Interview

An evolving career in personalized medicine: an interview with Dr Paul Billings

Paul Billings speaks to Tarryn Greenberg, Managing Commissioning Editor

Paul Billings

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Board certified internist and clinical geneticist Dr Paul R Billings serves as Chief Medical Officer of Life Technologies Corporation, a new position aimed at improving patient care through expanding the use of medically relevant genomic technologies in clinical settings. Dr Billings brings extensive expertise and healthcare experience in the areas of genomics and molecular medicine. Most recently, he served as Director and Chief Scientific Officer of the Genomic Medicine Institute at El Camino Hospital (CA, USA), the largest community hospital in the Silicon Valley. He was a member of the US Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society. He currently serves on the Scientific Advisory Board of the US FDA, the Genomic Medicine Advisory Committee at the Department of Veterans Affairs and the IOM Roundtable on Genomics. Dr Billings has had a distinguished career as a physician and researcher. He has been a founder or chief executive officer of companies involved in genetic and diagnostic medicine, including GeneSage, Omicia and CELLective Dx Corporation. Previously, he was Senior Vice President for corporate development at Laboratory Corporation of America Holdings (LabCorp). He has held academic appointments at some of the most prestigious universities in the USA, including Harvard Medical School, UC San Francisco (CA, USA), Stanford University School of Medicine (CA, USA) and UC Berkeley (CA, USA), and has served as a physician at a number of prominent medical centers. He is the author of nearly 200 publications and books on experimental and clinical medicine. His work on genetic discrimination was instrumental in the creation and passage of the federal Genetic Information Non-Discrimination Act of 2008. Dr Billings holds an MD from Harvard Medical School (MA, USA) and a PhD in immunology, also from Harvard University. Dr Billings is a long time Board Member and has previously served as Board Chair, of the Council for Responsible Genetics.

■ You obtained your MD & PhD in immunology from Harvard University (MA, USA), what led to your interest in genomic medicine?

The first thing to say is that I am the son of World War II refugees. There was always a sense in my house of the special nature of groups that were sometimes defined by ethnicity or genetics; these groups can experience discrimination or be terrorized. If you look at the history of genetics, its the leaders during the 20th century in the USA often had a personal story in their family as to why they were particularly interested in the field. For instance, Victor McKusick who was one of the great fathers of modern human genetics and created the great catalogue, Mendelian Inheritance in Man, was an identical twin, and several of the other leaders were political refugees or had discriminatory experiences. I think this type of experience played an important role in driving my interest in genetics.

My PhD project was on the genetic control of the immune response, and so I left Harvard with an interest in the genetic approach to problems. My thesis advisor was Baruj Benacerraf, who was later a Nobel Lauriate. Very early on in my internal medicine training in Seattle (WA, USA), I came across Arno Motulsky, who was a leader of human genetics in the 20th century in the USA. Arno was a wonderful character; he was an extremely good doctor (smart, good bedside manner and up to date on medical literature), but he also thought about things in human genetic terms. For example, during the Korean

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War, he noticed that some of the troops in Korea would take antibiotics when on leave because they were engaging in sexual practices that might result in a requirement for infection control. Some of the soldiers would become severely anemic when they took sulfur drugs as part of their leave routine. That was the seminal observation that Arno, who was the clinician who took care of those with a severe form of hemolytic anemia, made. As a result, he discovered G6PD deficiency, which in this case was an X-linked genetic disorder. It was not uncommon in American soldiers, although it occurred in other groups and nationalities as well, and he helped to describe that by being an observant clinician. When I met him during the 1980s, that is how I found him to be – he was a brilliant geneticist and also a very observant clinician, and that informed his work. So I had strong early influences from a Nobel Lauriate, during a doctoral project on T-cell genetics and then almost immediately in my clinical training, a really wonderful collaboration with a gifted geneticist and internist. This is what really led to my interest in genomic medicine.

■ **Are there any individuals in particular you have worked with who have had an impact on the path that your career has taken?**

There are three characters who really influenced my career. The first is Hans Popper, who was my uncle. Hans was a great hepatologist. He was the man who described the liver pathology associated with hepatitis, and was the President of Mount Sinai Medical School (NY, USA), a member of the National Academy, a gifted pathologist, physician and a very prolific researcher. He really gave me a respect for science, for the processes of science; this really set the tone for my sense that pathologists were ultimately the 'diagnostician'. While internists and treating physicians managed the care and the treatment of patients, pathologists were integral to the scientific diagnosis of disease and how important a proper diagnosis was. And he was also very much about subdividing disease into increasingly well-described subsets. That is the ultimate trend of genomics at this point, to accurately define, from the bottom up, biologically unique subsets of patients with distinct phenotypes as well as unique treatment approaches based on biological insight.

Second, was Baruj Benacerraf, who unfortunately passed away in August 2011. He was the Chairman of Pathology at Harvard for many years, the President of Dana Faber Cancer Institute (MA, USA), a Nobel Laureate in 1980, and he was my thesis advisor. Baruj was adamant in respecting scientific inquiry and research, and also for the participation of pathologists in the basic activities of medicine.

Finally, as I mentioned before, Arno Motulsky who bridged genetics and medicine for me. He really taught me the difference between clinical and basic research.

Those were the three pivotal characters of my professional life.

■ **You are currently the chief medical officer at Life Technologies (CA, USA). Can you briefly describe the personalized healthcare initiatives that are currently being investigated?**

I would describe our efforts in personalized medicine as threefold.

First, we are the champion of the highest-quality technology, particularly in nucleic acid analysis. With our next-generation gene sequencing, such as the Ion Torrent methods, and our next generation in PCR technologies, we are driving the quality of nucleic acid analysis as well as increasing the productivity of those analyses enormously. For example, the output of our Personal Genome Machine has increased over the course of 1 year by a factor of 100. So there has been a significant increase in our ability to analyze nucleic acids. That kind of rate of improvement will open up vistas for personalized medicine that have never been available before.

The second initiative in personalized medicine is that we are trying to integrate the data output that is coming off the nucleic acid analyzers with other medical analysis, other comparative genomic medicine information, and to create knowledge solutions. We want to use powerful new technologies, but also capitalize on databasing and the ability to integrate it all in an informatics platform.

The final thing we are doing as a component of personalized medicine is

integrating that whole knowledge and solution flow into the pathology world. In my view, the pathologist is the great diagnostician in medicine; when you have, for example, a cancer and want to know what type it is exactly, you ask the pathologist. And that is what we are hoping will happen in all of personalized medicine – we will gather data, run computer support, provide the result to a knowledgeable pathologist, and then out will come a description of the basic biology of the person, along with insights on treatments that might be available.

■ **What research projects are you currently involved with & can you briefly discuss them?**

Life Technologies has supported a project with the Translational Genomics Institute (TGen; AZ, USA), and we are just completing a study of whole-genome sequencing on 14 women with triple-negative breast cancer – breast cancer that is advanced and lacks the estrogen receptor, the progesterone receptor and has no Her2/Neu amplification. And these women, who are disproportionately African–American, have an unusually aggressive form of breast cancer, which has been relatively resistant to successful treatment in the past. In collaboration with our colleagues in Arizona (US Oncology is a partner on that project as well) we have sequenced 14 women with triple-negative disease; we have looked at their genome and their transcriptome, and we have analyzed normal tissue and tissue from the tumors. Although the study has not finished evaluating the data yet, I think we have made some very significant observations about, not only the biology of the tumors of those individuals, but have improved lives through research and provided new hope for virtually all of those people participating. We have learned a lot about the provision of whole-genome analysis in clinical situations, and so this is an important research project which has been going on for approximately 2 years. US Oncology has been a great collaborator on this work.

A second project is one we have initiated with the University of Oxford (Oxford, UK), which also involves Cancer Research UK and public entities in the UK. It is a study which will develop a panel of sequence-based genomic tests that will be applied across England to see whether the sequencing analysis of certain drug-related and cancer-related genes improves the care and lowers the cost of the treatment of cancer patients. So we are very excited about this project.

Internally, we have a whole series of new initiatives. These range from improving the isolation of DNA and its preparation for sequencing, creating new informatic tools for the analysis of data coming off of our high-throughput sequencers, or new confirmatory tests that would be ordered once an initial mutation in the genomic material was identified (likely utilizing sensitive PCR-based technology or our capillary electrophoresis sequencing methods). These are all internal projects which are currently underway.

■ **One of the goals at Life Technologies is to implement next-generation sequencing into the clinic, how do you think this can be achieved successfully?**

The first step in my view is what I have mentioned previously; turning the high volumes of data that are coming off these high-throughput machines into understandable solutions and information which can be used by a pathologist or treating physicians. The first step, I think, is really that we need to apply these tools in clinical research centers, generate data and collate and integrate that data into the practice of medicine.

Second, in my view, is that we have to understand how we are going to value that information; traditionally diagnostics have been relatively undervalued, not so much their content or in a philosophical sense, but in 'economic terms'. If you look at how much money is spent on diagnostics compared with therapeutics, the difference is staggering. If you look at the US healthcare budget, and that is approximately US$2–3 trillion on an annual basis, approximately 3–4% of that is spent on diagnostics, while therapeutics is somewhere between 10–20%, and hospitalizations represent 40% or more. So relatively speaking, diagnostics have been inexpensive and not a large component of spending. We have to understand how improvements in technology lead to changes in diagnostics

and better quality information being delivered to healthcare providers. As that data provides pathways for better care of patients, the test result becomes more crucial, valuable and should capture more of the healthcare dollar because of that. This investment return pays for more innovation. Since we are in an era where there is no or very little new spending but rather shifting of dollars, we have to rationalize the reimbursement for diagnostics, value diagnostics in a greater way than in the past. Find ways of saving dollars in other parts of medicine or healthcare, and delivering it back to diagnostics innovators. There is significant innovation and potential value in better diagnostics. There was little investment and study of it in the past. We really now are in a 'golden era' of diagnostic medicine and we need to capitalize on that important opportunity.

The final area we need to evolve is regulation. The models for doing clinical research or getting products and services, but mostly products, through regulatory approval and rapidly commercialized or available worldwide, are archaic in my view. They require modification. This was actually mentioned in an October 2011 Op-Ed in the *New York Times* published just before this interview. There are many discussions at various levels of professional societies, academic circles and national panels about modifying clinical trials and the US FDA regulatory oversight process, in ways that protect efficacy and safety, but also speed innovation and validation. And of course medically needy people exist all over the world in different cultures and socioeconomic strata, so there are many challenges.

I am often struck that medicine is fundamentally a conservative activity, which draws very much from the old Latin dogma of '*primum non nocere*' – first, do no harm. That has been a valuable tenant of medicine for the centuries since Hippocrates and the early physicians. But we are entering an era when we have better basic information and where the translating of this data into plausible medical advances takes less time. We are used to caring for patients in really, I think, inadequate, uninformed ways. We need to allow new knowledge to rapidly inform patient care. Not all that knowledge will turn out to be fundamentally important or lead to changes in patient care. But some of it will and we do not want to delay that; patient need has to be dominant in personalized medicine.

■ **What, in your opinion, are some of the major challenges that have prevented the translation of genomics into personalized healthcare?**

The most important challenges are first, the cost. The cost of molecular diagnostics and the basic methods of genomic medicine used to be very high, and the quality of the information was variable. That has been rapidly resolved by the methodologies and progress demonstarted by Ion Torrent. We are seeing unprecedented increases in productivity and the quality of information. Because of that, the cost of generating information is dropping dramatically.

The second challenge is an absence of evidence of the utility of this data and its economic impact. As I have said, this is extremely important to have; it is the basis by which the data will be integrated into the flow of medical information. We need to set reasonable standards for translation and the rapid application of new data generating methods for needy patients. Research must flourish.

The third challenge is the education base of physicians and the public concerning genomics. We have rather poor public education about what DNA is, and what genetics can or cannot explain in the world. Physicians have virtually no training about clinical genomics or its fundamental insights. We need better physician education; both of frontline physicians who are ordering the tests and treating the patients, as well as the pathologists and the other providers that are developing and interpreting that information.

So, cost, evidence and education are big barriers to implementing personalized medicine.

■ **Where do you think personalized medicine will be in the next 5 years?**

I think we are very much in a transition period between phenotypic, empiric medicine and a fundamental, personalized and genomically empowered medicine. I think in 5 years there will have been substantial

progress in that transition; we will see all sorts of applications: in the care of patients with cancer, redefining the cancers on a genomic basis as opposed to on a histopathology basis; a redefinition of many childhood syndromes that are currently either unknown or undiagnosed, and insights into the origins of those syndromes will come about; new approaches to prenatal diagnosis and the care of pregnancies that are affected with aberrant or congenitally affected fetuses; dramatic insights into the genetic basis of aging and late onset conditions, for example. All of that will be in transition over the next 5–10 years. Translational research will be needed to cull new fundamental data and define its clinical application. Finally there will be demonstrations of the fundamental important economic impacts that diagnostic innovation provides, and a shifting to increasing value placed on accurate and fundamental diagnostics, and better monitoring tools using molecular methods.

I think there will be applications that I just can not even imagine. We will be able to sequence and analyze your whole genome for a few hundred dollars in less than a day soon. That kind of powerful development opens up basic and translational research as well as clinical care, and new ways of people relating to each other in a socially networked world, in unimaginable ways. I recently wrote a blog for employees of Life Technologies in which I said what an incredible, exciting ride we are about to go on. But we need to buckle up – it is going to be fast! There will be some bumps in the road, but it is going to be a wonderful new world for people fighting illness or trying to prevent suffering.

Financial & competing interests disclosure

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