Chapter 8

Future Healthcare: Bioinformatics, Nano-Sensors, and Emerging Innovations

Shoumen Palit Austin Datta

Contents

8.1 Introduction

Proclaiming health as a human right [1] is a platitude when healthcare still remains inaccessible to millions, even in affluent nations, or billions elsewhere. Few dispute the fact that more than 30,000 children, less than 5 years old, die every day, many suffering from preventable diseases. According to the Institute of Medicine [2] at the National Academy of Sciences, healthcare is substantially underperforming on several dimensions: effectiveness, appropriateness, safety, cost, efficiency, prevention, and value. Increasing complexity in healthcare and regulatory steps is likely to accentuate current problems, unless reform efforts go beyond financing, to foster sustainable changes in the ethos, culture, practice, and delivery of healthcare. If the effectiveness of healthcare is to keep pace with the opportunity of prognostic, diagnostic, and treatment innovation, then the design must be based on systems thinking [3]. Information technology must be structured to assure access and application of evidence, at the right time, to facilitate continuous learning, and research insights, as a natural by-product of healthcare process. We need to reengineer the development of a research-driven learning healthcare organization [4] by integrating a systems engineering approach, to keep the individual in focus, while continuously improving concepts, quality, safety, knowledge, and value.

In particular, commitment to research may be emphasized by lessons from the past [5] to catalyze a future where creative cross-pollination of diverse concepts from unconventional [6] strategic thinkers is rewarded. It is equally essential to build multidisciplinary collaborative global research teams, imbued with the true spirit of discovery [7] in basic and applied domains. These teams must be enabled to drive an entrepreneurial [8] enterprise approach to create proof of concepts. Translation of unconventional concepts into reality may be guided by innovators with horizontal global vision rather than gatekeepers who prefer to stay "in the box" and avoid risks that leadership demands. The caveat in this process is the impatience of "practical" people for unconventional concepts, but the "nail on the coffin" is often driven by political polemicists who also get impatient with concepts, no matter how justified or pragmatic, because it gets in their way to sell their plans [9]. The latter may block funding or policy that may better enable the conversion of unconventional vision into reality, only limited by our imagination [10].

Yet, unconventional thinkers and business leaders [11] are largely credited for globalization [12]. Striking transformations have occurred through decision systems and process engineering, not only in established markets but also in creating new markets [13] despite omnipresent global uncertainty [14]. These changes have reshaped political economy [15], governments [16], the service industry, and manufacturing sector, including business process [17], software, hardware, banking, retail, airline safety, automobile industry, national security, and the business of the military industrial complex [18].

Lessons from the failures and the fruits of success, enjoyed by the business world, may not be irrelevant for exploration and/or adaptation by healthcare organizations, despite the irreconcilable differences that exist in the dynamics of mechanical versus biological and social systems. The current challenges in healthcare compel a fresh view of the organization, structure, and function of the delivery and monitoring processes in healthcare, not only for the industrial world that may afford the increasing cost (macro-payments) but for global healthcare services, in a manner accessible to, as well as feasible for, the billions (micro-payments). Financial sustainability of healthcare is a key issue in the design of innovative health services. The latter evokes the paradigm of services that may be deliverable for "micro-payments" rather than the current spending that claims a double digit share of the gross domestic product of rich nations.

One of many lessons from the business world is that to survive in business, businesses must exploit the power of "now" [19], perhaps best illustrated by the surge in using real-time data, almost for everything, through the use of radio frequency identification (RFID) tools [20]. To remain profitable in an RFID-driven world, industry must "adapt or die" [21]. Real-time consumer-driven supply chain [22] dynamics also determine the speed at which the industry must change to remain competitive [23]. Hence, business models are continuously focused on data, new technologies [24], cost reduction, and the quest for new growth without sacrificing quality of product and/or service. Systems that help to maintain "everyday low cost" at Wal-Mart and efficiencies at Dell that still allow "making boxes" a profitable pursuit deserve strategic exploration and integration of germane ideas to improve sustainable healthcare delivery. Healthcare systems were not designed with scientific principles in mind [25], and the ethos of "innovate or die" [26] is not salient to healthcare providers.

While software systems, like enterprise resource planning (ERP), generate benefits for business and industry, through some degree of integration of data and automation of planning, there are few healthcare electronic medical records (EMR) systems (EMRS) that have autonomous decision-making capability. Healthcare, even preventative or wellness, if available, is still dependent on expensive human resources for data acquisition, monitoring, analysis, reporting, and follow-up. Reengineering this cost structure and hospital-centric service model is necessary. Configuring a reliable business service model for health services may meet with entrenched resistance to change but may catalyze extended healthcare for billions and may even improve healthcare quality of service.

8.2 Problem Space

8.2.1 Background

The multitude of problems and issues in management of healthcare are beyond the scope of any paper or book. Here, I briefly touch upon only one issue: acquisition of medical data to improve healthcare. However, the fundamental nature of this issue forces us to address a series of integrated problems, some of which may be text book cases in basic physiology [27] and biochemistry [28]. Therefore, it is well nigh impossible to do sufficient and equal justice to all the interdependent processes and areas.

The naive thrust of this issue is to reduce healthcare cost but with concomitant expansion of improved healthcare services for billions. Healthcare cost reduction is a hackneyed topic of discussion, but the thrust of this chapter is to suggest solutions where emerging ideas and innovation may help expand and improve healthcare service at a cost that may be soon sustainable even by the developing countries of the world. Hence, the solution space shall deal with the issue in focus: innovation in acquisition and analysis of medical data. It is obvious that one can remain oblivious of the fact that innovation in data collection calls for innovation in tools for data collection as well as analysis of data, to extract information and knowledge that can add value to healthcare services. Due to the latter, the problem (and solution) space of this chapter is bound to evolve in multiple directions, each indicating a further line of innovation.

One general problem in global healthcare is due to the mimicry of the Western model focused on acute-care hospital-centric view of what health "care" is supposed to deliver [29]. The aphorism that "better health is inherently less expensive than worse health" is equally applicable in the West and the East [30] yet seldom practiced. In fact, the profitability of the acute-care hospital-centric Western model appears to be the preferred line of health service delivery (Figure 8.1). It reasons that the word "care" must be omitted from healthcare [31] because the hospital-centric revenue model is at odds with the "care" that health services are expected to deliver for an individual in a patient-centric view of personalized healthcare.

I hasten to add that in general, the acute-care hospital-centric model still offers appreciable services when it concerns accidents and emergencies (A&E). It is vital to respond to the challenges of uncertainty in healthcare stemming from A&E. But, the criticism surfaces when the A&E modus operandi is extended to other areas of non-A&E healthcare. The systemic efficiencies necessary to respond to A&E situations must continue to be supported. Suggestions in this chapter or elsewhere about patient-centric personalized healthcare must not be viewed as a replacement but as a realignment of the existing system that is necessary for economic transformation to keep healthcare sustainable. A&E and non-A&E approaches are not mutually exclusive, and there is a need for elements of both systems to coexist for mutual enrichment.

Another problem that has evolved over the past few decades concerns an inability or incongruent response of the healthcare community to adopt advances in

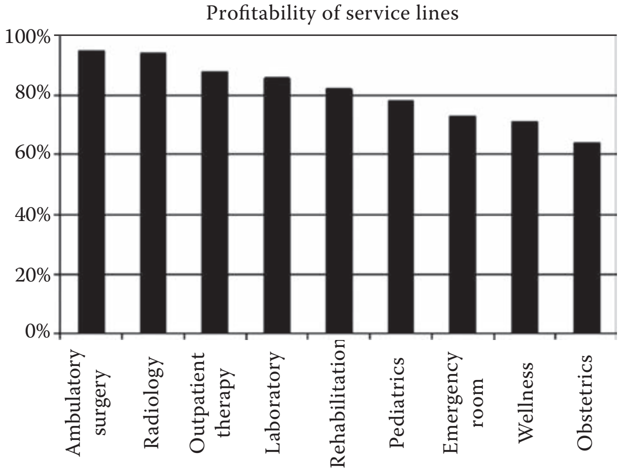

Figure 8.1 Reporting service lines as profitable (above 80% reporting) or unprofitable (below 80% reporting). (Adapted from Deloitte Consulting, *The Future of Healthcare: An Outlook from the Perspective of Hospital CEOs*, New York, 2005. With permission.)

information technology in order to develop an integrated systems approach to services. The human-driven decision model practiced by the medical community is adept in maintaining and/or sequestering data, information, and knowledge, about cases and patients in paper-driven silos. It prevents the improvement and development of a learning healthcare system based on insight and experience. Critics of information technology within the medical community will defend this status quo by pointing to issues of confidentiality of patient–doctor relationship, privacy of patient data, lack of standards for medical systems interoperability, and quagmire of ethical guidelines for medical knowledge diffusion. The critics are justified in their claims. But they also remain refractive to extract and use the principles that have increased profitability in the services industry and catapulted businesses such as GE, P&G, Nokia, and Wal-Mart to luminous heights of profitability. In addition, the chasm between medical education and engineering education creates a lack of awareness of the advanced tools and information technologies that exist and the potential for innovation in intelligent decision sciences, in order to provide data protection the critics demand and the patient and doctor deserve.

The business services approach to healthcare, admittedly, raises alarms if individuals or patients are to be viewed as cost-centers with the administration trying to function as a profit-center. This view assumes a literal translation of business services to health service, which is not what the proposal calls for. As an example of successful transformation of business service efficiencies, one may cite education, a domain with distinctly different dynamics from business. The Open University in

United Kingdom [33] and University of Phoenix in the United States [34] have pioneered profitable business service type approaches, integrated with extensive use of information communication technologies (ICT), to deliver education of a reasonable standard for vast number of individuals, who were unable to access traditional higher education, for a variety of reasons.

Remote access to education had humble origins in "correspondence" courses but was transformed by the growth of the ICT sector and accelerated by the diffusion of the Internet. This is a form of "personalized" education that enables individuals to move ahead in careers of their choice and contribute to economic growth. This educational–economic transformation may offer a paradigm for the healthcare industry. Of course, the academic level of OU and other similar outfits may not train an individual to be the next "big bang" theorist or lead researcher to garner a Nobel Prize. But for those elite purposes, the academic system is well prepared with its select institutions. The elite academic institutions may be analogous to the "elite" equivalent in healthcare, which may be the acute care and A&E. However, the elite model in healthcare system may exclude or restrict, on grounds of profitability or cost, the accessibility of non-A&E type preventative or early diagnostic modes of healthcare (analogous to OU and similar outfits) for the masses.

8.2.2 Focus

To reiterate, the focus of this chapter relates to innovation in acquisition and analysis of medical data to improve healthcare by expanding coverage for the masses yet deliver greater value of healthcare services. Service orientation, systems architecture, and the use of software as infrastructure depend on data sources and analytics needed from healthcare monitoring, sensing, and responding to situations. The business services concept of data, information transparency between systems, as well as data exchange and/or interoperability issues may be more complex in this context due to regulatory and security constraints. It may be quite useful if the business service type approach can also introduce some degree of automated decision making, even based on rules and workflow, for non-exceptional healthcare case management.

The next level of decision making based on acquired data with reference to standards (e.g., pulse rate, blood pressure, and normal range of blood glucose) may require some basic algorithms based on simple artificial intelligence (AI) principles that can induce a learning healthcare approach when evaluating data about a specific individual or patient. For example, if the individual is otherwise "normal" even under a higher systolic or diastolic blood pressure (BP) reading, then the analytical algorithm can learn that the deviation from the medical standard reference model (120/80 mm Hg) is not readily a cause for alarm in this specific case since the individual is physiologically "normal" even under an elevated or lower than standard BP reference data. Hence, billions of learning instances are necessary for a global model.

This very important decision, to conclude an individual or patient is normal despite a slightly aberrant standard data, must be made, under most current circumstances, by a trained medical professional. That translates to cost. Aggregated over numbers of inpatient- and outpatient-related data, these cumulative costs soon begin to destabilize the financial infrastructure. Equally and perhaps more important is the time spent by the trained medical professional to review the data and arrive at the decision. Time spent for non-exception management siphons away valuable time from exception management and patients who indeed need attention. Therefore, it is not difficult to comprehend that small changes in the healthcare process pose minimal risk, quantifiable using business tools (see Ref. [201]), yet may improve quality of service and reduce cost.

Documenting the acquired data, for example, the blood pressure reading mentioned above, is the next level that deserves exploration due to the cascade of events that this data may trigger. With a few exceptions, even in the most advanced industrialized nations, paper-based documentation is the norm [35]. Unless paper-based documentation is the exception, rather than the norm, healthcare systems may continue to be crippled from displaying their true functional potential. Given human errors of data input, the transformation of preexisting and accumulating data as well as notes and decisions poses a major challenge. Without the available information on existing patients and cases, the ability of decision systems to arrive at non-exception-management-related decisions, on these existing patients and cases, may be seriously flawed and hence may be rendered unacceptable, to help deal with existing patient management.

Thus far, we have referred to patients, but what about individuals who are not patients yet? Wellness or preventative medicine and early risk identification are critical to reduce the probability that an individual shall become a patient or need acute care or emergency attention. The acute-care hospital-centric model is largely viewed as a failure to address this broader spectrum of personalized healthcare even though it may be well equipped to deal with A&E in nations big (e.g., the United States) and small (e.g., Ireland).

8.3 Solution Space

8.3.1 Existing Electronic Medical Records Systems

Before embarking on the discussion of emerging trends and potential for innovation to address the problem focus outlined above (Section 8.2.2), it may be pointed out that medical data captured in electronic format (EMRS) exist in practice in some form or the other [36]. It may offer architectural clues or serve as a basic template (starting point) for nations beginning to grapple with the problem of creating EMRS. However, expecting the current EMRS to serve as a "best practice" or benchmark may not be prudent. There is ample room for improvement of EMR, which is essentially a generic data aggregation platform. The evolution of future versions or variations of generic EMR platform may not bear any resemblance to current systems that are generally command-driven, archival data stores, with little, if any, analytical capabilities, such as clinical decision support (see Ref. [63]).

Since 1907, the Mayo Clinic (the United States) claims to have kept unified medical records that exist in electronic format since 1993 [37] in a single database with 5 million records including patient files, x-rays, laboratory results, and electrocardiogram (ECG) records. Since 2004, it includes data mining and pattern-recognition tools to discover relationships among specific proteins, genetic makeup, and treatment responses (see Sections 8.3.2 and 8.5.1). Information can be shared between the different geographic locations of the Mayo Clinic, and physicians can conduct a virtual consultation on any patient because the EMRs are accessible from all three sites. This may represent the primordial role of data in personalized healthcare.

The VistA system in use by the Veterans Administration (the United States) hospitals covers 150 medical centers and 1400 sites across the country [38]. Eighty-five percent of 57 million outpatient visits and almost all inpatient notes are available online through VistA. In addition, 94% of outpatient prescriptions (equivalent to 200 million 30 day prescriptions) and almost all of inpatient prescriptions are entered in VistaA (EMR) directly by the prescribing clinician. A study in 2004 compared VA versus non-VA patients in 12 communities and found that VA patients scored higher on quality of care, chronic disease care, and preventative healthcare.

The scope of benefits that can be derived from EMRS, as one component in the solution space, is only limited by our imagination, but, at present, several thorny challenges remain. Unlike the Mayo Clinic records and their visibility across the three different geographic locations, the infrastructure of VA or Partners HealthCare [39] is more extensive. Patients can move between locations and their treatment can change over time. This introduces major systemic issues, as follows. Partial solutions are suggested, if applicable.

Of immediate concern is unique identification of data (see Ref. [39]). How do we uniquely identify the patient, and patient records, that may be assigned different ID numbers in different locations as well as different records of the same patient that may be numbered according to the system in operation at a given location? The critical value of unique identification that unambiguously links the individual to his/her records, irrespective of the physical location of the hospital, does not need emphasis. The sheer number of individual records (laboratory tests, x-ray, CT scan, ultrasound, physician's notes, medication, response) multiplies over time and may present a numbering scheme dilemma that requires a solution but without reinventing the wheel or introducing yet another "new" system.

Creating unique identification is not a competency of the healthcare industry. Hence, the health services may opt for an existing identification scheme that (1) can offer vast number of unique addresses [40] that can be organized in relationships or subclasses, (2) is truly portable, (3) Internet ready, (4) already in operation, and (5) globally pre-agreed in a manner that can aid adoption by the healthcare industry.

A proposal that can address this issue of unique identification of octillions of items using the globally agreed IPv6 format is presented in a separate paper (see Ref. [40]). Support for the potential use of IPv6-based identification may soon gain momentum [41], and the need for this approach in healthcare was highlighted in problems discussed elsewhere (see testimony that follows from Ref. [38]).

Personalized unique identification in healthcare may offer a robust id solution, but its value for the patient, who may move between various healthcare units (e.g., physiotherapy, stroke care, outpatient clinic) or hospitals, local and/or global, shall remain constrained without interoperability between systems of different healthcare providers, public and private, engaged with the patient. There is little value in deploying unique identification if an individual permanently resides in one location and receives healthcare from one medical professional, in one clinic or hospital, which is entirely self-contained in all its services and without any external interaction, guaranteeing total quality healthcare for the entire life cycle of the individual.

Interoperability segues to the issue of standards. The IPv6 standard governing the unique identification scheme mentioned above will make it possible to identify the unique number ("address") in any healthcare system anywhere in the world, because the standard has made provisions for assigning that number or address to that record, or patient, in a manner that shall remain unique over the life of an individual. It is logical to anticipate that a "number re-claiming scheme" that may be deployed to claim back and reuse dormant numbers (e.g., a patient number may be claimed back and reused every 150 years if it is assumed that a human being is unlikely to live for more than 150 years).

Standards shall prominently feature in EMRS solutions space when and if the healthcare system begins to experiment with rule-based or intelligent decision sciences to help evolve clinical decision support (see Ref. [63]). Standards or "rules of operation" are immediately necessary for the granular and diverse quality of record-keeping that commences with patient history and physical examination. It is most often carried out by the local primary care physician or general practitioner (GP), in communities where primary care may be in operation and where EMRS may be available for record keeping. Of course, the same could commence for individuals who report to the A&E.

Standard "history" data in an EMRS that is also interoperable are a complex problem that must dig deep and wide for multidisciplinary convergence to generate a working solution. It is complicated by the multitude of descriptive syntax that may be used by the patient and the written form in which the medical professional scripts the information. The natural language (mother tongue), cognitive abilities, culture, education, values, and experience of both the patient and the physician or medical professional shall color the content and context of this history document. It is apparent that existing ICT and computer systems may find it difficult, if not impossible, to extract with reasonable precision the "meaning" of the history written in words and transform them to a standard format that is medically relevant for EMRS interoperability. Even more crucial is to "understand" the importance of the phenotypic information relative to the context of the patient and his or her genotype, which, to be of value, must refer to a reference model of the community, geography, and environment where the patient lives or lived.

To the serendipitous reader, it may become obvious that the transformation from a paper-based localized healthcare system, with a limited number of professionals from a homogeneous background, to EMRS, may help to deliver global healthcare services, by any one, the myriad of diverse professionals. But it requires substantial research and innovation to develop standards [42]. The development of these standards requires integration with cognition and semantic theory. I will return to this issue when I discuss the proposal of molecular semantics (Section 8.4).

Before "boiling the biomedical ocean" in cognition and semantics, it may be useful if the healthcare system may globally agree to partially address the gulf between syntax and semantics in a "quick and dirty" approach, as adopted by business processes in global organizations [43] or the efforts spawned by the semantic web movement [44] to create biomedical ontologies [45]. These solutions, albeit temporary, if deployed and implemented in EMR type systems, are likely to offer some benefits, if the questions and content are less descriptive and are already expressed in a manner that is medically relevant, irrespective of the "background and culture" of the involved medical professional.

The development of "quick and dirty" rules and partial standards may help with (1) exchange of clinical data, (2) defining categories or circumstances when a physician in one healthcare organization can change or amend the problem list entry of a physician in another organization, (3) conditions under which clinical staff from one organization may discontinue medication prescribed by another clinician in the same organization or from another organization, and (4) types of data and information that must be secured by privacy policies and their enforcement, so that confidential data and patient information cannot be shared with, or released to, any external nonmedical organization without due authorization from the patient.

Finally, EMRS, even with its current healthcare service handicaps and restrictions, can still provide business value that may translate to cost savings. Because organization-specific EMRS like VistA operated by the VA cover a majority of its operations, the supply-demand profile of the operation can be deduced with a fair degree of precision. Using economies of scale, products, and services may be bought at a bargain. VistA offers an indication of volume of patients that are likely to be served and that volume information may be analyzed to forecast [46] inventory of supplies necessary to meet the projected demand. For perishable products (drugs, IV fluids, food), the design and management of supply chain [47] of vendors and partners can partner with the business operations unit to ensure adequate inventory of perishables to meet "peace" time and "war" time [48] type volatilities, analogous in the healthcare supply chain if one compares normal course of events versus epidemics, pandemics, natural disasters, or acts of terrorism. However, it is well nigh impossible to stress that the key performance indicators (KPI) for business operations and inventory management or purchasing decisions must be based on different operating principles and are significantly distinct between business [49] and healthcare (see Section 8.5.1). Nevertheless, gaining business efficiencies in healthcare is not an automatic process simply because EMRS offers an aggregated view of potential consumption of products and services. It is for this reason that some countries with national health service, whether servicing a large [50] or small [51] population, may still suffer from an inability to take full advantage of the economies of scale to drive business efficiencies.

8.3.2 Changing the Dynamics of Medical Data and Information Flow

The thesis of this chapter outlined in Section 8.2.2 selects medical data as one conduit that may offer the potential to catalyze low-cost, high-quality healthcare services. An analysis of the nodes of origin of data in the context of their relationship to cost (to acquire data) and quality of service (decision based on data) may form the basis for suggesting how the current dynamics may benefit from a paradigm shift (Figure 8.2).

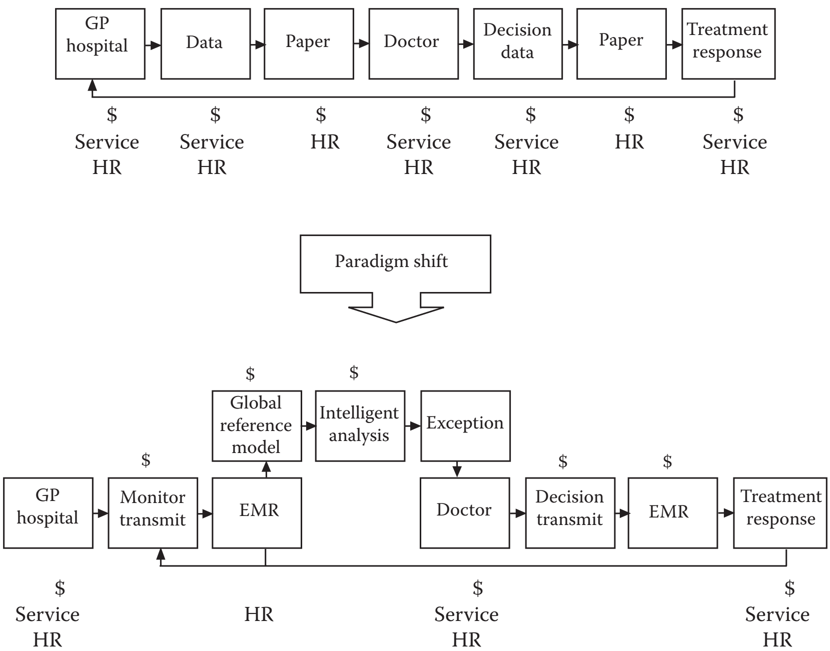

Figure 8.2 A generic model of data flow in healthcare and potential benefits of a paradigm shift.

In some industrialized nations and in the developing world, the current healthcare practice may be loosely represented by the schematic outline shown in the top portion of Figure 8.2. In the current scenario, almost all points of interaction (denoted by rectangles) incur cost (denoted by large $ signs), and each action consumes time from professionals (denoted by "HR" and "Service HR"). The latter, as a result, is a drain on the available working hours of medical personnel and is an improper use of valuable time, which could have been, otherwise, put to better use by offering health "care" service focused on the elements connected to the treatment of the patient.

The paradigm shift outlined in the lower portion of Figure 8.2 is neither new nor an innovative breakthrough. It is a strategic process engineering that is driven by common sense. It suggests how basic integration of some tools and technologies may lead to savings in cost and improvement in quality of care by focusing the time of medical professionals on the patient, rather than on standard tasks and chores. In this scheme, the lack of the large $ signs under the points of interaction (rectangles) indicates potential for cost savings. Above the points of interaction (rectangles), the small $ signs imply that implementing and maintaining these changes are not free, but the cost is lower (than the large $ signs) and return on investment (ROI) is higher if the cost of installing the systems is amortized over their productive life cycle. Less time spent by medical personnel at various stages (lack of HR and service HR) leaves more time to focus on patient care.

Three elements that drive the paradigm shift (Figure 8.2) are (1) data monitoring, addressed in Sections 8.3.3 and 8.3.4, (2) electronic data capture or EMR, discussed in Section 8.3.1, and (3) diversion in data flow. In the remainder of this current section, I will discuss the latter since it is perhaps the key in the proposed paradigm shift.

Diversion of data flow leads to an information loop that channels acquired data to flow through a global reference model and directs the outcome of analytics to medical personnel if it appears to be an exception. By concentrating on the patients that need attention (exceptions), the system is able to improve its quality of service.

Critics are eager to pose the thorny question: how reliable is the machine-based analytical process? Due to the experimental nature of the scientific process, I find it reasonable to conclude that there may not be, ever, a unanimously acceptable, complete, and absolute scientific certainty, with which anyone can predict that a machine-learning process can be guaranteed to be foolproof. Errors in medical diagnosis by medical experts are rare. Thus, neither humans nor machines are entirely infallible. It follows, therefore, that the "thorny" question is the wrong question. Attempts to find the precise answer to the wrong question have, thus far, fractured the determination of, and seriously distracted, the healthcare and decision sciences experts' (see Ref. [63]) effort, to focus on finding an approximately reasonable answer to the right question: how much and for what type of cases can we generally depend on the analytical tools in clinical decision support?

In the United States, healthcare spending was in excess of $2.1 trillion in 2007 and projected to double to $4.2 trillion by 2016. Thus, reducing 10% of health services workload through monitoring and analytics may save the United States nearly half a trillion dollars [52] in a few years. A small country like Ireland may save a couple billion euro [53] per year. It may also translate to a 10% improvement in the quality of service (QoS). Financial savings may be reinvested in community primary care centers, home help for independent living, and early risk identification, for example, for diabetes.

Therefore, the information loop proposed in the paradigm shift must be created and implemented, soon, even if the construction occurs in steps or modules. Inevitable "growing pains" are expected to accompany any change of direction. The "loop" is a generic expression that involves critical sub-elements of great depth that require precision knowledge. This chapter does not provide a prescription for building the sub-elements but strives to present examples that may convey the nature of these components. It goes without saying that the loop is not an "IT" job but demands collaboration between IT and medical experts.

Figure 8.2 alludes to a Global Reference Model (GRM) where the acquired data is fed via a database, such as an EMRS. The schema indicates that the data flow through the GRM into the intelligent analytics domain. What is unclear from the illustration and requires explanation is that the suggestion positions the GRM to represent an umbrella, or collection, of multiple modular databases, each embedded with some form of rule-based analytical engine that can evaluate the incoming data (streaming data) and use conventional workflow to query its database (specific to that module) to find relationships, homologies, or discrepancies based on its own stored data, specifically with reference to and in the context of that module of the GRM.

For example, a patient with elevated temperature suffering from severe bouts of coughing undergoes exploration in an outpatient clinic. A nurse records the blood pressure and temperature, draws blood for total blood count, and, based on the ethnicity of the patient, decides to take a sputum (saliva) sample in addition to administering a Manteaux test. It is an immunological test designed to detect tuberculosis (TB), an infectious disease [54], caused mainly by the microorganism *Mycobacterium tuberculosis*.

What types of modules in the GRM can process and analyze the data from this patient? Medical experts can define the nature of the GRM sub-modules, but, for the nonmedical reader, it may be of interest to note the following. Reference for normal blood pressure, correlated to age, is common, as is temperature. Total blood count is a common standard and is easily included in a GRM module. However, the GRM module that can deal with the results of the Manteaux test requires medical details as well as environmental details that relate to the epidemiology of TB, length of habitat of the patient in geographies where TB is prevalent, immunological profile of individuals with confirmed infection by *Mycobacterium tuberculosis*. The Manteaux test is an intracutaneous tuberculin skin test usually applied on the forearm and contains tuberculin purified protein derivative (PPD) to elicit the immune response that is visible on the epidermis within 2–3 days. For a patient who was born or lived in Southeast Asia or a resident of warm humid coastal areas in the United States, a positive Manteaux test, but measuring less than 10 mm in transverse diameter of induration, as detected by gentle palpation at 48–72 h, is not indicative of TB but rather indicates tuberculin hypersensitivity, resulting from contact with nonpathogenic environmental mycobacteria or childhood vaccination by Bacillus Calmette-Guerin (BCG), which is an attenuated strain of *Mycobacterium bovis* [55].

The above example illustrates the web of relationships that the GRM and analytics must be able to extract and transmit, to the point-of-care medical professional, using a visualization interface such as personal digital assistant or Blackberry type mobile phone. However, irrespective of the apparent complexity of the above example to the nonmedical reader, most of the data and information mentioned above are already available in several databases and are classified under variety of topics, including the obvious heading of infectious diseases. There is no need to create, de novo, any basic medical data or information database. For example, from the scenario above, the sputum sample from the patient may hold several clues for early detection and diagnosis, based on advances in saliva-based biomarkers [56]. The data from sputum analysis may be transmitted to the GRM, and it can query the SKB or Salivaomics Knowledge Base [57] to extract the information for further analysis. Several such databases exist with specialized knowledge and information, which are accessible via the World Wide Web. Unfortunately, the traditional web works as a directed graph of pages with undifferentiated links between pages. This is not conducive to the type of relationships necessary for healthcare analytics. Emerging principles from social networking may be quite helpful for healthcare service analytics (see Section 8.5.1). Blogosphere (see Ref. [10]) has a much richer network structure in that there are more types of nodes that have more kinds of relations between the nodes. Deploying the principles of blogosphere in healthcare analysis may be quite promising.

Thus, the challenge is to find new ways or tools to identify and relate the selected sources that may serve as components of GRM through a virtual amalgam. GRM requires a mechanism to search and detect the information database and then query the database depending on the case or patient under investigation. For every patient, these strands of data-dependent, symptom-dependent, or test-dependent tasks must be created, in real time, on demand, perhaps, as a higher layer integrated abstraction in the form of an application module (poor choice of word but hopefully, it conveys the concept). For example, continuing the TB scenario, the data from the Manteaux test plus the symptom of cough and the eosinophil count from blood test may serve as three variables that may trigger an ad hoc application that asks, either as single queries or collectively, "What is the potential diagnosis if the Manteaux test reveals a 10 mm transverse diameter, chesty coughs are persistent, and eosinophil count is 8%?" To execute this process, the system may create an ad hoc application-specific interface (ASI), application-specific query (ASQ), and an application-specific relationship (ASR) that can act, either alone or as a bundled application, to probe relevant knowledge repositories or databases, to extract the information. This information may be further refined by the intelligent analytics component in the information loop or transmitted to the point-of-care (POC) medical professional.

The scenario above may be loosely suggestive of a medical example of mash-up software [58] that is gaining popularity in business services utilizing SOA or service-oriented architecture [59]. SOA is touted to help business services remain agile and adaptable to meet the competitive challenges due to volatility of consumer preferences and uncertainty stemming from globalization of the supply chain. To capture sales, these business services, on demand, in real time, create a personalized web service and display a collage of objects, optimized for consumer choice. The collage is culled from different domains or databases that may or may not belong to the business but secure content on demand through licensing. The mash-up appears seamless through the wizardry of visualization tools. The consumer views it as a web page on a computer screen or mobile phone. The view may include, for instance, a company logo (a software object), price of a product (database table format, stored as an object) aimed at a market segment (extracts clients preferences and matches with stored classes of objects, e.g., sports), and ordering information (another standard shipping and handling object) with links to track and trace details provided by a third-party logistics provider (e.g., link to FedEx site).

The analogy in the above two paragraphs may fall short of the specifics or lack the precision that experts in respective domains (medicine and information technology) may demand, but it may convey the essence of case-specific exploration, on demand, integrated to knowledge discovery from databases, or other domains, necessary for delivering healthcare analytics. Each country may create their own GRM infrastructure to optimize how the GRM may be relevant to the nation and deliver value in medical analytics, at least in cases that are simple enough to be acted upon by machine intelligence, where reasonable confidence can be placed in the decision. Determining what is "simple" may vary, widely.

Triggered by patient data input, the search function of GRM may evoke the notion of Medical Google. One difference is that the search is not the end point of GRM but is for the Google search engine [60]. The granularity of the search process implicit in GRM also differs from that of Google in its quest for knowledge databases, followed by the extraction of relevant data and/or information and/or knowledge that must be first "discovered" and then resynthesized and presented to the intelligent analytical engine.

The "intelligent analysis" referred to in Figure 8.2 is a "place holder" for multiple analytical tools that are available and may be developed in future where the "learning" ability of the tools may be a key emphasis in addition to rule-based applications. The tools, for example, artificial neural networks (ANN), originate from the domain of artificial intelligence (AI), and new algorithms may continue to evolve. Since medicine is an intensely integrated science, the network of interrelationships between medical parameters and physiological function is key to understanding health. The plethora of reasons that may offer generic symptoms, for example, fever, makes it imperative that the point-of-care (POC) physician is sufficiently aware of the spectrum of reasons why an individual may present the symptoms of fever. Presentation of a list of reasons may stem from the use of rule-based engines that may search and compile a list. However, the value of the "list" is limited unless the context of the patient and history is taken into consideration.

Rules, to combine and select the best possible match between the list and context, may be created, but the rigidity of rule-based selection may make it less reliable if compared to a set of algorithms based on AI principles that can "learn" and forget the subtle, or not so subtle, changes in the context of the patient that may include parameters, such as age, activity, profession, environment, habitat, and nutrition. For this reason, GRM and the intelligent analysis cluster of the information loop may use data cubes [61] and components that may be country specific, nation specific, or community specific but may also draw on synergies between demographically related co-localized nations (e.g., Scandinavia or Eurasian Steppes).

Let us consider an example where Jane, 11, contracts a fever on Monday morning after a hot weekend that she spent on the beach and swimming in the ocean. On Monday, Patrick, 71, complains of fever, too. He also has chronic obstructive lung disease (COLD). The attending physician may focus on determining whether Jane may have an ear infection while gearing to treat Patrick for chest infection. But can we approach this level of interaction and perhaps a treatment suggestion without incurring the cost and time of the physician? The use of acquired data (see Section 8.3.3) and decision sciences may offer a route to savings. To execute this interaction and offer a reliable, low-risk decision or treatment suggestion, intelligent analytics views the GRM-evaluated raw data plus list of possibilities for the fever and integrates the context with patient history. It also checks the GRM pharmacology module. The system transmits the exploratory analytical sequence log and diagnosis and recommends age-appropriate antibiotics, in each case.

Although the use of artificial neural networks (ANN) and artificial intelligence-based algorithms (e.g., ant-based algorithms) was mentioned only for business services applications (e.g., mash-up), the use of AI-based agent systems [62] can provide a robust and granular system. The experimental use of AI in clinical decision making [63] and productive implementation of AI in industry [64], business [65], business-to-business exchanges [66], and other applications [67] provides confidence that agent-based systems may become the norm in healthcare, too. Due to the interrelated nature of medicine, numerous parameters must be concomitantly evaluated for any decision, and each patient must be treated as an independent instance that is specific for that patient only. Data related to the patient always remain patient specific without sharing, aggregating, or clustering data, in any form, whatsoever. For each patient, the classes of data and volume of data points are likely to be quite high. All data points must be stored and relationships evaluated for diagnosis and prognosis. Therefore, the use of data cubes and the ability of agent systems to connect between all data points through the cube-on-cube organization of data cubes may make this approach particularly essential and beneficial for the billions of instances necessary for healthcare services.

Revisiting the earlier example where a Manteaux test was administered, from an agent perspective, the applications, in that discussion, may be dissociated into single agents, each with its specific task in relation data and exploration of the web of relationships with respect to the data or task assigned to the agent. In other words, the agent that holds the results of the Manteaux test (data = 10 mm) for the observed induration is charged with the task to find out, through the medium of the GRM, the implications of the observed data (10 mm). The development of intelligent agents systems [68] is within the grasp of current technology (see Ref. [182]) and can be implemented in healthcare systems. The "bundled" higher layer abstraction of individual applications (ASI+ASQ+ASR) mentioned earlier in this section is analogous to multi-agent systems [69] that work with agents in a hierarchical fashion with higher level agents tasked to integrate the information or data from lower-level agents. It is likely that multi-agent systems (MAS) may become the workhorse of the AI-based intelligent analytics in healthcare.

AI-based agents generally use programming languages from the open source domain. Hence, agents are highly mobile and suited to query a variety of databases for knowledge discovery using open source tools, for example, RDF or resource description framework [70] and OWL or ontology working language [71]. Agents are likely to form an integral part of the emerging semantic web [72]. But, agents need special interfaces if interacting with proprietary databases. Proprietary software vendors [73] deny RDF from accessing their data dictionaries through the use of proprietary programming language, for example, the use of proprietary ABAP programming by the software behemoth SAP AG. These problems may spur novel approaches. One data transformation tool called Morpheus [74] may facilitate extraction of data from various locations by transforming them into a common format, which is then sent to "holding tank" or a repository of transformations. Morpheus, used as a browser tool, may help to find a repository transformation that GRM (Figure 8.2) may be seeking. The transformation tool may drag and drop data or information in a format used by GRM.

In another vein, the open source movement is catalyzing the diffusion of software tools that may make it easier for agents to access proprietary formats through standard application programming interfaces (API) that still preserve the proprietary nature of the system but through a "translational interface" or flat file type format exchanges data or information. If the data or information sought by the agent is secured and in need of authorization for release, agent systems are capable of exchanging proofs to provide such authorization and release the data. The mobility of agents raises important questions about data security and its implications for healthcare. It is well documented that agent-based models are more robust to ensure data security by virtue of the AI algorithms used in its construction. At present, generally, most software architecture, for example, of the type used in EMRS, depends on equation-based models that are inherently far less secure.

Taken together, agent-based architecture may soon become pervasive in emerging healthcare systems. Agent-based software may form part of the infrastructure of the healthcare system of systems (HSOS). HSOS not only consists of the components illustrated in Figure 8.2 but extends to include mobile agents that (1) monitor the functional status of medical devices, (2) schedule human resources, (3) aid in the planning of meal services to match nutritional needs or restrictions of patients, (4) guide business functions to benefit from economies of scale, and (5) oversee financial records to monitor the fiscal health of the healthcare service. Other forms of conventional non-AI software (Morpheus, mash-up, SOA, ERP, web services) may coexist within the agent-based software infrastructure for routine transactions.

Agent-based “learning” systems may augment the depth and precision of data mining and pattern recognition (see Sections 8.3.1 and 8.5.1). Rule-based data mining and pattern recognition may be out-of-date soon after “new” rules are updated. The latter may be particularly relevant to healthcare tools, data structures, and analysis of parameters in diagnosis or early risk identification. Systems must continuously learn, adapt, or improve to extract and use the subtle changes that may be indicative of future disease potential or can differentiate between closely related types of anomalies. Some of these parameters may differ or be altered sometimes, albeit slightly, between populations [75]. In the context of the patient, that can impact the outcome, considerably, to prevent false positives or wrong treatment. Agent systems can continuously “learn” about changes and hence offer greater confidence in the outcome of agent-based GRM-integrated intelligent analytics (AGRMIA) compared to rule-based tools. Algorithms for relation analysis are emerging from research on social networking [76] and reality mining [77] that may be adapted for use in AGRMIA (see Section 8.5.1).

Application of pattern recognition, in one study, achieved perfect discrimination (100% sensitivity, 100% specificity) of patients with ovarian cancer, including early-stage disease [78]. The study identified subset of proteomic biomarkers using mass spectroscopy of proteomic analysis of serum from ovarian cancer patients and cancer-free individuals. Statistical algorithms analyzed the mass spectral data and selected, using random field theory, all biomarkers that were significantly different in expression levels between affected and unaffected subjects. The best discriminating pattern was chosen among all significant biomarkers by using the best-subset discriminant analysis method (Linear Discriminant Analysis). Another study along the same lines developed an algorithm employing principal component analysis followed by linear discriminant analysis on data from mass spectrometry and achieved sensitivity, specificity, and positive predictive values above 97% on three ovarian cancer and one prostate cancer dataset [79]. Detection of ovarian cancer using sensitive molecular biomarkers is especially urgent in women who have a high risk of ovarian cancer due to family or personal history of cancer and for women with a genetic predisposition to breast cancer due to abnormalities in genes such as BRCA1 and BRCA2 [80].

Application of remote monitoring (see next section) of body fluids using protein microarray chips [81] that can transmit data, advanced mathematical tools for biomarker data analysis, AI-based intelligent pattern recognition, and agent-based

GRM information flow (AGRMIA), if taken together, may hold promise for global healthcare. Tools, such as mass spectroscopy (MS), provide clues about molecular identities of differentially expressed proteins and peptides in body fluids or in breath [82] that may be critical for early diagnosis. Agent-based systems, operating through the GRM (Figure 8.2), can extract these types of data as well as information catalogues of biomarkers from other fields [83] and apply the knowledge to patient data, to identify risk and improve diagnosis. Hence, MS analysis of protein or peptide biomarkers [84] in body fluids using micro-fabricated miniaturized MS device [85] operating as a low-cost wireless sensor may offer a general population-based assessment of proteomic pattern technology, as a screening tool for early risk identification for several diseases, to complement lab-on-a-chip type sensors for early detection of cardiovascular diseases (CVD) [86] and carcinomas [87]. A proposed systems approach, by which mass spectroscopic data (protein and peptide biomarkers) may be compared between systems, will be explored in Section 8.4 on molecular semantics.

8.3.3 Data Acquired through Remote Monitoring and Wireless Sensor Network

The paradigm shift in Figure 8.2 illustrates that data acquisition and transmission, even if partially assisted by the use of medical devices for remote monitoring tools and information communication technologies, may reduce cost and free up time for medical professionals. In principle, few can argue about the value of this approach. In Section 8.3.2, references were made to potential for remote monitoring and sensors to improve healthcare services. In this section, I focus on one remote monitoring device. The basic strategy, from a medical device perspective, may be similar for the majority of vital measurements (data) carried out by the primary care GP or at the hospital. Security of transmitted data and unauthorized access is preventable using agents. To guarantee even more stringent data security, recent research on PUF or Physical Unclonable Functions [88] may generate unique "fingerprints" that can distinguish identical chips or IC from the same manufacturing batch, that are used in bio-sensors and other medical devices.

Remote sensing technologies are well developed [89], yet their application to noninvasive, wearable bio-instrumentation capable of wireless transmission of reliable data has only emerged in the past few years. One innovative device, the Ring Sensor (Figure 8.3), has emerged from the convergence of robust self-organizing wireless radio frequency (RF) transmission and an improved photoplethymographic (PPG) wearable sensor to monitor vital signs [90]. The Ring Sensor minimizes motion artifacts when measuring arterial blood volume waveforms and blood oxygen saturation, noninvasively and unobtrusively, from the wearer's finger base. Figure 8.4 shows the results from Ring Sensor monitoring of heart rate (data transmitted through a wireless sensor network) and compares the results to conventional electrocardiogram and wired finger photoplethymograph. The latter is susceptible to motion artifacts.

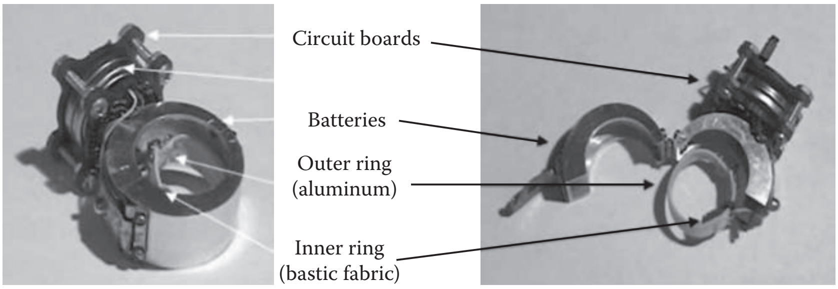

Figure 8.3 Noninvasive ring sensor for wireless monitoring of heart rate. (From Rhee, S. and Liu, S., An ultra-low power, self-organizing wireless network and its applications to non-invasive biomedical instrumentation, in *IEEE/Sarnoff Symposium on Advances in Wired and Wireless Communications*, West Trenton, NJ, March 13, 2002. © 2002 IEEE.)

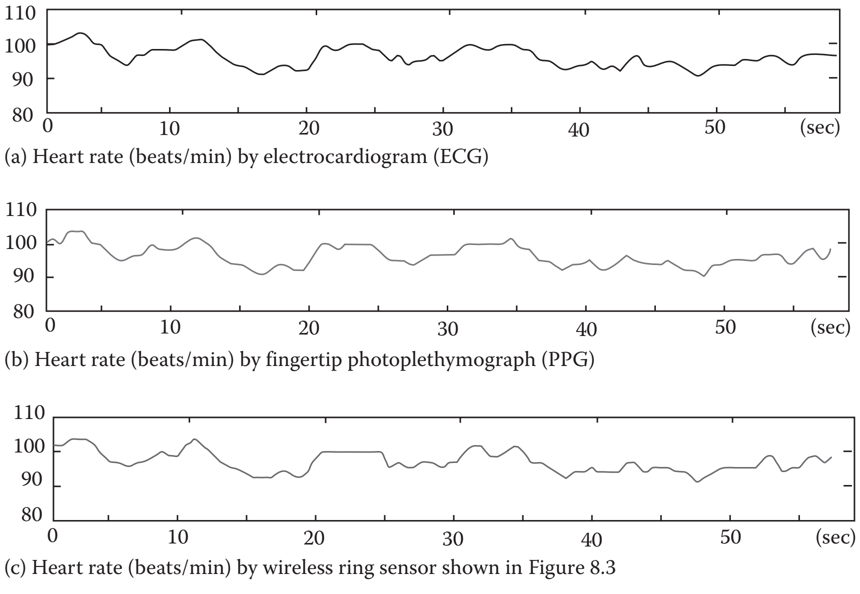

Figure 8.4 Heart rate monitoring by conventional, wired and wireless devices. (From Rhee, S. and Liu, S., An ultra-low power, self-organizing wireless network and its applications to non-invasive biomedical instrumentation, in *IEEE/Sarnoff Symposium on Advances in Wired and Wireless Communications*, West Trenton, NJ, March 13, 2002. © 2002 IEEE.)

It does not require any stretch of imagination to slip on the Ring Sensor (or a refined version of a similar device shown in Figure 8.3) on a patient's finger to monitor key vital signs, such as heart rate, continuously. Real-time streaming data under the "watchful eye" of a dedicated AI-based agent, embedded in the monitoring system or even in the Ring Sensor operating system (OS), monitor waveforms in real-time. It may be similar in principle to motes with TinyDB (database) and TinyOS [91]. If the Ring Sensor "senses" reasonable deviation of the PQRST wave in the context of the patient (rather than the PQRST standard in GRM or global reference model), then it immediately "responds" by sending an alert (code blue, code red) to the PDA or mobile phone of the medical professional on duty. Reference to context is important for patients with chronic CVD in order to prevent false alarms. Patients diagnosed with myocardial infarction or angina pectoris may display a PQRST waveform that may be different from the standard GRM version, but this altered PQRST waveform may be the "patient-specific normal" waveform. The data monitoring and analysis components of the system must be able to contextualize this difference.

This distinction in the analysis of monitored data highlights the need for caution to treat this suggestion as a medical device business bonanza. The challenge is to combine the sophistication of the waveform monitoring medical device (e.g., the Ring Sensor) with patient-specific context and history under the "supervision" of an agent (intelligent analytical tools). Agents may optimize the "sense, then respond" outcome, to be transmitted in a visual format comprehensible by a consultant cardiologist as well as a student nurse, to initiate the medical professional-driven response, decision, and treatment plan, if needed.

In practice, patients with cardiovascular problems are often required to wait. Intermittent monitoring of their vital signs is possible when the student nurse or trainee gets around to the patient. Physiological events that may happen in between the human resource-dependent monitoring may well determine the long-term morbidity (stroke victims) or mortality of the patient.

In the at-home scenario, Ring Sensor type applications offer greater value. Continuous monitoring is the key to preventative care, in this case, for people with chronic CVD or individuals at a high risk of CVD that may stem from other conditions, for example, increasing blood cholesterol or obstructive pulmonary diseases. Transmitted data from continuous real-time monitoring in the home, if subjected to real-time analysis (systems located in the community or primary care center or local hospital), are likely to (1) improve the quality of life for the patient; (2) reduce health service expenses by keeping the patient out of the hospital for longer periods; (3) optimize resource planning by creating a management plan and predicting when the patient may need to visit GP or outpatient clinic for non-acute follow-up or treatment; (4) reduce health service expenses and demand on service from A&E medical professionals by decreasing the probability for acute-care emergency services that may be required by the patient, more often, without remote monitoring provisions; (5) improve the overall quality of healthcare by extending

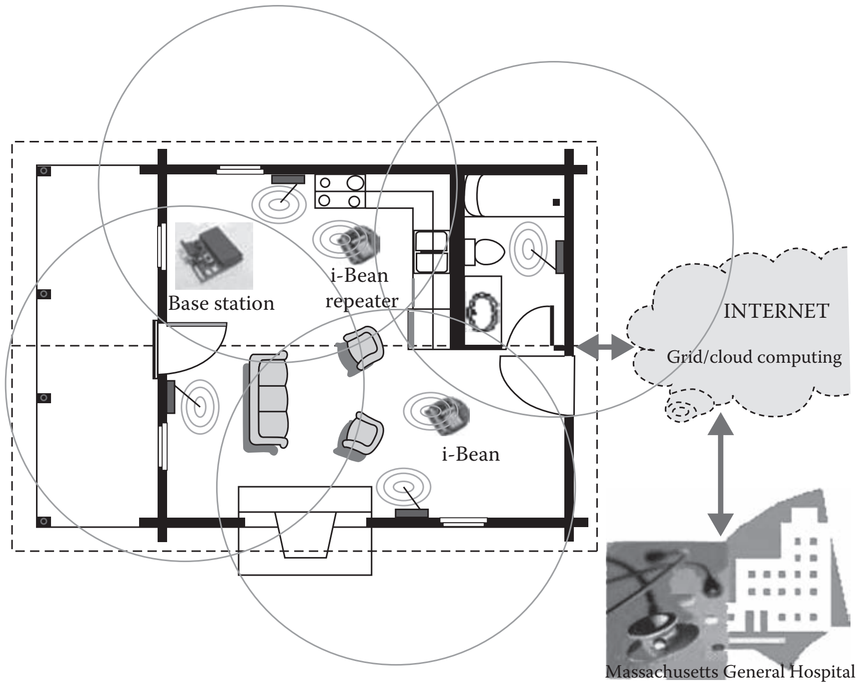

Figure 8.5 Wireless cardiac monitor uses plug-n-play i-Bean sensor network. (From Rhee, S. and Liu, S., An ultra-low power, self-organizing wireless network and its applications to non-invasive biomedical instrumentation, in *IEEE/Sarnoff Symposium on Advances in Wired and Wireless Communications*, West Trenton, NJ, March 13, 2002. © 2002 IEEE.)

remote monitoring not only for patients but the at-risk group, as well, by using the Ring Sensor with an ultralow power wireless device, the "i-Bean," which is an ad hoc, self-organizing network protocol that is as simple as plugging in a wireless WiFi router in home or office (Figure 8.5) or any location that can connect to the medical analytical system through the Internet; and (6) expand the reach of healthcare services (without mortgaging the treasury) by extending low-cost remote monitoring to an otherwise healthy demographic who may volunteer to keep an eye on their cardiovascular wellness profile.

The benefits from remote monitoring are undoubtedly robust, but it is also necessary to remain cautious because, whether remote or on-site, wireless or wired, local or global, healthcare produces data that may be difficult to interpret, and lack of proper interpretation may be fatal. The role of the medical professional and human-driven decisions, even for apparently routine instances, such as blood pressure check, may, sometimes, cast a doubt if data or symptoms are too generic. Table 8.1 (in Section 8.3.4) illustrates this point by highlighting that monitoring blood pressure and recording an elevated, lower, or normal reading, in some

Table 8.1 Single Gene Diseases That Elevate or Lower Blood Pressure

Disease	*Mutation*	*Molecular Mechanism*	*Effect on Blood Pressure*
Glucocorticoid-remediable aldosteronism	Duplication of genes encoding aldosterone synthase and 11β-hydroxylase, caused by an unequal crossover	Ectopic expression of a protein with aldosterone synthase activity regulated by corticotropin; increased plasma volume	Increased
Aldosterone synthase deficiency	Mutations in the gene encoding aldosterone synthase	Defective aldosterone synthase activity; decreased plasma volume	Decreased
21-Hydroxylase deficiency	Mutations in the gene encoding 21-hydroxylase	Absence of circulating aldosterone; decreased plasma volume	Decreased
Apparent mineralocorticoid excess	Mutation in the gene encoding 11β-hydroxylase	Absence of circulating aldosterone; decreased plasma volume	Increased
Hypertension exacerbated by pregnancy	Mutation in the ligand-binding domain of the mineralocorticoid receptor	Activation of the mineralocorticoid receptor by steroids lacking 21-hydroxyl groups (probably due in part to the rise in progesterone levels during pregnancy)	Increased
Pseudo-hypoaldosteronism type I (autosomal dominant)	Loss-of-function mutations in mineralocorticoid receptor	Partial loss of function of the mineralocorticoid receptor, impairing salt reabsorption; improvement with age and a high-salt diet	Decreased

(*continued*)

Table 8.1 (continued) Single Gene Diseases That Elevate or Lower Blood Pressure

Disease	*Mutation*	*Molecular Mechanism*	*Effect on Blood Pressure*
Liddle's syndrome	Mutations in the ENaC β or γ subunit	Deletion of the C-terminal domain of ENaC, resulting in increased ENaC activity	Increased
Pseudo-hypoaldosteronism type I (autosomal recessive)	Loss-of-function mutations in ENaC subunits	Impairment of ENaC subunits, which is not ameliorated by activation of the mineralocorticoid receptor by aldosterone; no improvement with age; massive salt supplementation required	Decreased
Gitelman's syndrome	Loss-of-function mutations in the sodium–chloride cotransporter of the distal convoluted tubule	Salt wasting from the distal convoluted tubule, leading to activation of the renin–angiotensin system; subsequent activation of the mineralocorticoid receptor increases ENaC activity, preserving salt homeostasis	Normal or decreased
Bartter's syndrome	Loss-of-function mutations in genes required for salt reabsorption in the thick ascending loop of Henle	Salt wasting in the thick ascending loop of Henle leads to activation of the renin–angiotensin system and the mineralocorticoid receptor, increased ENaC activity, and relative salt homeostasis	Normal or decreased

Source: Reprinted from Nabel, E.G., *New England Journal of Medicine*, 349, 60, 2003. With permission.

Note: ENaC denotes epithelial sodium channel.

cases, may not identify the reason or provide diagnosis based on that data, alone. Convergence of diagnostic tools is necessary to further any decision on such diagnosis. Current tools and tests may gradually undergo changes with the emergence of personalized healthcare, made possible by sequencing of the human genome [92] and development of genomics-based tools [93] (see Section 8.3.4).

The illustration in Figure 8.5 has yet another dimension that is particularly important in global healthcare, especially for emerging and developing economies where the number of and access to medical experts are limited. The goal is to support local data analysis either with information or connectivity that may enable access to experts, opinions, and resources. Various efforts to deliver information [94] through ICT [95] have been pioneered [96]. However, there is room for further advances with diffusion of broadband and other high-speed networks to the far corners of the world. It may transform the vision where a patient in a remote village clinic in Malawi may have access to an electrocardiograph (ECG) or low-cost Ring Sensor and can transmit that data through a standard network or innovative 3G system [97] that offers mobile phone service even from airplanes, during flight [98]. In the village in Malawi, a nurse practitioner may be the only medical professional in the clinic and may be unable to decipher the ECG and hence incapable of suggesting medication. It is here that the value of the transmitted ECG data becomes obvious. Through a consultancy network, on the other end of the world, a cardiologist [99] may review the data and diagnose cardiac arrhythmia due to repolarization abnormality (clinical effect) causing Long-QT syndrome [100].

This simple example and other types of analysis, which, in addition to connectivity, may also require computational power, for example, analysis of brain activity data from magnetoencephalography (MEG), may immensely benefit from grid computing [101]. Advances in microfabrication of atomic magnetometers could enable the development of precision magnetic resonance imaging (MRI) systems for self-monitoring, in any location [102].

The striking benefits that may emerge from the trinity of grid infrastructure, remote MRI monitoring, and intelligent or expert data analysis (AGRMIA) may be appreciated in view of the fact that mental health anomalies often display signs that may resist diagnosis due to lack of adequate expression of symptoms. Individuals may even fail to recognize that something is amiss because the rate of increment in the expression of some mental health conditions may be infinitesimal and over several years or decades. It may not be uncommon that individuals may even adapt to these changes as "age relevant" rather than differentiating them as potential symptoms of a disease and demanding medical exploration or treatment. Personal MRI devices coupled with microfabricated MS may create the remote ms-MRI personal monitoring device that could work as a noninvasive wearable wireless sensor that can be placed on the head to fit as a swimming cap. This development shall unleash a new horizon in "being digital" [103] in personalized medicine. In particular, remote monitoring using ms-MRI sensors may be instrumental for early detection of biochemical changes in the brain, either sporadic or due to aging.

The immeasurable value of ms-MRI remote sensors may be best illustrated by Alzheimer's disease. It is a condition where the activity of the choline acetyl transferase (CAT) enzyme, responsible for the synthesis of acetylcholine, shows a 60%–90% decrease [104]. Acetylcholine is a key neurotransmitter and a marker for cholinergic neurons. The ability of ms-MRI to detect and profile (using MS) biological and biochemical molecules is the driving technology to determine the shape and concentration of acetylcholine molecules and hence by extrapolation determine the activity of CAT. The biochemical identification of molecules (and in future identify differences in the structure or shape of the molecules) is critical in Alzheimer's disease and ms-MRI is one promising tool that is amenable to work as a wireless sensor for remote monitoring. The choice for ms-MRI over conventional MRI is based on the fact that conventional MRI only identifies physical structures. Recent developments in functional imaging using MRI have created the functional-MRI (fMRI) that can identify the rate of blood flow within a physical structure or area in the brain. Hence, fMRI may be useful to monitor learning disabilities where external stimuli may fail to activate certain regions of the brain, suggesting abnormalities. However, in Alzheimer's disease, the biochemical loss of enzyme activity of choline acetyl transferase occurs in the cerebral cortex, hippocampus, and related areas, but cell counts of the neocortex and hippocampus of patients with Alzheimer's disease did not reveal major reductions in numbers of cholinergic neurons when compared with age-matched controls. Thus, for the purpose of early detection, individuals developing Alzheimer's disease may appear "normal" by conventional MRI analysis since the physical structure of the potentially affected areas of the brain remains unchanged as far as the numbers of neurons are concerned. The formation of plaques in the brain of patients affected by Alzheimer's disease may be detected by MRI. Remote monitoring using ms-MRI wireless sensors may be also applicable to other conditions related to changes in neurotransmitter-related proteins and molecules in the brain, for example, Parkinson's disease, Huntington's disease, and some forms of dementia.

The adoption of these developments in personal remote monitoring of mental health coupled with the ability of individuals to obtain an expert opinion by transmitting the data as well as learn about the implication, of the changes recorded over time, may help determine a medical management plan that may improve the individual's quality of life. The analysis of data may require computational resources that may be unavailable in many locations, even in affluent nations. The ability of the transmitted data via the local network to access "medical grid"-based expert services offers immense benefits. The access to these resources through the network and medical grid services, even from the developing nations [105], can reshape the fabric of global mental health.

In addition to MRI, grid computing has the potential to add remarkable value to other forms of remote biomedical imaging systems as well as bio-telematics [106] since current operations [107] are limited to groups [108] that engage in stand-alone point-to-point systems [109] without the benefit of a platform to aggregate medical grid type services. Bringing together this platform may be similar in effort to creating the GRM and is expected to be a part of the GRM (Figure 8.2) that may run on a grid infrastructure. Several biomedical imaging databases are in existence, and taken together, they may form a biomedical imaging platform (BIP) tethered to a proposed "bMDs" services infrastructure [110] through an accessible open format where images (data) may be uploaded from anywhere in the world and viewed (analyzed) by expert(s) who will share observations and/or deliver their interpretation or diagnosis directly to the patient or the healthcare service provider. Tools for simulation and visualization are important and significant advances [111] can be resourced. Agents embedded in the architecture may monitor, device to device (D2D), machine to machine (M2M), and device to system (D2S) or vice versa (S2D), medical data to ensure data security and privacy issues.

Progress in the AI vision of autonomic computing may gradually transform BIP, either independently or in combination with an AGRMIA type infrastructure. Inclusion of embedded intelligence may provide opinions or recommendations or diagnosis or referrals (exception management) without active human intervention. The latter should be welcome news to the aging population in Europe and Japan who wish to remain independent and live in their own homes rather than in long-term healthcare communities that can drain national healthcare resources. Nations may be prudent to explore ms-MRI type high technology medical practices and find new ways to think about diseases [112] with long-term impact and challenge the medical governance [113] to reduce cost by investing in and accelerating the convergence of medical knowledge and engineering technologies. The convergence proposed in bMDs shall include advances such as ms-MRI remote monitoring platforms and may be a part of future healthcare tapestry.

Thus, grid computing is an enabling technology for healthcare service connectivity in much the same way that grid can facilitate business services [114]. In healthcare, as in business, grid computing may provide access to on-demand computational resources (that are in a different location) for real-time data processing and analysis, through grid-based tools, such as Globus [115].

8.3.4 Innovation in Wireless Remote Monitoring and the Emergence of Nano-Butlers

Nano-butlers is a facetious term but is expected to convey an "image" to suggest that nano (small)-tools and technologies act as "small butlers" serving the demands of healthcare. (Their "fees" are also small; hence, they work for "micro" payments.) The "tongue-in-cheek" image is expected to create an awareness that the detection of biological molecules including proteins or peptides at nano levels may be critical for the identification of biomarkers that may be associated with the risk of a disease. When the investment to develop nano-detection is recovered (return on investment) from the savings from reduced acute-care responses, if may be, the actual cost of nano (small)-detection will be small enough to enable global diffusion of the tools, which can be sustained by micro (small) payments, mimicking the concept of micro-finance that has gained global acclaim [116] for alleviating poverty in some parts of the developing world. This approach, due to the inclusion of the term "nano," may also draw some unfounded attention [117].

Early risk identification, prior to detectable symptoms, offers the potential to develop a management plan to contain the disease or even stop it from presenting any symptoms. This approach reduces the acute-care response that may be necessary if the condition was not detected and left unattended. A&E responses and acute-care are far more expensive and often increase morbidity and mortality if the response fails to be administered in near real-time. For example, from the time of onset of a cardiac attack, there is only a 30 min window for successful administration of tissue plasminogen activator (TPA) to dissolve clot(s) if a patient with CVD or stroke is the victim of thrombosis (blood clot). It is likely that more than 30 min may elapse between recognizing that a person is having a "heart attack" and the arrival of A&E services at the location, assuming not only that the paramedics will correctly diagnose the reason (clot) but also that they will have an inventory of TPA-type drugs in their mobile unit (ambulance). It is also assumed that the person is coordinated and coherent enough to call to A&E services if the individual is alone in the location.

Prevention through preventative healthcare may require, in the above scenario, the convergence of wireless sensors with remote monitoring technologies and data-driven analytics based on biomedical research knowledge bases. Advances in understanding the basic physiological, biochemical, and molecular relationships (Figure 8.6) that contribute to heart disease [118] offer hope for rigorous early detection mechanisms. There is ample evidence both from basic biological sciences [119] and clinical research [120] that early warning signs of CVD are amenable to identification from research on biomarkers. Several biomarkers for CVD are already in the market [121], but the commercial "kit" approach is far from the innovative potential of next generation diagnostics [122].

Innovation in detection is based on the generally applicable principle that physiological systems respond to thresholds. In other words, few, if any, reactions occur in the human body or fetus without a critical mass or concentration of molecules. If allowed to reach the "threshold" only, then the "rogue" molecules may trigger a cascade of events, which may, eventually, over time, present itself as a detectable symptom. Hence, molecular identification of the biomarkers and rogue molecules is vital for noninvasive detection. Tools for detection require convergence of the knowledge from identification of molecules from biomedical research with engineering-based detection technologies to determine the number and concentration of the molecules, beginning at the single molecule [123] level or at the pico (10–12) level, but most reliably at the nano level. A medical management plan or treatment must exist to prevent the concentration of the molecules from reaching the threshold, where it may commence the cascade of events leading to a disease or symptom or precipitating a heart attack. In case of fetal diagnosis, the management issues may be complex, but the early detection of sporadic or genetic diseases of the

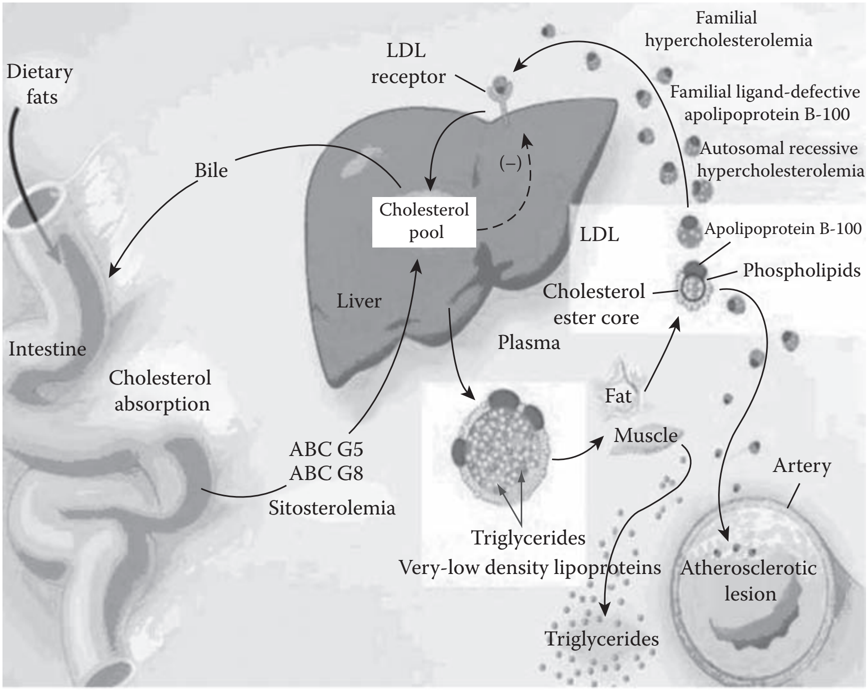

Figure 8.6 Components of cholesterol synthesis and excretion. (Reprinted from Nabel, E.G., *N. Engl. J. Med.*, 349, 60, 2003. With permission. © 2003 Massachusetts Medical Society. All Rights Reserved.)

unborn child may offer scope for medical intervention. Foolproof identification of specific biomarkers for multi-factorial diseases such as CVD is complex. Without reliable specificity, the next generation nano-diagnostic tools may offer less value. Therefore, the healthcare industry must remain vigilant to combine advances in one field with another through parallel investments both in medicine and engineering.

To illustrate, let me revisit the case of blood pressure (BP) measurement and what diagnostic information the BP data may provide if the BP is elevated, lower, or normal, compared to the standard reference. In short, the BP data, alone, provide little diagnostic value unless they are analyzed in conjunction with existing case history or other data. One reason for this is summarized in Table 8.1. If a definitive diagnosis of the BP data is sought, in some patients, it will be necessary to identify which particular gene is affected.

Sequencing of the human genome and advances in search tools and genomic technologies [124] makes it possible to extract the DNA sequence from the Human Genome Database [125] of the genes implicated in a disease (e.g., genes that may elevate or lower blood pressure). Based on the DNA sequence, anti-sense RNA may be used to determine gene expression profile. By extrapolation from the DNA sequence, protein-based peptide fragments can be synthesized for use in noninvasive proteomics-based microarrays, using the lab-on-a-chip wireless sensor, to detect expression levels of one or more proteins and/or their mutant variations, in body fluids, that may be involved in the etiology of the condition under investigation. Based on the gene and protein expression profile, in some cases and some diseases, the promise of gene therapy may be realized by "silencing" harmful candidate genes using RNAi [126] and snRNA techniques that are already under intense commercial exploration and have reported some degree of success [127] for future therapeutic applications.

This scenario, starting with a possible gene, followed by expression profiling data remotely monitored by a wireless sensor and potential for selective silencing therapy of the disease, is a part of the evolution likely to chart the future of individualized medicine and personalized healthcare. The value and impact of this approach may not qualify as a "disruptive innovation" [128] but may reflect the systemic lessons from the age of introduction of the electric dynamo, at the turn of the twentieth century [129], the wisdom of which may have been ignored by other emerging technologies [130].

The pragmatic credibility of this vision garners support both from current practices, albeit in part, and information based on recent research that clearly points to the need for this vision. Current practices already use one or more of the steps outlined in this strategy, for example, the use of genomic [131] and proteomic biomarkers in the diagnosis of CVD [132] and some forms of cancer [133]. But even more important support for this vision draws on seminal medical research [134] that has identified one single human gene, for low-density lipoprotein (LDL) receptor-related protein 6 (LRP6), that is involved in the etiology of a specific type of CVD, referred to as coronary artery disease (CAD). It is a leading cause of death worldwide, and early detection is essential to save lives.

CAD is commonly caused by a constellation of risk factors called the Metabolic Syndrome, the symptoms of which include hyperlipidemia, hypertension, diabetes, and in addition, osteoporosis. Analysis of LRP6, the gene identified as responsible for CAD, has uncovered a single nucleotide substitution that changes the wild-type (normal) cytidine base to thymidine. This single nucleotide missense mutation, located in the protein-coding region (exon 9) of the human gene for LDL LRP6, causes a single amino acid substitution, which inserts the amino acid cysteine to replace the normal counterpart, arginine, at codon 611 (R611C). The importance of this finding and the fundamental significance of the LRP6 gene in human evolution are further highlighted by the extremely high degree of conservation of the protein sequence from humans to amphibians, such as frogs (*Xenopus laevis*). Among the species surveyed, the amino acid arginine (R) is conserved from frogs to humans (Table 8.2). Substitution of arginine with cysteine (R611C) creates havoc and results in CAD and accompanying diabetes, hyperlipidemia, hypertension, and osteoporosis.

Table 8.2 Conserved Amino Acid Arginine (R) Is Substituted in LRP6 Gene and Causes Heart Disease

Human	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Chimp	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Monkey	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Mouse	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Rat	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Dog	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Cow	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Opposum	C	L	Y	F	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Chicken	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	L	E	L
Frog	C	L	Y	F	P	Q	G	P	R	C	A	C	P	I	G	L	E	L

Genomic technologies can help identify R611C mutation in at-risk populations even in the fetal state since this LRP6 is transmitted as an autosomal dominant trait. Lifelong management plan for inherited genetic diseases, for example, phenylketonuria, is common. Individuals homozygous for R611C, if diagnosed early, may follow a recommended lifestyle that may enable them to enjoy normal life expectancy. The evolutionary conservation of LRP6 gene and its protein product indicates a fundamental role of this protein in physiology. Indeed, LRP6 is involved in cellular signaling pathways, disruption of which leads to a plethora of problems. Proteins and other molecules, referred to as transcription factors [135], are often conserved and fundamental to gene expression [136] from bacteria to humans. Transcription factors can alter gene expression positively and negatively [137] or may serve as secondary or tertiary targets [138]. Early detection of nonfatal mutations in transcription factors is warranted because they may also cause profound physiological disturbances and present multiple symptoms, related in scope to mutation in LRP6.

While the case for early detection of genetic diseases needs little emphasis, the need for early detection of the bulk of sporadic cases such as type II diabetes mellitus and several other disease states deserves emphasis. Globalization has also created a need for remote monitoring. To make globalization work better for the world economy [139] it is imperative to contain infectious diseases by determining the risk and at-risk factors at the origin rather than at an immigration check-point of a country. The lightning spread of SARS, from its origin in Hong Kong to Toronto, in a few days, highlights the need for remote monitoring tools and the vulnerability of current healthcare system (in most nations) that is ill-equipped for global challenges and may actually aid an epidemic or pandemic.

Epidemics, however, are no longer limited to only infectious diseases. Type II diabetes may reach nearly epidemic proportions in many nations. It is alarming in some countries, where, despite a small population [140] a high number of sporadic cases of diabetes are documented. In addition, an equally high number of projected at-risk population are acknowledged, but the latter estimates exclude the segment of population projected to be defined as clinically obese. That can potentially increase the at-risk numbers for sporadic type II diabetes but remains unaccounted by the system. Individuals with other anomalies may also have diabetes, as pointed out in course of the discussion on LRP6 where heart disease and diabetes can occur simultaneously. Recent evidence suggests that in individuals without any genetic predisposition, there may be a direct effect of elevated cholesterol level on reducing insulin production by the β (beta) cells in the pancreas [141]. This increases the risk of diabetes for obese as well as for non-obese individuals who have elevated levels of cholesterol, without genetic predisposition.

Diagnosed diabetics often monitor their blood glucose levels using over the counter kits but its use in preventative healthcare remains dubious. For diabetics, the frequency of testing using kits is weekly or daily but expert interpretation and advice may be far in between. Let us assume that a weekly outpatient visit to the clinic for blood glucose test and insulin therapy costs the healthcare service an average of $25 in direct cost and costs the economy another $25 in indirect costs, such as the cost of time spent by patient, cost of travel and decrease in productivity due to time taken off work by patient. If only 1% of the population require weekly attention (serious diabetics), then for a hypothetical nation with a population of 5 million, there will be 50,000 diabetics requiring this attention. For 50 visits a year at $50 a visit, the attention to 50,000 diabetics for simple monitoring of blood glucose and administration of insulin, will cost the nation $125 million per year. The focus on those who need it the most aggravates the unattended conditions in other diabetics and at-risk population, driving them to seek acute-care services or catapulting them to the $50 category. However, a far greater concern is the need for inpatient services if some of the diabetic patients need hospitalization. Can the national healthcare system respond adequately [142] if only 1% of the 50,000 diabetics (that is, 1% of the 1% documented diabetics in the population) need hospital beds? For example, in Ireland, overall, there are 2.9 beds available per 1000 people [143].

Preventative remote monitoring can alter this vicious cycle of crisis, reduce cost, and improve actual care.

Apart from individuals who are obese or juvenile diabetics or those with history of genetic predisposition to early onset diabetes, the definition of "early stage" in monitoring is rather vague for sporadic diabetes. There is little scientific rationale either to include or to exclude young adults and individuals with dynamic vivacity in the prime of their life and in their 40s or even younger. Hence, effective monitoring of blood glucose that is not shunned by the otherwise healthy population may require a lifestyle approach that offers a product and service that are easy to use, of low risk, of low maintenance, socially acceptable, of robust value, safe, and medically effective. Since the adoption of this device may be voluntary, it may be less attractive if the monitor is a visible wearable [144] or a "thing" that an individual must "remember" to do. Thus, nanotechnology-based [145] monitoring tools may function as "always-on" wireless nano-sensors which remain under the epidermis. It may make blood glucose monitoring of general population an attractive modus operandi for early risk identification and prevention of diabetes as well as associated morbidity, such as diabetic glaucoma, which can lead to partial or complete blindness in severe diabetics or juvenile diabetics, if left untreated.

Early detection of diabetes as a function of monitoring blood glucose concentration benefits from a plethora of glucose sensors developed over the past 25 years, but challenges still exist. A key advantage in the development of a miniaturized or nanoscale device that can quickly and reliably monitor glucose in vivo, is based on the fact that the level of blood glucose detection does not require nano-level detection. The benefit of a nano-device or nano-sensor is to make the monitoring tool virtually unobtrusive to the user. The normal clinical range for blood glucose is in the millimolar (mM) range between 3.5 and 6.1 mM, but abnormal glucose levels may reach 20 mM. This concentration range can be easily monitored using electrochemical reactions. What is critical for diabetes is a tool that does not deter early-stage frequent vigilance about the changes in blood glucose levels, also measured in milligrams per deciliter of blood. Alterations may signal the ability or inability to maintain the standard equilibrium concentration of glucose (120 mg/dL or 3.5–6.1 mM). For example, if the blood glucose concentration in an individual takes longer to return to normal after meals, then it may signal germinating problems with glucose clearance and/or tolerance in the individual.

The innovation required to develop a wireless blood glucose nano-sensor that is capable of subcutaneous monitoring of blood glucose and transmission of the data to a wireless node may be simple and at hand. The core components are a nano-sensor [146] capable of detecting blood glucose concentration in vivo and a nano-radio [147] that can transmit the data. The combination is illustrated in Figure 8.7.

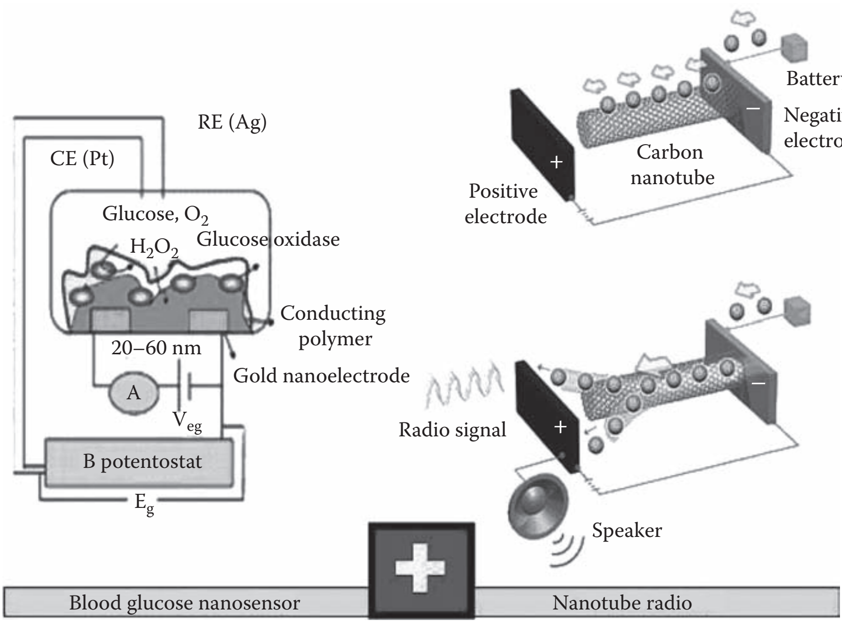

Figure 8.7 Blood glucose monitoring and wireless data transmission 24.7.365. (Adapted from Forzani, E.S. et al., *Nano Lett.*, 4, 1785, 2007; Jensen, K. et al., *Nano Lett.*,7, 3508, 2007. With permission. © 2007 American Chemical Society.)

The open questions presented by this innovative potential may be divided into two broad categories: data acquisition and data transmission. The issues are as follows:

1. Glucose sensor data transmission by the nanotube radio illustrated in Figure 8.7 and other similar [148] devices is not proven because they are constructed as receivers, not data transmitters. But, in general, single-wall nanotubes (SWNT) are like single-mode fiber for electrons (Figure 8.7) and hence have data properties that were made to act as a receiver (Figure 8.7) for the nano-radio but may be altered to transmit the acquired data from the glucose sensor.
2. Functional co-fabrication or simply co-locating or "housing" glucose nano-sensor and data transmitter on a nonallergenic matrix or platform suitable for use as a subcutaneous implant.
3. Optimizing signal-to-noise ratio.
4. Interference minimized nano-communication link to wireless sensor node.
5. Physical locations for safe subcutaneous insertion per customer preference.
6. Procedure for safe extraction of sensor device with minimal discomfort.
7. Foolproof immobilization of implant.
8. Containment of degradation or breakage of components within the housing of the nano-device.
9. Customer's ability to "forget" about sensor implant.
10. Customer control (agent-based web tool) over function of the device.
11. Customer control over data transmission or modulating the frequency of monitoring.
12. Low maintenance of sensor and transmitter.
13. Battery life of transmitter.
14. Explore use of electrolyte gradient of the body or energy from movement to power data transmission.

The responses to the open questions are beyond the scope of this chapter, but the different mechanisms of detection by sensors are important to review, briefly, because wireless nano-communication must be an integral part of the sensor or sensor combination in order to reliably transmit the data outside the body.

The glucose sensor in Figure 8.7 detects glucose based on principles of electrochemistry. The assumption is that the sensor will perform in vivo as well as it has performed in body fluids tested in vitro. Specific detection of glucose is mediated by glucose oxidase, GO_x, an enzyme (hollow circles with pink borders, Figure 8.7) that is immobilized onto PANI-PAA, a conducting polymer (green area, Figure 8.7) made up of polyaniline (PANI) polymerized with PAA (poly{acrylic acid}). Upon exposure to glucose, GO_x, with the help of a natural coenzyme, flavin adenine dinucleotide (FAD), catalyzes the oxidation of glucose to gluconolactone and becomes reduced, $\{GO_x(FADH_2)\}$, Step 1. The reduced GO_x form, $\{GO_x(FADH_2)\}$, is regenerated via reoxidization by oxygen (O_2) in solution to GO_x(FAD) and produces hydrogen peroxide (H_2O_2), Step 2. Polyaniline, which exists in its reduced (red) state (PANIred), is oxidized (ox) by H_2O_2 to PANIox and triggers an increase in polyaniline conductivity (Step 3) due to the sensitive dependence of polyaniline conductivity on its redox state. This change of conductivity is data, indicating glucose detection.

Step 1: Glucose + GO_x(FAD) → gluconolactone + GO_x($FADH_2$)
Step 2: GO_x($FADH_2$) + O_2 → GO_x(FAD) + H_2O_2
Step 3: H_2O_2 + PANIred → H_2O + PANIox (increase in conductivity)

Other types of construction use carbon nanotubes (CNT) but may still use the electrochemical principles for detection of glucose on a CNT scaffold (instead of PANI-PAA, as shown in Figure 8.7). Nano-wires [149] represent one such type of construction. Nano-wire-based glucose biosensors [150] use CNT nano-electrode ensembles (NEE) for selective detection of glucose based on the high electro-catalytic effect and fast electron-transfer rate of CNT but employ the same electrochemical mechanism described above. GO_x, glucose oxidase, is immobilized on CNT-NEE, instead of PANI-PAA, via carbodiimide chemistry by forming amide linkages between the amine (NH_2) residues and carboxylic acid (COOH) groups of the enzyme, GO_x, covalently linked to the exposed tips of single CNT, illustrated as perpendicular black bars in Figure 8.8 (center). Numbers of CNT on a CNT-NEE are in the millions, with each nano-electrode being less than 100 nm in diameter, thereby, increasing sensitivity of the sensor (by analogy, the speed of a processor, e.g., Intel Pentium, is a function of the number of microprocessor circuits etched on the chip). The catalytic reduction of hydrogen peroxide liberated from the enzymatic reaction of glucose oxidase covalently immobilized on the CNT-NEE, in the presence of glucose and oxygen, leads to the selective detection of glucose. CNT are excellent electrochemical transducers, and each CNT serves as a nano-electrode that detects the change in current (conductivity) when glucose reacts with GO_x-linked CNT (the coupling drives the specificity of glucose detection) in a CNT-NEE sensor. The sensor effectively performs a selective electrochemical analysis of glucose in the presence of interference from common molecules, for example, acetaminophen {AA}, uric acid {UA}, and ascorbic acid {AC}, shown in Figure 8.8 (top panel). But most important, the sensor is sensitive to increments of glucose. Detecting fluctuations in concentration of blood glucose is the key to early detection in diabetes (Figure 8.8, lower panel and inset).

It is relevant to note that nano-wire sensors that detect changes in chemical potential, accompanying a target or analyte binding event, such as DNA or RNA hybridization, peptide interactions, or oxidation reduction in electrochemical reactions, can act as a field effect gate upon the nano-wire, thereby changing its conductance. This is similar, in principle, to how a field-effect transistor (FET) works [151].

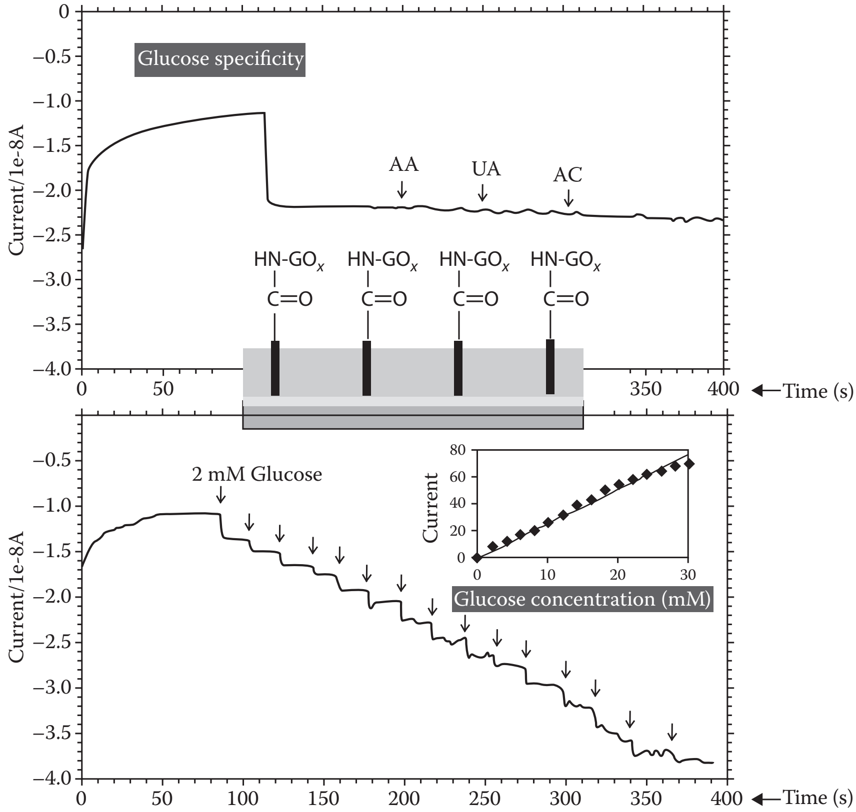

Figure 8.8 Nano-wire glucose sensor shows glucose specificity and sensitivity to concentration. (Adapted from Lin, Y. et al., *Nano Lett.*, 4, 191, 2004. With permission. © 2004 American Chemical Society.)

Today, FETs are low cost and in extensive use in environmental and agricultural monitoring. Advances in technology have made the expensive electronic marvel of a "transistor radio" of the 1950s only suitable for infant's toys mass manufactured in China and sold in discount chains. The transistor radio has evolved to dirt cheap FETs now used in animal farms to alert owners that the stench from the ammonia-rich waste from animal excreta in the holding tanks needs attention. The expensive transistor of yesterday is a low-cost (or no cost) component today that delivers significant value for environmental monitoring. It benefits the meat industry at such a negligible cost that it has only increased productivity of the meat industry and concomitant increase in global consumption. The evidence for the latter is gleaned from the beef and chicken consumption data from the United States and EU that exceeded 120 kg per person per year (330 g/day) compared to 16 kg per person per year (44 g/day) in China and India, combined [152].

Knowledge from research and applications of FET are available from archives that may date back to the initial discovery of transistors [153], nearly 70 years ago. The development of nano-wire, nano-sensors, and nano-communication may benefit from the experience and wisdom of the FET pioneers.

The principle of FET indeed may be crucial for nano-communication for wireless transmission of data from the in vivo sensor to a sensor communication link or node outside the body that can connect to the Internet. The characteristic of a CNT to act as fiber that can transport electrons is under scrutiny in order to use the material for high-speed data transmission in a variety of ways that includes the emerging field of plasmonics [154] that studies interactions between light and nanoscale particles and structures. Remote monitoring in vivo that may take advantage of light-emitting luciferase [155] enzyme-linked sensors, by immobilizing luciferase (on PANI-PAA matrix or) preferably on CNT-NEE type scaffolds, may find it useful to exploit the potential of nanoscale antennae that converts light into broadband electrical signals capable of carrying approximately one million times more data than existing systems [156].

The illustration in Figure 8.7 is simple to understand and conveys the image of the components necessary to drive the convergence of in vivo detection and transmission of data. But, caution is necessary to extrapolate the application of the components illustrated in Figure 8.7. Although it may be ideal for visualizing the concept, the components illustrated are not proven or guaranteed to be the combination of choice that could drive the development of an in vivo nano-device that is equally reliable as a detection tool and a nano-communication tool, for reasons that I shall explain in the next few paragraphs. But of course that argument holds for any innovation. We shall not know the outcome unless we attempt to create the device if there is even "just enough" reason that the innovation may bear fruit. Reasonably, one issue in the glucose nano-junction sensor is that it does not use nano-materials, that is, in this case, CNT, in its construction. Nano-wire glucose biosensors use CNT as the nano-electrode, as shown in the CNT-NEE sensor illustrated in Figure 8.8 (center). This may be an issue in terms of the ability to transmit the data out of the body.

If the nanotube radio receiver illustrated in Figure 8.7 can be modified or designed as an in vivo transmitter and if it can successfully detect the data emerging as the change in conductivity between the two states of PANI (PANI reduced versus PANI oxidized, as shown in Step 3) from the non-CNT glucose nano-junction sensor illustrated in Figure 8.7, then the nano-device may be produced, by the combination illustrated in Figure 8.7, for wireless in vivo glucose monitoring.

The preference for CNT-based sensors like CNT-NEE (Figure 8.8, center) is linked to the central need to transmit the data from the in vivo sensor and the potential for using individual nanotubes within CNT networks to carry information. Innovation in nano-communication using CNT communication network [157] is likely to become a core competency necessary for the future of nano-device use in healthcare, in general. It is in this context that the principle of field effect transistors (FET) springs back into action. Current technology utilizes an entire CNT network as semiconducting material to construct a single FET. Several FETs are required to build traditional or legacy network equipment. The result is that there are many nanoscale networks embedded within each device (FET) that might be otherwise more effectively utilized for communication. In other words, the CNT network itself is the communication media, and individual CNT are the links. But, individual CNT and tube junctions (forming nodes) do not have the equivalent processing capability of a traditional network link and network node. To compensate for this, the system needs to leverage large numbers of CNT. The illustration in Figure 8.8 (center) shows individual CNT linked to GO_x (black bars), but millions of CNT (black bars) make up an ensemble (CNT-NEE). The latter is precisely what is necessary for the single-wall CNT communication network (NanoCom) of the future. However, NanoCom may not function according to the traditional architecture of data communication layers [158]. Comparison of legacy communication and NanoCom highlights the changes necessary, as shown in Table 8.3.

At the bottom level (least sophisticated level), communication links may be between hosts and routers in a communication network, or they may be CNT overlapping at points that will be identified as nodes. A network functions by changing state. Data must either flow or be switched or routed through nodes. State may be implemented as a routing table on a router or an electromagnet field controlling the resistance within a specific area of a CNT network. Finally, a mechanism needs to be in place to control state (ascending level of sophistication, Table 8.3), be it a routing algorithm or FET gate voltages applied to a CNT network. The traditional networking protocol stack is inverted in this approach because, rather than the network layer being logically positioned above the physical and link layers, as in the

Table 8.3 NanoCom Requires Modification of Current Networking Concepts

Basic Network Components	*Traditional Networking*	*Nanoscale Networking*	↑
Protocol	Processors	Gate control	
State	Node memory	Semiconducting tube resistance	
Network	Links	Nanotubes	Increase in conceptual sophistication

Source: Bush, S.Y. and Li, Y., *Nano-Communications: A New Field? An Exploration into a Carbon Nanotube Communication Network*, Technical Information Series, GRC066, GE Global Research Center, Niskayuna, NY, 2006. © 2006 Inderscience.

standard OSI model [159], the CNT network and routing of information are an integral part of the physical layer.

Data transmission in a CNT network occurs via modulated current flow (changes in conductance) through the CNT network guided towards specific nano-destination addresses. The addresses identify spatially distinct areas of the CNT network that may be made up of nanosensor arrays. Since gate control is used to induce routes through the CNT network, nano-addresses are directly mapped to combinations of gates to be turned on that induce a path from a source to a destination. Is the "combination of gates" in any way analogous to the network, subnet, host type of partitions that specify a 32-bit IPv4 address of the type 151.193.204.72 or the 128-bit IPv6 format 21DA: 00D3: 0000: 2F3B: 02AA: 00FF: FE28: 9C5A (or equivalent 21DA: D3: 0: 2F3B: 2AA: FF: FE28: 9C5A with leading zero suppression)?

Does nano-addressing require an entirely new scheme for unique identification? Is unique identification necessary at the level of individual nano-addresses? If necessary, is a relativistic identification of information [160] necessary? Are "source" and "destination" comparable to client–server architecture?

These and several other open questions are likely to emerge. Figure 8.9 illustrates a conceptual network view of the CNT infrastructure. Superimposed on NanoCom are some of the medical benefits that make CNT-based sensors and data communication a powerful ally for healthcare improvements.

Diabetes is not the only disease that merits prevention and monitoring. For early detection and monitoring, several other diseases qualify prominently. Sensor

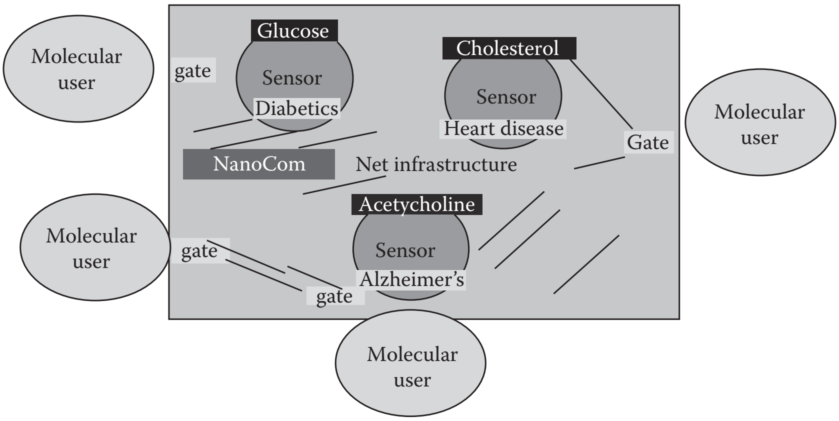

Figure 8.9 NanoCom transmits data for multiple biomarkers from in vivo sensor nano-array. (From Bush, S.Y. and Li, Y., *Nano-Communications: A New Field? An Exploration into a Carbon Nanotube Communication Network*, Technical Information Series, GRC066, GE Global Research Center, Niskayuna, NY, 2006. With permission. © 2006 Interscience.)

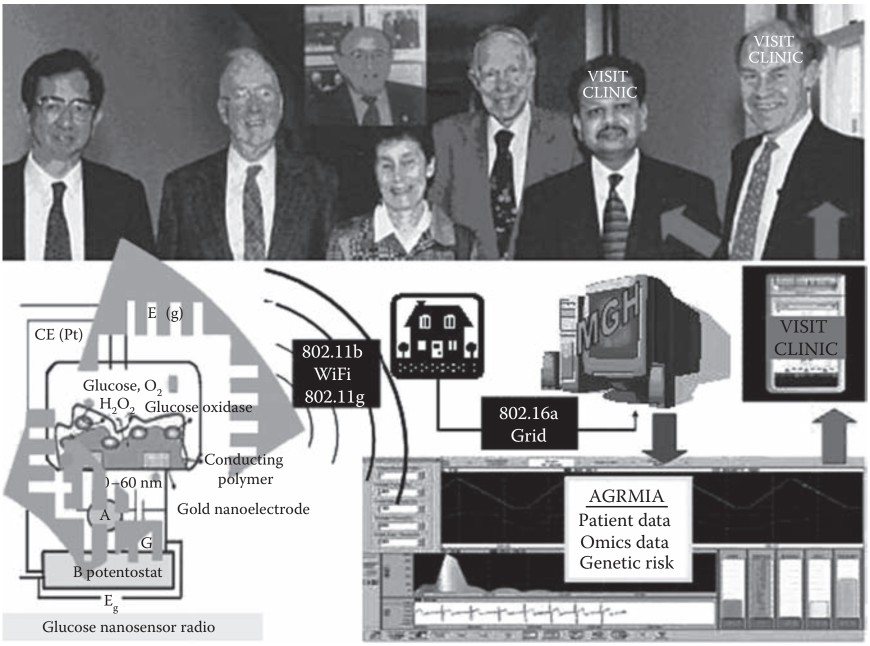

Figure 8.10 Improving healthcare from the home to the hospital: "sense, then respond."

nano-arrays may be one answer for a multifunctional detector, as conceptualized in Figure 8.10. Sensors constructed from nanotubes change their resistance based on the amount and specificity of the material or biomarker detected (sensed). Thus, the act of sensing may change the routing through the NanoCom network. In other words, in a staggered approach, the duty cycle and/or the sleep time [161] of the different CNT nano-sensors can be regulated to allow any one sensor to function in a specified interval and detect or sense its specific analyte (glucose, cholesterol, or acetylcholine, Figure 8.9). The change in the properties of the CNT, when the act of sensing is in progress, opens the appropriate "gate," and when a gate is turned on, the nanotubes within the gate area become conducting. Then, the data acquired for that specific sensor are transmitted to an external node. For complex diseases, where multiple pieces of data and vital signs may be necessary to make an informed decision, either by humans or initially by an AI-based intelligent analytical system (AGRMIA, Figure 8.2), properly choosing the sequence of sensor, hence gates, to turn on, changes the current flow to the edges of NanoCom, the CNT network. The latter effectively creates a controlled NanoCom, which may act as or provide weights in a neural network for AGRMIA type system requiring a collection of different biomarker data, to determine the relative impact or relationships or values of variables that may be co-integrated [162], which, if taken together, may better reflect the state of the patient and the status of the disease. The Metabolic Syndrome caused by the mutation in the LRP6 gene may be an example of a multi-factorial disease where multiple conditions are affected and may require simultaneous monitoring.

Although this chapter, thus far, may have synthesized a number of promising practical ideas, far better and innovative ideas and concepts about products and services, than the ones mentioned here, have perished. Rarely acknowledged is the observation that no matter how good an idea may be, it may only shine in obscurity unless there is a strategic plan that charts an appropriate use and adoption path in context of other complementary technologies and social awareness of its value. A common example is the introduction of the first hand-held "Newton," the personal digital assistant (PDA), from Apple that few may recall. Apple only sold 140,000 Newton PDAs at its peak in 1993–1994 and soon discontinued production. A few years later, 3Com introduced the Palm Pilot PDA with features that were even primitive to Apple's Newton but with the option of Internet access. Today, it may be hard find anyone in the industrial world and professionals in the developing world who do not have a PDA, of some form or the other. The "social awareness" of the value of PDA accelerated with the penetration of the Internet. Newton, RIP, was slightly ahead of its time.

Calls to contain the unbridled cost of healthcare are demanding exploration of tools and technologies. The need for wireless remote monitoring and the use of nano-biosensors in healthcare are as vital as desalination projects, carbon sequestering, metabolic engineering, clean water, and clean air. Hence, innovative tools and technologies must also outline a strategic path for their integration and potential for adoption by healthcare systems without expecting a complete overhaul of the existing system, anytime soon.

The overall strategy for the use of wireless remote monitoring tools and the manner in which it may function in the landscape of healthcare cost reduction (Figure 8.2) is illustrated in Figure 8.10. The time saved by attending to the two individuals identified in Figure 8.10 instead of outpatient visits by seven individuals (Figure 8.10) saves cost of service and supplies and enables healthcare professionals to devote necessary time to those who need the attention, hence improving the quality (QoS) of healthcare.

The normal clinical concentration of glucose in blood is in the millimolar range, and that precludes the need for nano-level detection. However, early detection of other diseases may indeed be far more effective if detection is possible at the nano-level of proteins, peptides, molecules, or degraded macromolecules that may hold clues to problems in their embryonic stages. The task of medical research is to identify these markers, and the task of the technical experts is to find ways to identify these markers through remote sensing tools. Differential profiling of gene and protein expression between normal and disease states may be helpful to identify biomarkers that are only expressed in disease states. The amounts of such disease-dependent biomarkers may benefit from pico or nano-level detection and offer “true” early detection.

Data and detection as components of the systems approach to future healthcare require medical science and engineering technology to create tools linked to systems that may be purchased, as ubiquitous generic plug-n-play commodities, from the local pharmacy or convenience store in a gas station or corner grocery store. Consider the revolutionary discovery of transistors that produced FETs. The field has been shaped by evolutionary market forces over the years, and FETs are now used as low-cost commodities in the design of environmental and agricultural monitoring. It is this trend that Figure 8.7 illustrates, in concept. The value they deliver through specificity and sensitivity is illustrated in Figure 8.8. The strategy for integration and adoption pathway is illustrated in Figure 8.10, which includes one of the key “behind the scene” drivers that may materialize as modular analytical engines of the AGRMIA type collection of resources, illustrated in Figure 8.2, connected on global grids. Taken together, remote monitoring by internal wireless nano-sensors or external sensors (as fashion rings, bracelets, wrist watches) will coevolve and diffuse as a lifestyle approach in healthcare, not because individuals are sick but because they prefer to stay healthy. The healthcare industry may benefit from business advice in order to take advantage of time compression. In other words, the time to market from idea (Figure 8.7) to adoption (Figure 8.10) may be shorter than the decades between the discovery of transistors and the use of FET as a dirt cheap commodity for agricultural and environmental monitoring.

This is the “writing on the wall” for what is in store for remote monitoring by wireless nano-sensors, the nano-butlers, that can deliver value at a reduced cost, for micro-payments, in local and global healthcare. Ignoring the suggestions in this and other reviews or the failure to accelerate the necessary convergence to create the suggested healthcare services as well as support research [163] may lead to chaos.

Healthcare imbalances will continue to proliferate in the United States, and severe consequences are also predicted for EU nations, particularly Ireland. Projected rise in age-related government spending as a share of GDP of Ireland, over the ext 40 years, is among the highest in the euro zone [164]. In the absence of reforms and adequate investments in Ireland, the advances in innovative convergence suggested here may be sluggish, at best. But, the cost of healthcare in Ireland, which is approaching €3000 per capita, may continue to increase (see Ref. [53]). Rising public debt in Ireland may force spending cuts with a concomitant decrease in the quality of life for those who need healthcare services. Cost containment in healthcare services may grossly reduce preventative measures, selective or elective procedures, palliative care, and all nonemergency services. Individualized medicine and personalized healthcare will be a matter of fiction, and A&E type acute-care services may be the healthcare skeleton. Enterprise, academia, and government can prevent this state of affairs.

8.4 Innovation Space: Molecular Semantics

The proposal of molecular semantics, whether right or wrong, does not impact the implementation of nano-butlers. Introducing the concept of molecular semantics as an independent paper may have been prudent, but the preliminary idea merits inclusion in this chapter to indicate the importance of structure in medical science. Current systems, such as EMRS and AGRMIA, may be, in general, incapable of dealing with structures unless dedicated programs are used.

8.4.1 Molecular Semantics Is about Structure Recognition

Classical semantics includes descriptive ontologies and extracting word relationships that form bulk of the thinking [165] prevalent presently to move from the syntactic to the semantic web. Molecular semantics may not be necessary for general usage but may aid special analytical applications in the future to uniquely identify molecular or chemical structures or units of structures or epitopes, in a manner that may have some similarity with the concept of digital semantics (see Ref. [40]). Unique identification of structures may enable diverse systems to compare structures in a catalogue or database with those that may be identified in some disease states, or query, if an identified structure has any known homologies or close similarities to one or more parts of chemical or biological molecules. The significance of partial structures and segments of structures or epitopes in healthcare diagnostics may be better appreciated from the discussion, later in this section, on autoimmune diseases and molecular mimicry [166].

To deliver value in healthcare, part of the solution calls for analytical tools to extract information from data. Healthcare presents three types of data that may need to work together, in some cases:

1. Numerical data in EMRS and AGRMIA platforms may be fed directly to the analytical engines.
2. Syntax from patient history and physician "notes" still on paper is likely to create syntax versus semantics nightmare if transcription is necessary to create EMRs. The syntactic web of today also plagues the business world. The semantic web movement and organic growth of ontological frameworks contributed by experts from various disciplines are continuing their valiant efforts to enable computer systems to "understand" and extract meaning from syntax. In this context, I have proposed a parallel approach to explore semantic and ontological frameworks using an IPv6 type unique identification scheme to enumerate data, information, and decision in a relativistic approach (see Ref. [40]).
3. Molecular patterns may be partially novel and especially relevant for healthcare diagnostics.

This section on molecular semantics is similar yet distinct from "digital semantics" proposed earlier (see Ref. [40]), but both share the concept of unique identification to enable global systems interoperability without ambiguity of identification or errors due to ambiguity in ontological frameworks that may be incomplete. Both proposals, however, are also likely to be incomplete.

The current proposal on molecular semantics addresses the third type of healthcare-relevant data structure, that is, molecular patterns or molecular structures. Organic chemistry and biomedical sciences place a great deal of emphasis on patterns and structures. Hence, it may be worthwhile to dare to forward this new idea of how to enable computer systems to recognize patterns and structures through the use of agreed units of molecular structure that form parts of macromolecules. This proposal freely borrows ideas from seminal works of great scholars but with rudimentary understanding of their depth and without any guilt. In addition to a few building blocks of linguistic theory [167], I have also stretched the outlines of semantic theory and cognition [168], perhaps to an unnatural and unreasonable extent.

Cognition as related to structure in natural language is mapped to the units of molecular structure in biological macromolecules. I have extrapolated the ideas and elements of the linguistic system to fit molecular semantics in a way that proposes the use of molecular units of structures (of macromolecules, such as proteins) as "agreed lexicon" to catalyze recognition and understanding of these structures between diverse systems to aid systems interoperability. However, in my biased view, elements of the linguistic system (Figure 8.11) seem to resonate with the proposal of molecular semantics. But, I shall be the first to recognize that this convergence, however attractive, may not be right, in the form proposed, and admit that it may be in error, if it is.

There may be other ways, but the concept of molecular semantics may be yet another tool to explore this scenario: MS analysis of serum from a patient with unidentified type of fever has identified a high concentration of a short peptide with some ambiguity about its sequence, but it appears that the peptide may be part of a common protein, myelin. First, a GP may rarely send a serum sample for MS analysis. Second, if the MS data are uploaded and an AGRMIA type system is available, is there a tool to compare the MS signature from this patient (MSpat) with other MS data in a database? The data (MSpat) entry point in the linguistic system is the conceptual structure, the EMRS part of the EMRS-AGRMIA system, in this context. The computational resources that may be needed to perform the comparative search, one MS data at a time in the database, may make this approach untenable. If there is a catalogue of unusual MS signatures (MScat) in the form of a (data) dictionary, then, perhaps, it may be feasible to perform this search and determine if a match or close relationship exists between MSpat and a pattern in MScat.

In the linguistic system, the dictionary equivalent may be the Lexicon (Figure 8.11). Is it really necessary to bring the Lexicon into this discussion? The MS data

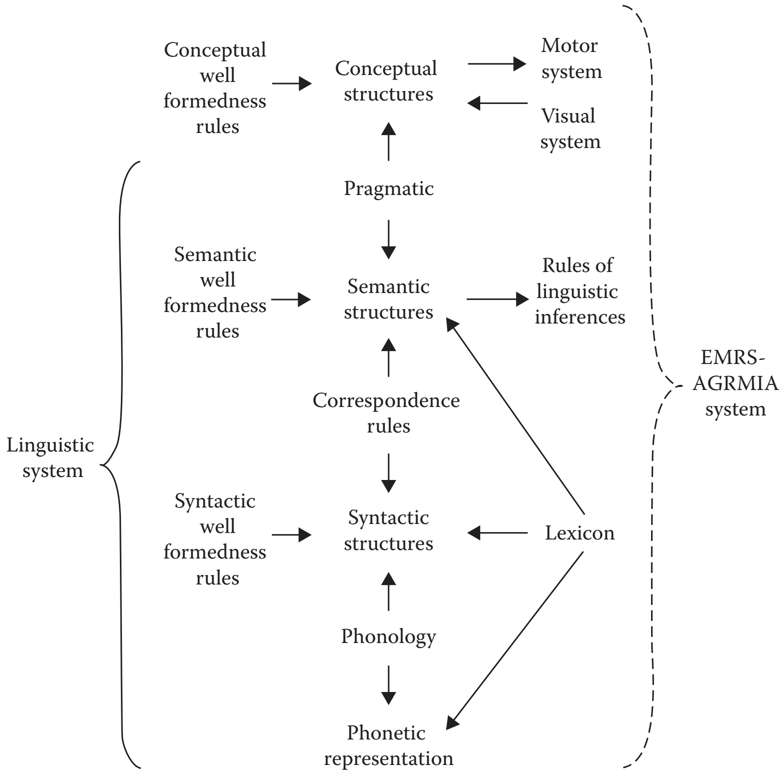

Figure 8.11 Proposed molecular semantics extrapolates concepts from the linguistic system.

and accompanying explanatory notes could also exist in a relational database, and it may suffice for this exploration. The introduction of the Lexicon in this scheme may seem, initially, on shaky grounds, but following the model of the linguistic system, it reasons that if the MS data catalogue (MScat) does exist in a Lexicon equivalent, it may also have links to syntactic structure and semantic structure (Figure 8.11). The wide variation in syntax needs no extra justification. Hence, the difficulty to match syntactic structures with respect to the Lexicon even if it contained a match to MSpat may not be unexpected. But the data (MSpat) could point to descriptions that may be more specific in the semantic structures. It may identify MSpat as belonging to neural proteins (myelin is a neural protein). Once the MSpat data matched to data from the Lexicon (MScat) points to neural proteins in the semantic structure, the correspondence rules could point back to the syntactic structures and identify one or more descriptions of neural proteins that may offer matching segments to MSpat. The real finding is however the match between MSpat and the potential link to myelin that may happen if an extensive MScat is matched by protein sequence and classified in the semantic structure. It is quite possible that an equivalent set of rules may work in place of the Rules of linguistic inference to relate the MS data with MSpat and point out the class of neural proteins and the ontological relationship: myelin is a neural protein. The Lexicon (data) and Rules of linguistic inference (rules) may be working in concert to indicate the semantic structure, and another set of rules, Correspondence Rules, could point to syntax or descriptions in the syntactic structure that builds on the identified semantic structure. The extent of the classification, precision, granularity, and other factors of the semantic and syntactic structures could be determined by rules; the equivalent in the linguistic system are the Semantic and Syntactic Well Formedness Rules (SemWFR and SynWFR, Figure 8.11), respectively. The presentation of the data may find some far-fetched relatedness to the phonetic representation and phonology domains in EMRS-AGRMIA, when visualization of the data is important.

Thus far, I have not addressed molecular semantics but attempted to explore how the linguistic system seems may offer a parallel in data analysis. The latter is expected because linguistics and artificial intelligence share common elements such as cognition, semantics, and ontology. The idea of molecular semantics was camouflaged in the discussion because the data (MSpat) attempted to find a match to an existing equivalence relationship to a description of relevance of the structure. Molecular semantics indeed performed its task in trying to find a match between MSpat and MScat. The location of the MScat in the lexicon may not be an optimal explanation, and the lexicon may have a database equivalent where the incoming data through EMRS, equivalent to the visual system that feeds the conceptual structures in Figure 8.11, are formatted by certain rules (equivalent to the Pragmatics in Figure 8.11) and channeled to MScat that operates under the AGRMIA umbrella, which could be a database with MS data, linked to the Lexicon (dictionary).

Molecular semantics, the definition and identification of structures, may contribute to the ability of the system to compare MSpat to MScat profiles. Although MS analysis does not deliver an actual structure, the spectral data offer a pattern, and for this discussion, this pattern or profile is referred to as structure. This comparison can be performed today only by special applications.

Current semantic web efforts are striving to stimulate global groups to contribute descriptive ontologies for chemical and biological systems that may be accessible by the software tools and standards promoted by the semantic web experts. That effort may not include the potential for considering ontological frameworks for chemical and biological structures or data patterns. Tools such as MS, echocardiogram, and magnetoencephalography do not generate syntax and thus may be excluded from ontological frameworks. This deficiency in the current practice is addressed by this proposal on molecular semantics.

Conservation of the amino acid arginine in LRP6 protein product from frogs to humans may help make it less surprising to understand, following the logic of evolution, why viruses and bacteria may also share homologies with sections of human DNA or why viral proteins [169] and bacterial proteins [170] may have some homology to amino acid sequences found in normal and common human proteins, such as myosin. This apparently benign observation often produces some disastrous medical consequences. Because small segments of proteins are involved, these segments or epitopes may have structures that may be distinct. Understanding the form (structure) is crucial to understanding the function in biological systems, hence the need for molecular structure in healthcare analysis, albeit only in special cases, and the potential importance of a mechanism that enables analysis of structure, that is, molecular semantics.

Disastrous medical consequences are observed due to the phenomenon commonly referred to as molecular mimicry. The situation is often caused by a foreign protein from a virus or bacteria that share a short stretch of amino acid sequence homology to a normal human protein. The immune system happens to target the foreign protein but for some reason specifically recognizes this homologous region that serves as the antigen. The body elicits an immune response and attacks the protein. Because this antigenic region (epitope) is also a part of a normal human protein, the antibodies produced by the body's immune system also recognize the epitope that is present on normal "self" proteins. Unfortunately, the immune system begins to destroy the self protein (autoimmune) with severe consequences for the patient. Because the short amino acid sequence of the foreign protein, as short as only six amino acids [171], may mimic the corresponding sequence of the normal self protein, the phenomenon is referred to as molecular mimicry.

This autoimmune response is partly to blame in some cases where an individual in almost perfect health suddenly drops dead from cardiac arrest or succumbs to a heart attack. The etiology may be linked to common Streptococcal infection (strep throat) that most children and adults experience at some stage or the other. Segments of some proteins from Streptococcus share homology to proteins specifically found in heart tissue [172]. Various other cases of molecular mimicry are well known including T-cell-mediated autoimmunity [173] and ankylosing spondylitis caused by only six amino acids (QTDRED) found in *Klebsiella pneumoniae* nitrogenase enzyme (protein) that exactly matches the human leukocyte antigen (HLA) receptor protein (HLA-B27) antigenic epitope [174].

Do these very short stretches of amino acids create antigenic epitopes with certain structures that may form a class of "super antigens" responsible for eliciting the human immune response that leads to autoimmune diseases? Using basic rules of protein structure and conformation, these epitopes may reveal structural patterns that may influence "function" in biological systems, such as eliciting an immune response. The structure of a short sequence of amino acids may be almost identical to another structure of a short sequence of amino acid, but the structural homology may not indicate that the two short stretches of amino acids share sequence homology. Computer systems of the syntactic web and of the semantic web may help in the data analysis that involves sequence (words, such as QTDRED) homologies or differences but may be incapable of dealing with structures that may be homologous whereas sequences are not. The likely analytical result of a system presented with QTDRED versus QTDREG may suggest, erroneously, that the structures are different. However, if the system, in future, could use the tools of molecular semantics and refer to the Lexicon (Figure 8.11) of structures, it might reveal that the two stretches of six amino acids analyzed are different in sequence but produce identical structures. Because antigen–antibody binding is structure dependent as long as the side chains and groups are similar, it is possible that two slightly different amino acid sequences may result in nearly identical structures that can still elicit the same autoimmune response. A relevant scenario often occurs in organic chemistry where the empirical formula of a chemical or compound is same but the properties of the resonant structures may be different. The current semantic web may be impotent to address these structural issues. In combination with the power of the semantic web, there may be a need to address structural issues in healthcare diagnostics, hence the value of the proposal of molecular semantics.

Why did I choose molecular mimicry and autoimmune diseases to make the case for the value of the structural approach in the proposal of molecular semantics? The partial answer is based on the fact that almost an infinite number of allergens and antigenic epitopes can share short homologies to self proteins. By exploiting molecular mimicry, it can lead to autoimmune diseases. Healthcare, in general, and clinical immunologists, in particular, may wish to understand at a greater depth the form and function relationship in biological systems and autoimmunity. It cannot be done without structure and structural comparison, for reasons already elaborated above. Globalization now provides wide access to food from all around the world. This window on world cuisine has the potential to spawn new and undocumented forms of allergies to various ingredients and antigens foreign to the body. The potential to cause some forms of autoimmune reaction may manifest as inflammatory bowel disease [175] or the generic irritable bowel syndrome [176].

Globalization and mobility will usher new domains of healthcare and seek knowledge about many more issues to diagnose complex diseases, for example, autoimmunity caused by antigens in food products. Early detection of antigens, which can pose the threat of molecular mimicry, may be of great significance. Research is needed to determine how to identify candidates for molecular mimicry and what type of assays, in vivo or in vitro, can detect these short segments. Only time can tell whether the growing demand for detection and need for analysis in healthcare may trigger an exploration to "productize" molecular semantics. In some cases, structural analysis may be necessary or even pivotal to complement numerical data and syntactic/semantic information for use in EMRS-AGRMIA (Figure 8.2) type systems that must be globally interoperable and locally responsible.

Molecular semantics or ideas that may originate from linguistics [177] may evolve when more people, on both sides of the aisle, medicine and engineering, can better appreciate the value, however subtle, of form versus function in biology. This proposal in its current format may become irrelevant, but it may provide some clues or may even serve as The Golden Key [178] to unlock creativity and innovative patterns in the mind [179] of young people to drive convergence of syntax, traditional semantics, numerical data, and structure, to improve analysis and benefit healthcare.

8.5 Auxiliary Space

8.5.1 Potential for Massive Growth of Service Industry in Healthcare

Adoption of this data-driven model may increase the diffusion of a new class of service industry. The growth of health services may create new markets and trigger new business and revenue models (pay-per-use) even in sectors not directly involved in healthcare, but it offers products that may be used by health services, for example, (1) software vendors deploying cloud and grid computing platforms, (2) telecommunications companies billing for data transmitted in real-time, (3) data routing or IP connectivity architects to ensure privacy, data confidentiality, and address verification using Internet Protocol version 6 (IPv6) and other security tools, and (4) data mining outfits that may create intelligent differential decision engines (IDDE) running on grids, cloud computing environments, in-network processing, embedded browser applications, or a host of other platforms yet to be determined or discovered.

The pivotal role of data mining in healthcare data analytics is expected to evolve in ways that are yet to be defined. Data mining as applied to so-called "business intelligence" applications may play a role but may be inadequate to address the service part of healthcare because the "service" of healthcare is about an individual or patient-centric data. On the other hand, the healthcare industry may have distinctive needs, but, in general, it is about business and operational efficiencies. Data, information, and knowledge hold the potential to improve both healthcare service and the healthcare industry, but the tools and applications are expected to differ in their pursuit of different goals and functions. This is where the prevalent view of data mining is expected to diverge.

The tools of data mining were enriched with a sea of changes when principles associated with complexity theory and swarm intelligence [180] emerged to offer practical business solutions [181] for a wide variety of routing and scheduling needs. A similar wave (see Ref. [10]) is imminent under the generic banner of data mining tools that may stem from reality mining (see Ref. [77]) and its link with social networking relationships (see Ref. [76]). Principles extracted from reality mining and social networking paradigms may yield tools applicable to a variety of fields including business services and healthcare analytics.

Data mining in healthcare, service, and industry perspectives taken together also offers a fertile ground for exploring whether the convergence of economic principles, tools, and techniques in healthcare data analytics may lead to further innovation. The healthcare ecosystem offers the opportunity to test at least four different economic principles as analytical tools. For healthcare service, the focus is on patient data, and these data are generated by the physiological system. Since human physiology is highly integrated, it may follow, naturally, that the physiological variables (e.g., blood pressure, heart rate, pulse rate) are likely to be co-integrated (see Ref. [163]). In other words, because physiological systems strive to maintain homeostasis, it follows that the goal of physiology is to attain equilibrium. When one variable is affected, for example, pulse rate, its effect is "integrated" or reflected or related to another linked variable, for example, blood pressure. Physiological balancing mechanisms within the human body will attempt to rectify this situation and may try to restore the blood pressure of the individual to 120/80 mm Hg, the normal reading. Due to the innate physiological drive to restore equilibrium, data analysis in healthcare service may benefit from a potential exploration and application of the principles of Nash Equilibrium [182] to predict from a set of patient data what other parameters (co-integrated) are likely to change or may be influenced by the change documented (data at hand). It may provide clues to improve diagnosis.

Data mining tools for the healthcare industry may benefit from some traditional approaches coupled with a few emerging concepts. Like most businesses, healthcare industry suffers from systemic gaps of data and information in its complex supply chain. Consequently, the healthcare industry is prone to information asymmetry [183] and expected to benefit if information asymmetry could be reduced through appropriate acquisition of data including real-time data, for example, from RFID. Availability of high volume data from deployment of automatic identification technologies (see Ref. [131]) may help improve forecasting to better manage human resources and inventory planning in the healthcare industry. High volume data may be instrumental in improving the accuracy of forecasting using time-series data in combination with a host of forecasting tools including the econometric technique of generalized autoregressive conditional heteroskedasticity (see Ref. [46]).

Contrary to public opinion in business consulting, except in specifically designed business collaborations, the application of Nash equilibrium in business (see Ref. [65]) may be conceptually flawed. It is less useful for business decisions but better suited to healthcare analytics for healthcare service. In contrast, the concept of information asymmetry is foreign to human physiology but is almost a second nature to the competitive dynamics of business, which makes it useful as an analytical tool in the healthcare industry.

The global growth of the health services industry through the model illustrated in Figure 8.5 will dwarf the current revenues of $748 billion [184] from business services. The three major global giants that currently offer business services (IBM, HP, Microsoft), taken together, command less than 10% of the $748 billion in revenues. Therefore, by extrapolation, it seems reasonable to suggest that small companies, start-ups, and small and medium enterprises (SME) shall find the barrier to entry in the healthcare service industry to be low or nil. The healthcare service industry will be driven by innovation, which is best executed by small "skunk" works of talented individuals. Due to multiple convergences necessary to produce a complete product and/or health service, core competencies will be a driving factor. The latter may stimulate the need for collaboration and partnerships between a number of small or medium enterprises with local and global research institutions and medical facilities. Each group or alliance or SME may contribute its own specific module or component but may find it essential to cooperate with multitalented team made up of scientists, other companies, medical personnel, patient advocates, and strategists to act as an interface to catalyze implementation.

Stringent requirement for a higher level world-class advising and supervision to guarantee credibility of the process, products, and health services is necessary and essential. The noncommercial ad hoc supervisory team may begin their involvement from the conceptualization stage and continue through the cycle of planning, research, product development, service creation, testing, and implementation. Critical evaluation by a team of academic and commercial experts [185] may help define performance indicators (KPI) and determine the strength of this emerging vision of healthcare by exploring (1) quality of care improvements, (2) impact on human resources in terms of time savings for medical professional, (3) reduction in cost and potential for savings, (4) length of time required for return on investment, (5) profitability of businesses (SME) and growth of high potential start-ups, (6) economic benefits for the nation's healthcare system, (7) reproducibility, portability, and sustainability of the services model as a global template, (8) business opportunities to implement similar services in other communities or nations, (9) creating market alliances in emerging economies to implement healthcare services, and (10) liaison with global organizations (World Health Organization, United Nations Development Fund, World Bank, Asian Development Bank, Bill & Melinda Gates Foundation) to help in the global diffusion and adoption of health services industry model.

8.5.2 Back to Basics Approach Is Key to Stimulate Convergence

The discussion in this chapter, in general, has continuously oscillated between medicine, engineering, and information technology in an attempt to emphasize convergence and suggest fruitful analogies between the fields. This chapter is about data, analytics, and tools from research that may improve healthcare. Hence, the preceding sections seek to harvest advances in systems engineering and information communication technologies (ICT) as well as translational medicine to improve healthcare through multidisciplinary confluence. Therefore, I shall be ethically remiss if I do not digress and fail to highlight in this section why the need for convergence is accepted but in reality organizations are sluggish to address the challenges in the clinical enterprise [186]. The problem has deeper implications, and unless reformed, the ramifications are bound to be increasingly disappointing.

In its simplest form, implementing convergence is often inhibited by the general biomedical illiteracy of technical experts and technical illiteracy of biomedical experts. Insightful degree programs in biological engineering [187] and health science technology [188] are key mechanisms to create the supply chain of talented individuals who have understanding of one field and depth in another, to act as a knowledge bridge, which is key for the progress of convergence. The U.S. physician-scientist programs [189] that produce graduates with a PhD and MD are equally valuable and other countries are beginning to implement related strategies [190]. However, these programs only attract the crème de la crème of the nation, and in some countries the total number of these highly qualified individuals fails to reach a critical mass. Consequently, the few who succeed often move to other parts of the world where a critical mass of talent exists and where their multiple skills are valued, duly rewarded, and challenged to guide the nation or global groups.

What is sorely needed and missing in most countries is the focus on training programs for "middle level" workforce executing the bulk of the work yet remain firmly sequestered in one job or domain without the scope or the desire to become multifunctional. Programs with financial incentives, paid leave of absence, structured academic training, and practical internships are necessary to provide technical education for medical experts [191] and other healthcare professionals (consultants, GPs, nurses, physiotherapists, home-helpers, mental health workers) to understand (not necessarily gain expertise) the fundamentals of medical device engineering, sensors, remote monitoring, communication technologies, transmission protocols such as TCP/IP, software architecture, statistics, principles of artificial intelligence, basic principles of logic, and programming. Similarly, experts in engineering and technology should be offered the attractive opportunity to gain understanding of human physiology, pathology, pharmacology, anatomy, cellular and molecular biology, neurology and mental health, genetics, principles of internal medicine, nuclear medicine, medical imaging, biomedical data, inpatient and outpatient management in hospitals, hierarchy of decision-making, nutrition, social, and environmental factors in health, laboratory data reporting, and epidemiology. Cross-pollination of ideas is a key to innovation.

Implementing these parallel training programs may not pose an insurmountable barrier in most countries even if their vision of the future and commitment to financially invest in its people is modest, at best. What is likely to surface is the difficulty of attracting sustainable number of cohorts to the programs. The problem to attract mature mid-level working class for retraining or lifelong learning, at the tertiary level, is partially rooted in the primary and secondary education of the nation. The emphasis or lack thereof on mathematics and science education either due to (1) archaic policies, (2) compromised rigor to feign inclusion, (3) misguided teacher education programs that chooses process and dilutes content to serve the lowest common denominator, (4) emphasis on test preparatory teaching without room for problem-based learning, (5) inability to stimulate increasing number of female students to take up advanced mathematics and science or catalyze young women to pursue career paths in the hard sciences, or (6) shoddy and second grade teacher qualifications (especially in mathematics and science) masquerading as good enough [192].

In the United States, a seminal report [193] revealed that 51% of mathematics teachers in the U.S. public K-12 (primary and secondary) schools never took mathematics as a part of their college curriculum. A third of the "education-school-certified" science teachers never took science as a major in college. A national survey [194] of high school physics found that 25% of students took "some" physics in high school and 1.2% of senior students (33,000 out of 2.8 million) enrolled in advanced physics. About 18% of certified teachers teaching high (secondary) school physics had degrees in physics while 11% certified teachers had "degree in physics education but not physics," and 27% certified teachers teaching physics had neither a degree nor any relevant experience in the subject.

In the Third International Mathematics and Science Study (TIMSS), the United States ranked 28th in mathematics and 17th in science, lower than countries like Slovakia, Slovenia, Bulgaria, not to mention nations in Asia [195]. In 1998, U.S. high school students outperformed only two (Cyprus, S. Africa) of the participating countries. In addition, the TIMSS classroom study revealed 90% of U.S. middle school mathematics lessons are of low quality compared to Japan (10% low) and Germany (30% low). The quality of mathematics teaching was reflected in the poor performance of U.S. eighth graders (middle school) reported in the 1999 TIMSS analysis.

The declining effectiveness of mathematics and science education is reflected in the fact that U.S. colleges and universities awarded 24,405 bachelor degrees in computer science in 1996, 50% less than 1986 (30,963 in 1989), and engineering graduates dropped from 66,947 in 1989 to 63,066 in 1996 [196].

Despite these disappointing trends, the United States is still regarded as the "cradle of innovation" by global experts and organizations [197]. The enigma clears if one considers the actual number of qualified graduates: in thousands. It generates a critical mass of talent to innovate and contribute to economic growth. Each qualified individual contributes several magnitudes more than the average per capita contribution to the U.S. gross domestic product (GDP). As an example, by 1997, graduates of one U.S. institution, alone, had founded 4000 companies employing over 1.1 million people with annual sales close to $250 billion [198]. A recent analysis of the same institution indicates that innovation and inventions of this one institution, annually, create new companies that add 150,000 jobs and $20 billion in revenue to the U.S. economy, each year [199]. By extrapolation, this institution alone, therefore, thus far, has created companies that may directly employ over 2.5 million people and generate about half a trillion dollars in annual revenue. The dedication to research-based entrepreneurial spirit coupled with the freedom of some U.S. institutions to think out of the box as well as the strength of the U.S. investors to assume substantial risks are factors that continue to ignite innovation and profit even though investments, both academic and financial, are not immune from failure.

Attempts by other industrialized nations, with far smaller population, to partially mimic the U.S. strategy have produced mixed results. The striking visibility of the global success of the graduates and faculty from U.S. research institutions in creating innovative companies, products, and services is buoyed by investors willing to assume great risks. In addition to the favorable financial environment, the numbers or critical mass necessary for innovation is a major determinant to spawn success, and it may not be available for countries with limited population. Equally, a public basic education system that lacks emphasis on rigorous mathematics and science education at the primary and secondary level reduces the supply chain of talent for the future MD or PhD pool. It may be one reason why mature mid-level professionals in one field prefer to cast a "blind eye" to convergence and stay in their comfort zone rather than acknowledge and take measures to improve their basic skills in mathematics and/or science. The latter prevents them from exploring training options to acquire new dimensions or pursue lifelong learning, as is necessary to create the type of multidisciplinary convergences important for healthcare and help build a knowledge economy.

8.6 Temporary Conclusion: Abundance of Data Yet Starved for Knowledge?

Patients want answers, not numbers. Evidence-based medicine must have numbers to generate answers. Therefore, analysis of numbers to provide answers is the Holy Grail of healthcare professionals and its future systems. Lack of action due to paralysis from analysis of risk associated with the complexities [200] in healthcare is no longer acceptable in view of spiraling costs. Generating data without improving the quality of healthcare service and extracting its value for business benefits [201] will not provide the return on investment (ROI). Distributed data and their relationships are dispersed in multiple network of systems or system of systems (SOS). The role of data analysis is central. The comatose stage of the Information Age due to data overload and information overdose is predicting its demise unless new ideas [202] emerge as its savior. The imminent death of the information age makes it imperative to better understand the systems age. The single most important system that deserves our attention in the twenty-first century is the healthcare ecosystem. The convergence of characteristics such as enterprise, innovation, research, and entrepreneurship (EIRE), often common in organizations with foresight in parallel with the vision to drive convergence of biomedical sciences, engineering, and information communication technologies, may act as the purveyor to advance healthcare for the progress of civilization [203].

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