthcare and Personal Health

As we think about the impact of information on the subject of the third plenary session, healthcare systems and personal health, the question that must remain foremost in our minds was one posed at the outset of this paper: when does more information become less knowledge?

The *aspiration* here is that more information—presented not as large data sets but in a highly contextualized and rapidly accessible fashion—can lead to more effective and more efficient healthcare systems. Similarly, the hope is that more information will lead not simply to better healthcare systems but also to demonstrably positive impacts on individual health.

The challenge, I believe, lies in our understanding of the word "accessible." I would argue that accessibility has very little to do with passive "availability." Given modern digital archiving and context-sensitive retrieval, these meanings of accessibility are relatively trivial, and will have no discernable impact on either health systems or individual health. Instead, accessible healthcare information must cease to be merely technologically and temporarily accessible and instead begin to be intellectually, psychologically, and emotionally accessible. For information to become knowledge and for knowledge to translate into wise decisions, the information must convey to the healthcare provider and patient: "This is how this information affects you; this is how you can make a better, wiser, more timely decision." An astonishingly minor percentage of healthcare information today does this, and that which does serves only those in the highest socio-economic tier.

Given the range, stature, and contacts of participants at the Summit, our *opportunity* is quite unique: to find "translators" for a rapidly increasing volume of healthcare information that empowers rather than burdens. In order to empower, the new generation of biomedical and clinical information must become truly accessible to individuals and systems at the deepest levels. Thus, we should reach outside of the current range of participants to bring in a whole new set of skills as exemplified by these translators and communicators who make the complex visible and accessible. To make this information truly accessible would require anthropologists and sociologists—or even artists, entertainers, and poets? We need many different skills to help make the flood of healthcare information "accessible," and to turn this information into knowledge and wisdom so that it can have a full impact on both healthcare systems and individual health.

Science, Health, and Economic Growth

As healthcare information grows in quantity, we hope that it will positively impact economic growth in several ways. First, the generation of clinical and biomedical data, information, and knowledge is a powerful and beneficial economic activity in itself. Second, the appropriate application of healthcare knowledge and wisdom leads to healthier, more economically engaged populations. Thus, the *aspiration* of the Summit should be to find ways to use healthcare data and information knowledgably in order to promote both of these economic drivers.

While healthcare information can drive economic growth, our *challenge* at the Summit must also be to spread these beneficial effects equitably. The questions we must ask ourselves include: How do we build economic growth for all by fostering more and better healthcare information and knowledge, yet not have these benefits limited to just a few? How do we help assure that existing national and cultural disparities in the generation of, and access to, healthcare knowledge do not continue to widen? How do we assure that the healthcare information industry does not diverge into a small number of "producers" servicing a very large number of "consumers"?

Our *opportunity* lies in harnessing the talent of the Summit participants to work toward a robust, transnational "marketplace" of high quality healthcare data information, knowledge, and wisdom. This marketplace will foster economic growth and, by means of strong international dynamics, support the delivery of the full range of solutions required across the healthcare spectrum.

If we achieve this goal, we will have succeeded; more information will not lead to less knowledge but rather to better healthcare.

The Promise of Molecular Diagnostics

Lee Hartwell
President, Fred Hutchinson Cancer Research Center

During the last forty years, we have achieved an impressive understanding of the molecular fundamentals of cell biology and how disease perturbs normal cellular behavior. For instance, we knew nothing about the molecular biology of cancer when I began my career in researching this disease in 1964. We now understand that this disease arises in a single cell as a result of genetic changes that alter a number of cellular processes—growth control, immortality, apoptosis, angiogenesis, and metastasis—and that these changes are driven by an abnormally high rate of mutation due to defects in the control of cell division and the repair of DNA. Moreover, we have identified not only many of the genes and proteins that function in normal cellular processes but also many that are altered in cancer. That is an amazing accomplishment for only a short forty years of effort.

Moreover, new advances are still occurring at an astonishing rate. For example, in just the last few years we have seen the completion of the human genome, providing a catalogue of all human genes; the development of RNAi technology, permitting the sophisticated genetic analysis of human cells for the first time; and the identification of cancer stem cells. The question we must then ask today is: can we now translate our knowledge into improved healthcare?

The Use of Molecular Information to Answer Diagnostic Questions

I believe that the major impediment to improving healthcare is our limited ability to provide patients with diagnostic molecular information. Why molecular diagnostics? Because our current level of sophistication in understanding the molecules of disease cannot be employed to interrogate the molecular basis of disease throughout the entire body. Our current methods require us to remove tissue from the patient for testing. This need for invasive tests greatly limits our ability to apply

our knowledge broadly—for instance in screening healthy populations for early stage disease. Molecular diagnostics would be empowered by an advance that permitted us to apply our depth of molecular information to the whole patient. To put this in perspective, consider what each new cancer patient wants to know:

- Do I have cancer?
- What stage is my cancer?
- What is the most effective therapy for my cancer?
- Is my therapy working?
- Have I been cured?
- Is my cancer recurring?

These are diagnostic questions, answers to which can be found in the molecules of the cancer cells themselves. But we must be able to access these molecules non-invasively and with relatively inexpensive but highly reliable tests. In these areas we are beginning to make some headway. In the last few years enormous strides in molecular diagnostics have occurred, primarily at the DNA and RNA level. Genetic translocations or transcript array profiles are stratifying many organ-specific cancers—such as breast, leukemia, lymphoma, and sarcoma—into different types according to their distinctive therapeutic outcomes. For example, amplification of the Myc gene predicts the outcome of the current therapy for childhood neuroblastoma. The quantity of Bcr-Abl DNA predicts disease recurrence in chronic myelogenous leukemia long before clinical symptoms recur.

Early Diagnosis

One of the most important benefits of improved diagnostics will be in detecting disease at an early stage, when it can be more easily cured or managed. Although diabetes is easily managed by continuous diagnostic testing for glucose levels, if monitoring is neglected then very serious consequences may occur—including loss of limbs and even loss of life. For most cancers early detection is the difference between life or death; five-year survival is often near 90% for cancer detected at stage one, but may be only 10% or less for cancer detected at stage four. The identification of more diagnostic molecular markers (biomarkers) for early stage

disease—ones that can be detected in blood and other body fluids—would permit screening of healthy populations to reveal those with early stage disease.

Risk Assessment

The cost and efficacy of screening programs can be vastly improved by focusing such screening on individuals at high-risk. Success in identifying individuals at increased risk has been achieved for many cancers through epidemiological studies that identify strong environmental (for instance, HPV for cervical cancer) or behavioral risk factors (such as smoking for lung cancer), and for rare inherited cancer syndromes (e.g., BRCA for breast cancer). Cholesterol, HDL, and LDL levels are all important risk factors for the onset of arterial and heart disease. We have not yet identified strong risk factors for many diseases, however, and it seems that a multitude of weak factors are often at work. Since many diseases have precursor states that increase the likelihood that the disease will manifest itself (such as cancer), it may be possible to discover biomarkers for risk.

Many are also optimistic that correlations of inherited genetic variation with disease will reveal common polymorphisms that increase the risk of disease in the larger population; technology for the large-scale monitoring of genetic variation is, moreover, soon to be available. Another approach is to identify individuals at risk by phenotypic, rather than genotypic, tests. For cancer, DNA damage is a primary causative agent. Most familial-prone cancer syndromes are due to defects in DNA repair. A study by Scott and Roberts revealed that, prior to treatment, about 40% of breast cancer patients exhibited a defect in double-strand DNA repair in their white blood cells. Further efforts at risk stratification based on phenotypic testing—such as DNA repair capacity for cancer, fat metabolism for heart disease, and mitochondria function for obesity—could be very fruitful.

The Power of Protein Diagnostics

Although we are currently experiencing impressive advances with DNA-based diagnostics in the cancer field, this disease is probably unique in that the diseased cells have DNA alterations. Moreover, accessing the information in DNA and RNA often requires knowing ahead of time that cancer is present so that it can

be biopsied, often with highly invasive techniques. The greatest power of molecular diagnostics will likely be found in the use of proteins as biomarkers, which carry much more diagnostic information than nucleic acids and can be sampled from easily accessible body fluids. There are many reasons why proteins are useful. First, proteins are more diverse, given that alternative splicing and more than 100 different postranslational modifications can result in 10–100 species of protein from each gene. Moreover, proteins are much more dynamic and reflective of cellular physiology. Protein phosphorylation can signal the presence of a single double-strand break in DNA within seconds to minutes of the activating event. Indeed, many of our most useful diagnostic agents are proteins found in the blood—such as troponins for heart attack and hormones for pregancy.

Need for Organized Effort

Biomarkers thus show enormous promise to translate our understanding of the molecular biology of the cell to the molecular biology of the human. In order to fulfill this promise, we as a global society must expedite the search and implementation of biomarkers for disease. We need to develop a rigorous science of biomarker discovery. In the last few years two advances have vastly improved the potential for protein diagnostics. The first is improvements in mass spectrometry which have allowed thousands of peptide features to be displayed, bar-coded by molecular mass, and quantitated with commercially available machines. The second advance is the unlocking of the human genome information, which provides a limited catalogue of what proteins are present in the human body, thereby permitting efficient identification of proteins displayed by tandem mass spectrometry.

The realization of the potential of protein diagnostics will, like the genome project, require highly organized activity. Industry is not likely to undertake this activity because of the limited financial return on diagnostics and the fact that the technology for biomarker discovery is still primitive. Building a robust technology for biomarker discovery is, however, a necessary precompetitive platform that should be organized as a partnership between academia and industry. An effective search for the sentinels of disease will require a team effort: many labs working on

the same samples, sharing data, developing standards, and pooling information. Such an effort will require an informatics platform that can support these coordinated activities and thousands of standardized antibodies and peptides.

The Use of Molecular Information as Basis for Action

Molecular Targeted Imaging

If we can discover protein biomarkers that predict early-stage disease, what would then be our next step? We will need to know where a disease like cancer is located, how large it is, and whether it is confined; put differently, we will need to "see" the cancer. Although we can image cancer by CT, MRI, ultrasound, or PET, each of these imaging modalities can be greatly enhanced with contrast agents—protein biomarkers as well as other metabolites that offer the opportunity to see not only where the problem exists but also the nature of the problem itself. By tagging antibodies with contrast cargo specific for the proteins that are localized and functioning at the site of disease, these markers allow us to visualize apoptosis, proteolysis, angiogenesis, and metastasis. With informative contrast agents, we can tell which cells are currently repairing DNA damage. We can distinguish cell division from apoptosis in a tumor mass. We can image the characteristically leaky blood vessels in both tumors and the altered lymphatic vessels.

The remarkable response of gastrointestinal stromal tumors overexpressing the KIT kinase to the drug imantinib can be seen within days of treatment through PET imaging of glucose metabolism.

Targeted Therapy

Therapeutic strategies can also benefit directly from an understanding of the proteins that are prominent in each type of cancer via the development of new molecularly-targeted therapeutic approaches. Many of the broadly toxic agents could become cancer-specific reagents if coupled to antibodies that deliver them specifically to the cancer cells. There is at least one FDA-approved targeted therapy of this

type, Myelotarg, which couples an antibody specific for tumor cells with a toxic reagent, calicheamicin. Many more antibody-based therapies are in development.

Improved Clinical Trials

The consensus view has been that the best way to cure cancer is through developing new drugs (such as Imantinib) that target the molecular changes in cancer cells. This is, however, too narrow of a view. The hope that more miracle drugs would cure cancer has been frustrated by the high cost of new drug development, the poor predictive power of animal models, and the complexity of the disease. Although many new drugs are currently in clinical trials, the success rate of such drugs has traditionally been low, and several drugs targeting cancer stem cells are likely to be required in order to cure each type of cancer.

Improved diagnostics could greatly accelerate new drug development by shortening clinical trials, identifying responsive patients, and revealing toxic side effects. For example, one of the first trials approved with a molecular end point is currently underway for chronic myelogenous leukemia. By using the end point of a reduction in the DNA marker, Bcr-Abl, a trial that originally would have taken several years to complete will be reduced to a mere twelve months.

If we could routinely follow a patient's response to therapy in real time, then the selection of the most appropriate agent and the most effective dose could be individualized. A series of agents could be tested on the same patient in a matter of weeks. Combinations could be tested by adding new agents serially to others displaying some efficacy. If a tumor becomes nonresponsive or recurs, a series of different agents could be immediately tested for efficacy.

Molecular diagnostics should be seen as an essential partner to developing new therapeutics. Indeed, Steve Burrill—the guru of the biotech industry—has described the coming era as one of "Rx Dx": emphasizing the necessary role of integrating diagnostics with therapeutics.

Imagine a Future

Imagine a future where health is not left to chance, a future where you know your risk of disease and can act either to prevent it or to detect it at its earliest—and most curable—stage. Imagine knowing which therapy will cure your disease or alleviate your symptoms before you receive it. Imagine treatments tailored to your individual characteristics. This is not only possible but will be the future of healthcare—the revolution is beginning now. The scientific advances that will enable this future to come about are taking place in molecular diagnostics that will allow us to test for and to image molecularly-based physiological changes in organs and tissues. Recent advances have created powerful diagnostic tests—based on DNA markers—for infectious disease and cancer. Even more effective and broadly applicable diagnostic tests will come from protein molecules. Coupling these markers with molecular-targeted imaging will allow real time anatomic assessment of disease and its response to therapy.

Global Health in the 21st Century: The Role of Innovation

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Improving global health is the paramount challenge that we as a global society must address in the 21st century. We must come together in this new era to help bring about and manage at least three types of innovations:

- **Innovation through the creation of technology.** New tools and strategies are needed to address diseases and health conditions that affect billions in the developing world—such as vaccines for HIV and malaria.
- **Innovation through the creative adaptation of appropriate technology.** Health tools must match the needs and requirements of all global communities. This is the aspect of global health innovation that carries the most profound implications for science, technology, and industry.
- **Innovation through creative partnerships.** There is a pressing need for innovative approaches to the financing, security, delivery, and measurement of health interventions for those around the world who have not so far benefited from general health care advances.

Global Programs for Global Health

I have been fortunate enough to be involved in three important global health programs launched by The Bill & Melinda Gates Foundation, all of which were designed to help bring these three innovations to life in practical and concrete ways. These include the "Grand Challenges in Global Health" project, the "Global HIV Vaccine Enterprise," and the "Global Alliance for Vaccines and Immunization and the Vaccine Fund." Let me discuss each of these in turn.

Grand Challenges in Global Health

Over a century ago, the mathematician David Hilbert inspired generations of innovators with his famous speech "Grand Challenges in Mathematics." Two years ago, we in the health field began a global process designed to define a set of scientific and technical grand challenges in global health. We solicited ideas from the world's science, technology, and health communities by posing the question: "What specific scientific or technical breakthroughs would be required to overcome one or more roadblocks that are standing in the way of solving a critical health problem of the developing world?"

We received thousands of pages of ideas from over 80 countries. Using this input, a twenty-member international scientific board created fourteen specific "Grand Challenges in Global Health." We then called for proposals— pragmatic, radical, and even high-risk—aimed not at exploring the problems but at solving them. Examples of some of the problems include:

- How to create vaccines in entirely new ways:
  - To create life-long immunity at birth with a single dose of an antigen
  - To solve the thermostability of vaccines
  - To create effective, needle-less delivery
  - To make immunization predictable and not empiric
  - To solve the classic antigenicity-immunogenicity paradox
- How to create definitive and safe ways, via either new chemistry or novel genetics, to control insect vectors carrying and spreading disease
- How to create safe, efficient, and novel approaches to optimizing the complex energy and nutrient content of staple foods via genetic breakthroughs
- How to cure latent infections
- How to design drugs unlikely to select for resistance
- How to measure both health and disease in novel, accessible, and affordable ways

Over 10,000 scientists from over 70 countries proposed solutions. Over 400 grants were submitted, requesting over $4 billion—an amount much more, unfortu-

nately, than we could fund. Having put these proposals under extensive review, we will soon be announcing approximately ten percent of these as recipients of Grand Challenge grants.

We hope to achieve four goals with this program: 1) raise the visibility, stature, and excitement of global health science; 2) inspire the world's scientific community and especially young scientists to think about what is actually required to solve a problem; 3) like Hilbert, create a list of those problems that have not yet been solved, that are worth solving, and on which many individuals would work on solving; and 4) direct hundreds of millions of dollars to fund new communities of global health problem-solvers in science and technology.

The Global HIV Vaccine Enterprise

There are few single medical technologies that would have as profound an impact on global health than would an effective HIV vaccine. Finding such a vaccine, however, is one of the most scientific and technically difficult problems ever faced. Progress has been painfully slow. This virus seems to have perfected the ability to avoid the immune system, and of the 60 million people infected, none have proven to have acquired immunity.

About two years ago, several dozen scientists began a conversation to ask whether we believed that our current approach to solving this problem was optimized. The universal answer was "No."

In response, the Gates Foundation proposed a new approach called the Global HIV Vaccine Enterprise. Inspired by the Human Genome Project, the Enterprise has created an ongoing process of producing, through the work of hundreds of scientists, a scientific strategic plan and a mechanism for continuously updating that plan. The Enterprise is an alliance of funders who have agreed to align their HIV vaccine activities against this public, highly debated, and evolving global strategic plan. Enterprise success will rest on at least three principles:

1. We must clearly formulate the questions that must be answered, the tools and technologies that must be created, and the resources and structures that are needed to fulfill this scientific plan.
2. The responsibility of research funders is to ensure that there is adequate funding to provide a definitive answer to those questions and to create the technical tools and data sets needed.
3. Participating scientists must agree to share data, focus on the priorities laid out in the shared plan, and set clear experimental standards that will provide us all with a scientific basis to measure progress toward an effective vaccine.

The Enterprise principles can be summed up with the following warning: no technical advance occurs without tools of measurement that are robust, relevant, reliable, and universally available.

Yet in trying to develop an HIV vaccine, we have uncovered none but the most rudimentary ways to measure the human immune response. Because there has been no work in developing new technologies for isolating antibodies, and no available mechanisms to bring together immunologists, structural biologists, and synthetic chemists, we have virtually abandoned the development of neutralizing antibodies. The Enterprise will change that, creating a global Human Immune Response Measurement Network that will replace the nearly random empiricism of current vaccine trials with a set of scientific guideposts designed to objectively direct real progress as we move from generation to generation of vaccine candidates. This will lead both to a new way of cooperating toward a common goal while maintaining the essential competition of ideas that compels scientific progress. Such a network will also provide the resources to create a mechanism for holding ourselves accountable to a shared, global, and transparent plan—a plan that is alive and changes with new knowledge, tools, and ideas.

(GAVI) and the Vaccine Fund

Another area in dire need of spectacular advances in health technologies is in child immunization. Until we are able to immunize every child in the world with

vaccines of proven effectiveness, we will continue to lose over two million children per year, virtually all in the developing world.

New vaccines take twenty or more years after their introduction in the industrialized world to begin to be adopted systematically in the developing world. In the year 2000 a new global partnership called The Global Alliance for Vaccines and Immunizations (GAVI) was created to address this time lag. GAVI was coupled to a free-standing purchase fund called the Vaccine Fund, and was launched with a $750 million grant from the Gates Foundation. The goal of the partnership is to close the immunization gap between rich and poor by bringing order, reliability, accountability, and clear technical paths to the manufacturing, financing, and delivery of vaccines to the 75 poorest countries of the world.

In 2000, approximately one-third of all children in these countries did not receive even the most basic recommended immunizations. Newer vaccines—such as hepB, Hib, pneumococcus, and yellow fever—were unavailable to virtually all of these children.

In the five short years since GAVI, nine million additional children have been immunized with basic vaccines, 42 million with hepB, six million with Hib, and over three million with yellow fever—with an estimated 500,000 lives saved.

To make immunization safer through new technologies, almost half a billion auto-disable syringes have been used, preventing over 600,000 infections from hepatitis B alone.

By making both product demand and the supply market predictable and creating a new way of doing business in the public sector, within five years we have gone from having only a single manufacturer of DTP-hepB combination vaccines to the current total of ten. This change has occurred alongside both a huge increase in demand and a twenty-percent drop in price.

The public sector can neither shun nor replace the private sector but must creatively engage it in order to harness the power of markets where markets have failed.

Global Health and the Asia-Pacific

So why bring the challenges of global health to the Pacific Health Summit? For the first time in human history, there exists a convergence of three forces: 1) science and technology can, without a doubt, create the solutions to the major health problems facing all Pacific Rim countries; 2) there is no longer an acceptable or defensible moral ground from which to argue that the basic opportunity for a healthy life is not a right shared by every human being; and 3) the world, as a whole, has the resources to achieve this universal health imperative. It takes no great judge of history to see, feel, and experience the achievements and, even more, the potential of the countries in the Asia-Pacific to contribute to the three major innovations that I outlined at the beginning as being so crucial for the improvement of global health.

In the health industry, those who will successfully compete will be those who learn to create products whose efficacy is not merely incremental, whose toxicity is minimal, whose cost and ease of delivery can access the truly global market, and whose cost-effectiveness will actually define the competitiveness of these products.

Finally, I would like to end with the prospect that, just as million dollar computing machines of the 1950s gave way to the ubiquitous microchip, the industry will one day be able to create products that will be accessible to every man, woman, and child on the planet, and will develop new products and technologies with applications unimaginable today.

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