

Health Analytics, Economics and Medicine toward a 21st Century Health Care System

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Abstract

After a review of recent developments in precision medicine, population health sciences and innovative clinical trial designs, and in health economics and policy, we show how innovations in health analytics can capitalize on the advances in biomedicine and health economics towards developing a data-driven and cost-effective 21st century health care system. In particular, we propose a mutually beneficial public-private partnership that combines individual responsibility with community solidarity in building this health care system.

Keywords

Analytics, Big Data, Comparative Effectiveness Research, Health Insurance, Moral Hazards, Population Health Sciences

1. Introduction

We began by indicating that the second part of the title was inspired by [1], in which two Nobel laureates in economics, Kenneth Arrow and Daniel McFadden, coauthored with other economists, public health scientists, physicians, hospital administrators, and domain experts from industry and government to delineate in 2009 essential foundations for successful reform of the US health care system. A year later, landmark health care legislation was passed through two federal statutes: the Patient Protection and Affordable Care Act and subsequently amended by the Health Care and Education Reconciliation Act, and had offered new challenges and great opportunities for the three fields in the title. Health economics has become one of the major research areas in eco-

nomics in many economics departments. While the seminal economic principles and models of Arrow [2] and Grossman [3] have laid the foundations of this subfield of economics, we show herein that time is ripe for this subfield to branch out and collaborates with other fields in developing the 21st century health care system envisioned in [1]. Such collaboration is already evident from the multiple authors of [1] with expertise in diverse fields. We also show that this outreach has the benefit of bringing in new insights and techniques to address the constraints and complexities of the problems and challenges in health economics.

This paper is organized as follows. In Section 2, we describe several recent developments in population health sciences, health services and biomedical research and education. Section 3 reviews some concurrent developments in health economics and ongoing politico-economic debates about health care reform. While these two sections touch on the second and third fields “economics” and “medicine” in the title, Section 4 describes recent developments in health analytics, the first field in the title. Section 5 discusses the important role it is envisioned to play in advancing the other two fields and in building a 21st century health care system, not only in the US but also globally, and also gives some concluding remarks.

2. New Trends in Translational Medicine, Population Health Sciences, and Health Services and Education

It is widely recognized that whereas the 20th century was the century of chemistry and physics, the 21st century would very likely go down in history as the century of biomedicine, which already entered a golden age in the last 50 years; see [4]. Quoting John Lechleiter, CEO of Eli Lilly & Co., J. Rago [4] says that for most of the pharmaceutical industry’s existence “since the Civil War veteran Col. Eli Lilly began to improve on the patent medicines of the day,” the science was not mature enough for exploitation, leaving one with the feeling “around a dark room”, but that “suddenly the lights are on” and one could understand “in a cell, this pathway and that pathway both contribute to, say, tumor formation”. The article comments that Lechleiter’s optimism that the pharmaceutical industry is “gaining the sorts of productivity that hoped for or predicted based on this explosion of knowledge”, however, “runs against the growing laments that new drug development has stalled and progress against disease is slowing down”, and “certainly runs against markets, where the pharma’s P/E ratios—which anticipate profits growth—are historically low and trail most other consumer businesses”. We will elaborate on the economic aspects and changing landscape of drug development in the next section.

This section focuses on the biomedical advances in the golden age and how they will realize their potential in breakthrough treatments in the 21st century under the framework of translational medicine and population health sciences. Besides the development of new treatments capitalizing on the breakthroughs in biomedicine, it also considers comparison of existing treatments in comparative effectiveness research that was mandated by the health care reform legislation. Patient-centered outcomes research that the legislation also touches upon is described under the emerging subfield of population health sciences. In addition, new trends in health services such as the polyclinics and medical education that will be important building blocks in the 21st century health care system will also be discussed.

2.1. Translational Medicine

Translational medicine is a rapidly growing discipline in biomedical research and aims to expedite the discovery of new treatments and diagnostic by using a multi-disciplinary, highly collaborative, “bench-to-bedside” approach. “Bench” refers to laboratory experiments to study new biochemical principles and discover novel treatments. The experiments with promising results are followed by pre-clinical animal studies. After understanding the effect of the treatment on animals (e.g. rodents), the next stage of drug development consists of clinical trials involving human subjects, starting with Phase I studies to determine a safe dose or dosage regimen and/or to collect information on the pharmacokinetics and pharmacodynamics of the drug. Phase II trials are precursors of Phase III trials. Their goal is to demonstrate the effectiveness of the drug for its approval by the regulatory agency (FDA in the US and EMA in the European Union) and to provide adequate evidence for its labeling. The evidence of effectiveness culminates in the regulatory approval of the new drug that can be used at the “bedside”, that is, to treat patients. Phase III trials also collect safety information from the relatively large samples of patients accrued to the trial. Safety of the drug is evaluated from data obtained from all three phases of clinical trials prior to marketing approval of the drug, and continues to be evaluated through post-marketing Phase IV trials. Despite the sequential nature of Phase I-III trials, trials are often planned separately, treating each trial as an in-

dependent study whose design depends on results from studies in previous phases. The need for innovative study designs to better integrate the phases is now widely recognized and major advances, particularly in the area of adaptive designs, were made in the past decade; see [5]-[14]. In particular, one of the major hurdles in bringing the new genomic-guided and risk-adapted personalized treatments, which are devised to attack specific targets in individual patients, to the market is the exorbitant cost and time needed to conduct confirmatory Phase III trials using standard randomized clinical trial designs for drug approval in industry. This is the background of the paradox that [4] finds in Eli Lilly CEO's optimism about the bright future of the pharmaceutical industry's pipeline of innovative treatments based on "mature science" and yet diminishing number of drugs successfully passing Phase III trials.

To achieve the potential of the biomedical advances for personalized therapies of cancer and other complex diseases, the first step is to identify and measure the relevant biomarkers. The markers can be individual genes or proteins or gene expression signatures. The next step is to select drugs based on the genetics of the disease in individual patients and biomarkers of drug sensitivity and resistance. The third step is design economically feasible and risk-manageable clinical trials to provide data for the development and verification of personalized therapies. A partnership between the pharmaceutical/biotechnology industry, the regulatory agency, and researchers from academia can make use of the aforementioned and still ongoing advances in adaptive design [13] to break the innovation bottleneck and resolve a long-standing problem in translational medicine.

2.2. Comparative Effectiveness Research and Population Health Sciences

One of the provisions of the Patient Protection and Affordable Care Act is the establishment of a non-profit Patient-Centered Outcome Research Institute (PCORI). The role of PCORI includes: (1) to undertake comparative effectiveness research (CER) in examining the relative health outcomes, clinical effectiveness, and appropriateness of different medical treatments; and (2) to provide funding for selected pragmatic clinical trials or large sample representative patient populations for CER. Observational studies are often used to provide data for CER. For example, Stukel *et al.* [15] describes statistical analysis of medical and surgical treatments for acute cardiovascular disease. The key problem with observational approaches, however, involves confounding by indication—the tendency for freely choosing clinicians and patients to choose treatments with their anticipated effects in mind [16]. Randomized trials can remove such confounding.

About 50 years ago, Schwartz and Lelloch [17] distinguished "pragmatic trials" (of the type that PCORI would fund) from "explanatory trials" (exemplified by Phase I, II, III trials in the development of a new drug). A pragmatic trial should be conducted under "real world" conditions, in which blinding of treatment assignment is not required; hence it is also called a "naturalistic trial". A landmark example is the Antihypertensive Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT), which was a randomized, double-blind, multi-center clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) [18]. It recruited more than 42,000 patients from 623 primary care clinics and its aim was to determine if the combined incidence of fatal coronary heart disease and non-fatal myocardial infarction differs between diuretic (chlorthalidone) treatment and each of three alternative antihypertensive pharmacologic treatments: a calcium antagonist (amlodipine), and ACE inhibitor (lisinopril), and an alpha adrenergic blocker (doxazosin). A lipid-lowering subtrial ($\geq 10,000$ patients) was designed to determine whether lowering cholesterol with an HMG Co-A reductase inhibitor (pravastatin), in comparison with usual care, reduced mortality in a moderately hypercholesterolemic subset of participants. ALLHAT, which cost over \$1 million, was the largest antihypertensive trial ever conducted, and the second largest lipid-lowering trial. It recruited many patients over age 65, women, African-Americans and patients with diabetes. The study was conducted between 1994 and 2002 largely in community practice settings. In ALLHAT, hypertensive patients were randomly assigned to receive one of four drugs in a double-blind design, and a limited choice of second-step agents were provided for patients not controlled on first-line medication. Patients were followed every three months for the first year and every four months thereafter for an average of six years of follow-up. Although it was anticipated that the results of this pragmatic trial, showing chlorthalidone to be superior in preventing one or more forms of cardiovascular disease and no worse in preventing heart attack, would translate into clinical practice [19], the actual impact judged six years later was disappointing, due to difficulties in persuading doctors to change, scientific disagreement about the interpretation of the results, and heavy marketing by the pharmaceutical companies of their own drugs [20].

To avoid the pitfalls with ALLHAT and other traditional designs of comparative effective research (CER) studies, Lai and Lavori [9] propose a point-of-care (POC) approach that embeds a clinical trial at the point of

care where patients are treated. An embedded clinical trial with outcome-adaptive randomization can bring the benefits of automatic, statistically valid learning to the participating health care systems, and improve care without having to mount a separate implementation strategy. Such automatic learning may be crucial to taking full advantage of CER. The US Department of Veteran's Affairs is capitalizing on its superior informatics to launch an effort directed at fostering embedded clinical trials, in which the option to randomize is offered as part of the automated system of guidelines and computer-aided ordering of treatments [21]. A recent enhancement of the POC design in [21] was proposed by Shih, Turakhia and Lai [22] that uses a stage-wise design to accommodate the budget constraints of these comparative effectiveness trials at the VA. The stage-wise design functions as a group sequential design with adaptive randomization insofar as the entire trial and its overarching objectives are concerned, but also separates itself into stages with their own specific questions that can be addressed at the end of a stage. Each stage can therefore also receive additional funding from other agencies that are interested in the stage's specific questions.

Population health is a relatively new subfield of Medicine, and has gained prominence because of the urgent need to reform health care not only in the US but also in many other countries, especially due to changing economies and demographics. The field is highly interdisciplinary and encompasses not only epidemiology and statistics, but also engineering, information technology, and biomedical sciences. Indeed, population health sciences involve Web-based observational data, point-of-care comparative effectiveness trials, adaptive randomization, mobile health and personalized care, as pointed out by Mark Cullen (<http://med.stanford.edu/phs.html>):

Population Health Sciences refers to the analysis of data derived from any large population—defined by geography or membership in some large group—to three ends: better *care of individuals*; enhanced decision-making for *public interventions for health*; and *discovery of underlying causes of health and disease in a population*. In this way, PHS helps to bring lab discoveries to the bedside and public, while at the same time aiming to *explain* patterns of health and disease observed in the population... Population health is the study of health outcomes, patterns of health determinants and disease states in populations. Looking at social, environmental, cultural and physical factors, the term “population” looks beyond geographic boundaries, encompassing a variety of subsets such as “people with jobs” or “patients served by a specific medical care system”.... Rising health care costs, increasing prevalence of chronic disease, persistent health care disparities, and an aging population underlie the urgent need for partnerships between academic medical centers and all sectors of the community to address personal and population health imperatives.

To summarize, this new subfield of medicine brings together physicians and scientists “from across the university and its medical institutions to leverage population-level evidence to revolutionize care at the bedside and to improve the overall health of society”. It aims not only at better care for the sick and better treatments of diseases, which translational medicine focuses on, but also at improved preventive maintenance for the healthy and better health outcomes for society. The latter also involves syndromic surveillance, environmental monitoring and methodological innovations in epidemiology.

2.3. Innovations in Health Services, Medical and Health Education

With the rising costs of medical care on the one hand and the fast pace of technological and operations management advances on the other hand, the past decade witnessed many public and private efforts to innovate hospital and clinics. Start-up companies and major hospitals have been involved in these efforts. For example, New York-based non-profit NXT Health teamed up with Clemson University's Healthcare and Architecture Graduate Project on a US Department of Defense (DOD)-funded project “Patient Room 2020” (<http://nxthealth.org/patient-room-2020/>) to enhance patients' experience and improve doctors' workflow. A related healthcare issue is patient flow in hospitals, which plays an important role on the quality of care and patients' satisfaction. In particular, the overcrowding and prolonged waiting time in the Emergency Departments may compromise the quality of care and put patients at greater risks in morbidity and mortality. Novel methodologies in addressing the patient flow scheduling problem have been developed in this area of active research [23]-[25].

In countries including France, Germany, Russia, and Singapore, innovations that combine the function of a hospital outpatient department with a general-practitioner health center have been implemented via polyclinics

to deliver more accessible integrated health care services. These outpatient clinics may be a model that can provide 21st-century care in a more economic and efficient way than hospitals for management of chronic conditions. Establishing polyclinics to reshape national health services has also been proposed. A related proposal is to use polyclinics to provide the much needed integration between general practice, community, and secondary care services, which could in turn lead to more cost-effective, accessible, and better coordinated care [26]-[28]. In particular, the model of polyclinics in Singapore has evolved to efficiently provide a comprehensive range of services to screen, prevent, and manage the range of medical conditions of epidemiological importance to the Singapore population [29]. In 2010, there were 18 polyclinics in the country, serving 20% of primary healthcare; these clinics are managed by two healthcare networks that were formed in 2000. The innovations in health services, coupled with the advances in information technology, and hospital and clinic operations management, also pave the way for innovative initiatives and ideas in medical education. A qualitative study to evaluate the reactions of medical students at the National University of Singapore to a mobile application employed to learn about healthcare services within the polyclinic illustrates such an opportunity [29].

3. Health Care Financing, Spending, Policy and Other Economic Issues

In this section, we continue with the economic issues raised by the biomedical advances mentioned in the first paragraph of Section 2. The following trend was noted by Rago [4]:

Over the last decade, most of the (pharmaceutical) industry has been slashing research and development in favor of meagdeals; many of the blockbusters coming off-patent were created by companies that no longer exist.... Fewer companies means fewer R & D departments, fewer scientists looking at the same problem from different angles, fewer teams capable of making the investments needed to run the regulatory gauntlet to get an idea into the pharmacy.

There is also worry from the pharmaceutical industry about global price controls that may stifle the innovation ecosystem. Thus, innovations in the pharmaceutical industry and the broader health care sector using the advances reviewed in the preceding section would face economic headwinds in the absence of contemporaneous innovations in health economics and policies. We therefore focus in this section on new possibilities and principles to address these economic challenges.

3.1. Health Care Spending and Financing

According to Reid [30], there are four major forms of international healthcare financing-spending systems.

- *The Bismarck model*, introduced by Otto von Bismarck in the unification of Germany as a welfare state in the 19th-century and modified since then by different countries adopting it (including Germany, France, Belgium, the Netherlands and Japan), uses private insurance to provide health care to all citizens without any conditions. The insurance companies operate as non-profits managing “social insurance” or “sickness funds”. Doctors and hospitals can also be private in these countries. All citizens are required to sign up for one of these health insurance plans. Although this is a multi-player system, tight regulation gives the government much clout in setting prices.
- *The Beveridge model*, named after the British economist William Beveridge whose report on Social Insurance and Allied Services to the British Parliament in 1942 was implemented by the post-war government led by the Labour Party, is a single-payer system, with the government providing health care to all citizens and using tax payments to finance it (just like the police force or public education) in the countries adopting it (including the United Kingdom, Spain, most of Scandinavia, New Zealand, Cuba and Hong Kong as a Special Administrative Region of People’s Republic of China). Most hospitals and clinics are owned by the government. Many doctors are government employees, but there are also private doctors who can collect fees from the government. Because the government, as the sole payer, controls what private doctors and pharmaceutical companies can do and charge, these countries tend to have low health care costs per capita, but rising costs have put the single-payer system under pressure.
- *The National Health Insurance (NHI) model* has elements of both the Bismarck and Beveridge models. It uses private-sector providers, but payment comes from a government-run insurance program that every citizen contributes to through income tax. It has been adopted by Canada since its Health Act of 1984. The insurance program does not cover prescription drugs, home care or long-term care, vision or dental care, which

means that citizens have to pay out-of-pocket for these services or rely on private insurance. Private health expenditure amounts to about 30% of health care financing. In each province, each doctor handles insurance claims against the provincial insurer, namely the provincially based Medicare. Since there is no need for marketing and no financial motive to deny claims, these non-profit universal insurance programs tend to be cheaper and much simpler administratively than the for-profit health insurance programs in the United States. Since Canada's single-payer system has considerable market power to negotiate lower prices from health providers and drug companies, many Americans south of the border have substituted their own pharmacies by those in Canada. The NHI system, founded in Canada, is also adopted by other countries, including Australia, Taiwan, and South Korea.

- *The Out-of-Pocket* model is for the individual users pay for the medical/health services and products they receive out of their savings ("pockets"). Only the developed, industrial countries (about 40 of the world's 196 countries) have established health care systems. Countries without these systems adopt the out-of-pocket model by default.

The United States essentially maintains different systems for different classes of people—the Beveridge system for veterans, the Bismarck system for those whose employers provide health insurance, the NHI for Americans over the age of 65 or Medicare, and the out-of-pocket system for about 16% of the population without health insurance prior to the health care reform legislation in 2010. It is a global leader in medical innovation, having solely developed or contributed significantly to 9 of the top 10 most important medical innovations since 1975 as ranked by a 2001 poll of physicians. According to WHO, the US spent more on health care, both per capita as a percentage of its GDP (17.2%), than any other nation in 2011, and yet lagged behind other industrialized nations in such measures as infant mortality and life expectancy. An analysis by Kelley *et al.* [31] using a nationally representative Health and Retirement Study cohort found that despite Medicare coverage, about 25% of the senior citizens' out-of-pocket healthcare expenses exceeded baseline total household assets in the last 5 years of life. After the enactment of the Patient Protection and Affordable Care Act (PPACA) in 2010, the US has been undergoing changes in the uninsured rate, insurance coverage and financing, but there has also been ongoing debate about the constitutionality of the law, prescription drug prices, health care quality and equity and other political issues, with increasing polarity along party lines.

Another country that resembles the US, especially after PPACA, is Switzerland which combines public, subsidized private and totally private sectors in providing universal healthcare to all people residing in the country, within three months of taking up residence or being born in the country. Health insurance is compulsory for the residents, with exemption of international civil servants, members of embassies, and their family members. Insurers are required to offer basic health insurance, which provides for treatment in case of illness or accident and pregnancy, regardless of age or medical condition, and are not allowed to make a profit from this basic insurance, but can make profits from supplemental plans. The insured person pays the insurance premium for the basic plan up to 8% of the person's income, but also pays for the supplemental plans. It is pointed out in [32] that "patients in the Swiss system incur substantial out-of-pocket costs: one third of health care spending comes from copayments, deductible, and other private payments", but "consumers can choose among various models—the standard model or any of several managed-care models, which limit access to specialists in exchange for lower premiums". Moreover, [32] also notes that "over the years, the Swiss health care system has been mentioned by commentators as a potential model for the US" because its performance among the best of OECD (Organization for Economic Cooperation and Development) countries, with high levels of patient satisfaction and one of the highest life expectancies. In addition, "competition among health care providers and payers has an important place in the design of the Swiss health care system" and is "supposed to guarantee high quality as well as efficient and cost-effective service delivery". Because Switzerland's governance involves direct political participation, any changes in health care policy may be subject to popular vote, and therefore "policymaking is usually pragmatic and consensus-oriented to avoid further delay in processes". The central government's role is "to issue federal health legislation, regulate the health insurance market, define the package of health care services covered", and overall the private health care sector "is seen as a flourishing, important, innovative industry and a strong motor for economic growth and prosperity". This is evidenced by Basel being the headquarter of Novartis and Hoffman-La Roche, the second and third largest pharmaceutical companies in the world, and Switzerland being the home country of Merck Soreno, Janssen-Cilag and many companies in the biotechnology and medical devices and technology.

We next consider Singapore, which is often referred to as the "Switzerland of Asia" because of similarities in

their economies and their geopolitical characteristic of being a small country surrounded by large, powerful nations. According to WHO, Singapore ranks sixth in the world's healthcare systems [33]. As a city state in just 50 years since its independence in 1965, Singapore has transformed from a low income country to one of the highest per capita incomes and health outcomes in the world [34] [35]. A major move soon after it became an independent country was to develop a network of satellite outpatient dispensaries and maternal and child health clinics in order to bring primary care services closer to the people [35]; these outpatient clinics have since been consolidated into modern polyclinics. Community hospitals and private nursing homes provide home nursing and rehabilitative care services [35]. To finance healthcare, the Singapore government placed "the emphasis on individual responsibility supported by an enabling state", adopting the policy that nothing, not even medical services, should be provided free [34]. This principle of copayment is a central feature of Singapore's approach to cost containment. Singapore is "relatively unique amongst governments in its ability to plan for the future" [35]. Over a period of 30 years, it has successfully planned and executed strategies integrating the activities of most government ministries. The government unveiled a National Health Plan in 1983, detailing the planned health care infrastructure for the next 20 years, and announced Medisave, a novel scheme to finance individual health care. Singaporeans make mandatory monthly contributions to their Medisave account, thus building savings for their health care needs. Medisave is a savings and not a risk-pooling scheme [34]. Medishield, a voluntary insurance scheme to cover basic, low-cost catastrophic illness, was introduced in 1990. In addition, since the inception of Medifund in 1993, a state-funded safety-net covering the health costs of those without the means to pay, has given financial assistance to the 99% of those who turned to the fund for assistance. "No Singaporean would be denied the treatment he needs because of lack of funds" [34]. The country's health care system also emphasizes on health promotion and disease prevention. In addition, preventive health strategies are tailored to suit the needs of special groups including children and the workforce. As pointed out in [34], the government favors a largely free market as the most efficient allocator of scarce resources, but also uses incentives to encourage demanding responsibility and discourage supply-side waste as an intervention if needed. Its cost sharing and savings scheme encourages "consumer prudence", and the private services and the granting of greater autonomy to public institutions "reduces state-funded health spending and frees up tax-based resources to meet health promotional and preventive activities that benefit the public good as well as other national priorities".

Finally, we consider China, the most populous country in the world with a population of 1.36 billion in 2014, of whom 46% living in rural areas [36], compared to a population of 1.2 billion, with 80% living in the countryside in 1990 [37]. The remarkable changes in the population distribution in the rural areas and GDP in China have been accompanied by changes in its healthcare system, and by its willingness to undertake a series of experiments [36] to correct its mistakes in a learning healthcare system. Its health system has gone through four phases, as described in [36]:

- 1949-1983: The health system was similar to other communist states in which the government owned and operated all healthcare facilities and employed all healthcare workers. All services were nearly free so there was no health insurance. Community health workers provided basic health services in the rural areas; see [38] for the experiments and changes in this period.
- 1984-2002: The role of the government was reduced in all economic and social sectors, including healthcare and the country converted to a market economy. Although the government continued to own hospitals, it had little control over the behavior of healthcare organizations, which turned into for-profit entities in a mostly unregulated market, with the physicians receiving hefty bonuses for increasing hospital profits. In addition, the vast majority of the population was uninsured since no coverage was provided by the government, and private insurance industry was non-existent. However, the government controlled the pricing of healthcare in which it limited the prices charged for physicians', nurses' and other services, but allowed for more generous prices for drugs and advanced imaging.
- 2003-2008: A modest health insurance scheme covering some hospital expenses for rural residents was introduced. But this hospital focus reflected "limitations in the leadership's understanding of the critical role plays in managing health and disease and controlling the costs of care" [36]. The reforms were insufficient to improve the country's health care problems.
- 2009-present: The government realized that to improve the healthcare system and ensure social stability, major reforms in insurance and the delivery system were necessary. By 2012, a government-subsidized insurance system provided 95% of the population with modest but comprehensive health coverage. A primary care system including an extensive nationwide network of clinics was also created. The leaders also an-

nounced in 2012 that “they would invite private investors to own up to 20% of China’s hospitals by 2015, doubling the preexisting rate”; see [36] which concludes that it is easier to reform health insurance than delivery systems and that primary care plays a vital role in the creation of effective delivery systems, as the lessons learned from China’s evolving health care system.

3.2. Health Insurance Economics, RAND Experiment and Novel Designs

In economic theory, health insurance is often used as an example of a market that suffers from both adverse selection and moral hazard. The insured person may choose to conceal private information such as unhealthy habits and genetic traits that make the insurance contract attractive for that person but unprofitable for the insurer, illustrating adverse selection: When based on private information, one party values the goods or service more highly than the counterparty prior to their contract agreement. Moral hazard occurs when after getting the insurance, the insured person becomes more negligent because the insurance contract will pay for the full cost of damage caused by such negligence. Both selection and moral hazard have been well documented in the context of employer-provided health insurance, and have been used in policy debates and economic analyses of health care programs and in health insurance contract design. Whereas traditional economic analysis tends to treat selection and moral hazard as distinct exogenous phenomena, an important new approach, called *selection on moral hazard*, was recently introduced by Einav *et al.* [39] to include the possibility for individuals to select insurance coverage partly based on their anticipated behavioral (“moral hazard”) response to insurance. Empirical evidence of heterogeneous moral hazard and of selection on moral hazard is also presented [39].

A classic experimental study that has been the data source for much of the academic literature and public policy discussion on how health insurance affects public spending is the RAND Health Insurance Experiment (RAND HIE). Between 1974 and 1981, RAND HIE provided health insurance to 5809 individuals from 2000 households in 6 regions across the US, and randomly assigned the families to health insurance plans with different levels of spending ranging from full coverage to almost no coverage for the first \$1000; see [40]. As pointed out by Aron-Dine, Einav and Finkelstein [41], the study provides valuable insights into how reforms and increased spending in health insurance programs would impact on the health outcomes and medical spending of the insured. Moreover, “more than three decades later, the RAND results are still widely held to be the gold standard of evidence” and “have enormous influence as federal and state policymakers consider potential interventions to reduce public spending on health care” using the estimates obtained by this gold standard. Focusing on RAND HIE’s “two enduring legacies—its estimates of the impact of different health insurance contracts on medical spending”, [41] reexamines the validity of the estimates of treatment effects and the estimate -0.2 of elasticity of medical spending with respect to the out-of-pocket price, which is often used to forecast the spending effects of other insurance contracts. Beginning with a careful analysis of the experimental design of RAND HIE, [41] notes that families were in fact not assigned to plans by simple random assignment, but instead stratified randomization proportions had been used to maximize the sample variation in baseline covariates and to achieve better balance across a set of baseline characteristics than equal randomization. Moreover, the subjects enrolled to the study had to agree to sign over all payments from their previous insurance policy (if any) to the RAND experiment and to file claims through RAND as if it was their insurer. This experimental design could have resulted in selection bias across experimental treatments, and potential non-reporting bias due to differential incentives to report medical spending across different plans. After making adjustments for these potential biases, [41] finds that the RAND experiment still rejects the null hypothesis of no treatment effect (*i.e.*, utilization response) to cost sharing. A further sensitivity analysis shows, however, considerable uncertainty about the magnitude of the treatment effect. In addition, [41] also points out potential pitfalls of extrapolating the price elasticity estimate of -0.2 under the experimental design of RAND HIE to “forecasting out-of-pocket change in cost sharing” in contract design and policy applications.

The RAND experiment has many similarities to the randomized trial ALLHAT described in Section 2.2. As noted by [39], “on cost grounds alone, we are unlikely to see something like the RAND experiment again” as the overall cost, funded by the now-named US Department of Health and Human Services, was roughly \$295 million. While this landmark study “was uniquely ambitious, remarkably sophisticated for its time”, and exemplary in randomized experiments in the social sciences, there are difficulties in applying its results out of sample, as in ALLHAT except for somewhat different reasons. The knowledge-implementation gap has appeared again in randomized experiments on moral hazard effects of health insurance and in other social science experiments.

The novel point-of-care stage-wise trial designs [9] [21] [22] for comparative effectiveness studies described in Section 2.2. have the potential to close this knowledge-implementation gap in these social science experiments on behavioral response to health policies.

“Novel designs” in the title of this section refer not only to study designs of social science experiments but also to contract designs for health insurance contracts discussed in [39] and other insurance contracts. There are similarities of this problem with comparative effectiveness studies whose goal is to find the best treatment (now changed to contract) for a subpopulation defined by certain covariates (biomarkers in Sections 2.1 and 2.2). The heterogeneity among insured individuals, found by Einav *et al.* [39] for moral hazard response to health insurance, also plays an important role in predicting claims and setting premiums for other insurance contracts.

3.3. Health Policy: Cost Control, Job and Product Creation

The high and rising costs of health care and related cost-benefit analysis, cost control and efficiency improvement plans have constituted an active area of health policy research and discourse in the past five years; see e.g. [42]-[51]. There are two important aspects of government spending that have been left out in these health policy research and debates, but time is ripe for them to be considered now. The public has become increasingly aware of taking care of their personal health despite the moral hazard argument that has dominated health care economics; just look at the increasing popularity of organic food, healthy (despite somewhat pricy) meal plans and menus, fitness clubs, etc. The debates about government spending on health care programs have also educated the public about the importance and the available resources for them to stay healthy. The broader scope of health care includes not only medical care when one is sick but also preventive maintenance to stay healthy.

We return to Switzerland, which Section 3.1 has already touched upon, to illustrate this point. The June 2015 Euromonitor Report (<http://www.euromonitor.com>) on health and wellness in Switzerland says:

Health and wellness showed no signs of weakening in 2014. On the contrary it posted an increase in current sale values... Swiss consumers attribute great importance to environmentally-friendly and locally-sourced products, with “Swissness” and regionality playing important roles and implemented accordingly by manufacturers whenever possible. Most consumers associate naturalness, freshness and premium quality with organic packaged food and beverages... Overall health and wellness continues to be led by private label products from retail giants Migros and Coop... Given the strong positions of the two main Swiss retailers, Migros and Coop, the most important distribution channel for health and retail products remained supermarkets in 2014, followed by discounters, with an increasing value share... The fastest growth towards the end of the review period was achieved by internet retailing, which offers a competitive advantage for more specialised products, such as fortified/functional products and products for food intolerance.

Thus, government spending on health care in Switzerland has also created new health and wellness products and new jobs, including internet retailing, making Switzerland not only home to the world’s largest and highly profitable pharmaceutical, biotechnology and medical technology companies (including US-based companies Amgen, Biogen-IDEC, Celgene and Ireland-based Medtronic that have regional headquarters in Switzerland) but also home to the emerging health and wellness industries. An October 7, 2013 article in Huffington Post (www.huffingtonpost.com/2013/10/07) explains “Why Switzerland has some of the Happiest, Healthiest Citizens in the World”:

- They have excellent health care.
- Their people are not only healthy, but happy.
- They invest in top-notch education.
- They care about talent and education.
- They’ve created an environment where people can thrive.

Another issue that has often been brought up is the apparent lack of improvement in health outcomes due to increased government spending on health care. Cutler, McClellan and Newhouse [52] quote Fuchs’ famous “tale of two states” [53] comparing the 1960’s mortality rates in Nevada and Utah that were similar in income, environment, and the availability of medical care and yet with 40% higher infant mortality rates and similarly higher mortality rates at most ages for males and females in Nevada, leading [53] to attribute health outcome differences to lifestyle rather than subsidized health care and differences. They also cite the RAND HIE results showing little or no effect on the additional medical care available from free care. They point out, however, that in

health insurance, “many interventions for low-probability events may be expensive relative to income” and “consumers may value income extremely highly when sick”. Moreover, “in a dynamic context, the evidence that the marginal value of medical care at a point in time is low does not imply that the average value of medical-technology changes over several decades is low”. To this we want to add that many changes in health outcomes can occur even over one or half a decade; just think of global warming, climate change and the environment, aging and elderly care. Environmental health, which is a subfield of public health (or even the broader subject of population health sciences discussed in Section 2), is also under the government’s purview of health care policy.

3.4. Investment Aspects of Health Care Innovations

As pointed out in the first paragraph of Section 2, we are at the beginning of the biomedical century, but translating the remarkable scientific advances into treatments also incurs exorbitant costs and high financial risks, which many pharmaceutical companies do not want to take. On the other hand, these breakthrough treatments can also generate huge profits if they pass Phase III testing successfully. This poses challenging problems not only for translational medicine concerning economically feasible and efficient clinical trial designs that we have discussed in Section 2.1, but also for financial economics on investment strategies that can cope with the high risks. We list two such problems and opportunities below.

Fagnan, Lo, Stein and other coauthors [54]-[58] have recently proposed the following solution to attract investors to develop these drugs. Their idea is to fund many drugs simultaneously by structuring investment products that would appeal broadly to big investors. By combining a large number of drug-development projects within a single portfolio or a “megafund”, it becomes possible to reduce the investment risk to such an extent that issuing bonds backed by these projects become feasible. One example they suggested was to invest in 150 projects at once. Assuming each project needs \$200 million, a total of \$30 billion would be needed for the investment. Although a vast amount of money is required, they argued that a much lower risk would also result as more “shots on goal” translated into a higher probability of scoring. Assuming a 5% success rate for each project, the probability of at least two successes out of 150 independent trials is 99.59%. Moreover, using as a benchmark the profits made by a blockbuster drug, which typically generates \$2 billion per year for 10 years before its patent expires, they estimate a ballpark net present value of \$12.3 billion for each successful drug. In this light, an amount of \$30 billion investment is not exorbitant with a 99.59% chance of earning \$24.6 billion or more after 10 years. They propose that with these odds, a large part of \$30 billion could be raised by issuing long-term bonds, which would attract more investors than stocks or venture capital. By funding many biomedical projects through a single “megafund” and issuing a variety of securities to pay for it, investors can earn attractive rates of returns on average. Using a “megafund” financing structure, NCATS (National Center for Advancing Translational Sciences) data, and valuation estimates from a panel of industry experts, [55] simulates a hypothetical megafund of 28 projects in which senior and junior debt yielded 5 and 8%, respectively. The simulated expected return to equity was 14.7%; these returns and the likelihood of private-sector funding can be enhanced through third-party funding guarantees from philanthropies, patient advocacy groups, and government agencies.

In view of the aging middle class of many industrialized and newly industrialized countries, a burgeoning asset class for investments is related to elderly care. Elderly care specialists, real estate developers, wealth management firms and investment companies have found niches in this market. Ease of access to, or cost-effective provision of, geriatric care in the retirement communities or assisted living homes for seniors is a challenging business model, especially for countries such as China, which has a very large market with demand outstripping supply and whose government’s current Five Year Plan lists senior care as a high-priority issue. A June 6, 2012 article titled “Is China’s senior care housing industry ready to mature?” (Knowledge @Wharton, which is the online business analysis journal of University of Pennsylvania’s Wharton School) quotes Benjamin Shobert, managing director of Rubicon Strategy Group LLC that specializes in senior care: “The biggest obstacle is that there is no existing proven model [for senior care and senior care housing]. It is simple to say but it is a profound problem”.

4. Health Analytics and Its Role in a Modern Health Care System

In the preceding section on private-sector investment opportunities in health care, we have left out the fast growing health analytics industry because we want to discuss it here in connection with health analytics. Since

health analytics is a voluminous and evolving topic, we need to be brief and selective here, with our selections based on how they relate to the challenges and opportunities discussed in Sections 2 and 3, and in particular, the role that health analytics can play in building a technology-aided, data-driven and cost-effective system which in turn opens up innovative products, employment opportunities and training programs in the technology sector. As pointed out by Morris, VP of the health analytics Archimedes Inc., the quality of health care has stagnated while costs skyrocketed, fueled by a reimbursement system that is based on volume rather than impact on health, and using recent advances in data analytics and computer technology to fully leverage patient and payment data can greatly improve quality and reduce costs [59].

Electronic medical and health records. The explosion of digital data, high performance computing, data processing, development and management of databases, data warehousing, mathematical representations, statistical modeling and analysis, and visualization are crucial in extracting information from the data collected for domain-specific applications [60]. *Electronic medical records* (EMRs) contain the standard medical and clinical data of patients gathered and stored in digital format by a care provider. An EMR is a major advance over paper records because it allows the care provider to track data over time, identify patients who are due for preventive visits, monitor the progress of patients automatically and improve the overall quality of care. *Electronic health records* (EHRs) go beyond the EMRs collected in the provider's office and include more comprehensive data such as medical history, immunization status, health measurements, and lab test results over time. The records can be shared across different health care settings, from all providers involved in a patient's care. Unlike EMRs, EHRs allow a patient's health record to move with the patient, to other health care providers, hospitals and across states. On the other hand, due to the ease of searching the digital information in a single file, EMRs are more effective for examining the medical data of a patient by the primary care provider. The sharing of patient information between health care organizations and IT systems has opened up possibilities for a global shared workflow; for example, radiologists can serve multiple health facilities across large geographical areas.

Text mining and web-based healthcare studies. Using the World Wide Web support for information retrieval tasks that are carried out by search engines or text input in online surveys and questionnaires provides new avenues to conduct health care studies. The surveys can be health questionnaires where the patients' inputs include text. The benefit of text mining comes with the large amount of valuable information latent in texts which is not available in classical structured data formats for various reasons. Although text has always been the default way of storing information for hundreds of years, time, personal and cost constraints prohibit bringing texts into well-structured formats [61]. Text mining has become a burgeoning new field that aims at gleaning meaningful information from natural language text, and there has been increasing demand for innovative text mining methods; see [62] that also contains a number of text mining tools for clinical and research applications.

Mobile health. Clinical point of care (POC) refers to clinical delivery of services and/or healthcare products to patients at the time of care. Mobile devices and tablets provide accessibility to electronic medical records for clinical POC documentation. Francis Collins, the current director of the US National Institutes of Health (NIH), wrote about the usefulness and promise of cell phones and mobile sensors [63]: "Mobile devices offer remarkably attractive low-cost, real-time ways to assess disease, movement, images, behavior, social interactions, environmental toxins, metabolites and a host of other physiological variables. It is incredibly cool to pick up your iPhone, fire up an application to monitor your heart rate and rhythm, and then beam your ECG reading to a cardiologist halfway around the globe". On the other hand, he also cautioned that "as a physician-scientist, I also know that cool technology is not necessarily synonymous with good science or sound health practices and therein lies a challenge". Technology is alluring, allowing measurement of daily activities and real-time physiology outside of hospitals and clinics, and helping scientists to keep track of subjects' sleep patterns at home so that they do not have to rely on lab-based studies or self-reporting. But "to make all this happen, health researchers, technology developers and software designers must pull together to find ways of evaluating new technologies", and "maintaining privacy and security of health data, as well as learning how people are actually using mHealth in their everyday lives are challenges that call for research". Big data analytics features prominently to address these issues and in the construction of mobile health systems.

Shared decision making. This is a new trend in cardiovascular medicine, which has promoted evidence-based medicine by developing clinical practice guidelines, performance measures, and appropriate use criteria for the treatment of common cardiovascular diseases. Since patients are the best experts about their context, goals, values, and preferences for health care, it is widely recognized that their participation in decision making helps clinicians make informed judgments about how to translate the research evidence into practice and improve the fit

between the management plan and the patient who will implement it and live with its intended and unintended consequences. Moreover, shared decision making might improve patient fidelity to the mutually agreed plan and improve safety by reducing the misdiagnosis of patient preferences. Decision aids containing evidence-based information designed to assist patients in making decisions that involve weighing benefits and harms are crucial for shared decision making [64]-[66]. Based on the patients' shared decision roles on their cardiovascular health, the American Heart Association announced in 2014 a new Shared Decision Making (SDM) series on Circulation: Cardiovascular Quality and Outcomes [66]. Innovative study design and data analysis feature prominently in the development of these shared decision aids [22].

Wearable devices and healthy living aids. Wearable technology is on the rise in both personal and business use. According to a study by Gartner, Inc., the world's leading information technology research and advisory company, 68.1 million wearable fitness trackers were expected to sell in 2015, and 91.3 million in 2016 [67]. The wearable devices can have great impact on health care systems and the quality of life. People who wear these devices will be able to integrate the data from most wearables into a single account where their data can be analyzed using computing to provide useful insights to the wearers. Funding initiatives from Google (Google Fit), Apple (HealthKit), Samsung (S.A.M.I.), Microsoft and others will build on early innovation in wearing fitness and health monitoring and create the infrastructure for merging data that are relevant to health and fitness [67]. Health research studies have also begun using wearable devices to monitor subjects' health problems. For example, a study assessed the use of a textile-based wearable system with its associated apnea detection algorithm to monitor the subjects with Obstructive Sleep Apnea Syndrome (OSAS) [68]. The results showed that such a wearable system could be successfully used for the early detection of OSAS and could stimulate people to better self-healthcare by seeking specialized medical examination and eventually undergoing proper treatment to avoid the onset of OSAS co-morbidities. Similar devices (or even medical apps on smartphones or tablets) can be used to remind and advise the user about healthy diet and lifestyle.

5. Conclusions

The big data revolution has changed biomedicine and economics to different degrees, but the changes will continue as this century progresses, particularly in relation to health care. We have now entered the era of precision medicine [69], and in his State of the Union address on January 20, 2015, President Obama said: "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes and to give all of us access to the personalized information we need to keep ourselves and our families healthier". In Section 2, we have reviewed some advances in this direction. Einav and Levin [70] point out that the "data revolution in the past decade is likely to have a further and profound effect" on economic science that "has evolved over several decades toward greater emphasis on empirical work". Section 3 also discusses some aspects of this data revolution on health economics and policy and suggests some new research directions.

In their 2015 commentary on the Swiss health care system, Biller-Andorno and Zeltner [31] point out several features of the public-private partnership that has both an egalitarian and well-functioning public component and a very profitable private component. Although the system seems to have worked well in combining respect for individual choice and responsibility with communal solidarity that provides basic health care to fellow citizens who lack financial resource, it is "confronting a number of challenges": an aging society, possible overtreatment, and patchy records of the quality and equity of health care delivery. To address the last two challenges, they describe proposals to create a "better database for a learning health care system" and to conduct studies on "the clinical effectiveness and cost-effectiveness" of treatments, thereby providing "reference points for medical decisions and policy debates". The overviews in Section 2.2 and Section 4 basically take these recommendations further, and our discussion in Section 3.4 also addresses their first challenge.

Health analytics, considered in Section 4, is expected to provide a natural linkage between health economics, precision medicine and population health sciences and integrates them to build a 21st century health care system. This is how we envision it to work. Cost constraints make it economically infeasible to realize the full potential of precision medicine. Politico-economic debates and uncertainties have been hurdles to change existing health care systems and funding mechanisms. However, data analytics and innovative study designs can go a long way towards providing evidence-based recommendations. The 21st century is envisioned to be data-driven, self-learning and adaptable to time-varying factors such as aging demographics and economic cycles. It will involve a public-private partnership, in which the private sector can create new and well-paid jobs besides product/

technology/service innovations, and many of these jobs are related to the health analytics engines that support the 21st century health care system.

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