COMMERCIALIZATION OF IMPLANTABLE BIOSENSORS TECHNOLOGY IN HEALTHCARE

STRATEGIC PLANNING USING SCENARIO ANALYSIS

Nanda Ramanujam, Ph.D., M.B.A.

The Wharton School

University of Pennsylvania

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Nanda Ramanujam, Ph.D., M.B.A.
Ramanujam Consulting Group | nanda@ramanujamconsulting.com

2 EXECUTIVE SUMMARY

Implantable biosensors for healthcare applications have been in the popular imagination for several decades now. One may recall early examples of diagnostic sensors and implantable probes in the *tricorder* from the television series Star Trek, used to non-invasively scan for illnesses in the body, and the *micro vessel* in the film Fantastic Voyage, where a miniature craft is piloted through the human body for exploratory aims. However, this science fiction is now poised to become reality, with several enabling technologies taking shape and some early versions of the implantable sensor technologies, such as pacemakers and glucose monitors, already capturing mind share if not market share. The path to *commercialization of implantable biosensors technology in healthcare* is the subject of this study. The study looks forward 5-10 years into the future to examine what fundamental forces will shape the evolution of this technology and what forms these implantable medical sensors are likely to take.

Recognizing that emerging technologies are fundamentally fraught with high levels of uncertainty, we have chosen to apply the strategic framework of *scenario planning* to craft *future scenarios* after gathering, analyzing and aggregating subject matter experts' perspectives on the key strategic forces influencing the commercialization of implantable biosensors. The goal is to understand the degree of uncertainty surrounding these often highly intertwined forces, and to speculate on potential scenarios that could emerge. This disciplined imagination of the multiple potential futures enables the strategic planner to prepare – by essentially 'remembering the future' or 'learning from the future'[1] – for any vitally important and even highly improbable future scenario that may present itself at a later date.

Background information about the state of implantable sensor technology and the current trends that have bearing on their future commercialization were identified through review of secondary sources such as technology and tech-business

[1] E. K. Clemons, The Wharton School, University of Pennsylvania—private communication.

publications. Various subject matter experts from the wide set of stakeholders were consulted. They included: corporate managers from leading businesses in the medical devices sector, early-stage venture capital investors, technology entrepreneurs, and technologists/ scientists in academia and industry. The subject and the framework for analysis were presented to them, and a preliminary set of forces that may influence the technology were introduced to ground the discussion. The results of the interviews were compiled and the forces were categorized into one of two categories: (1) relatively certain trends, and (2) forces about which there was considerable uncertainty. These key forces were then aggregated and submitted to the experts group for their follow-up assessment.

With consensus from a majority of the experts on what forces are most likely to influence the evolution of this emerging technology, we developed four scenarios that anchor and provide deeper insight into how implantable biosensors technology will evolve. The four scenarios are:

1. Modular adjunct sensors supporting implanted devices,
2. Proliferation of multiple, stand-alone sensor applications,
3. Coordinated health management with targeted biosensor applications, and
4. Broad preventive care with autonomous integrated biosensor networks.

3 INTRODUCTION: SCOPE OF PROJECT

Biosensors are devices that detect and transmit information regarding a physiological change or the presence of various chemical or biological materials in a given environment. The development of biosensor-based medical devices for diagnostic and therapeutic applications in healthcare may be crucially enabled by the present parallel development of a web of new technologies: nano- and micro-scale structures, biocompatible and resorbable materials, wireless telemetry, mesh networks, miniature power cells, and ever-increasing portable computing power. As a result, implantable biosensors, at the confluence of these enabling technologies, may represent arguably the most disruptive technology in medicine to date. Biosensor technology is already penetrating consumer, environmental, counter-terrorism security, and military sectors, with applications such as identity tagging, biohazard detection, and early-warning systems to counter biochemical warfare.

With regards to biosensors in medicine, the landscape of care delivery is being transformed by the economics of healthcare, with the demand from the 'payor side' for lower-cost as well as preventative care. The ability of biosensors to potentially continuously monitor not only a patient's disease but also the patient's wellness, through the use of minimally invasive sensor technology, therefore represents a significant opportunity for healthcare businesses and value to the end-consumer.

There is also a growing trend in the diffusion of sophisticated medical device technologies as lifestyle-enhancing products through direct-to-consumer channels e.g. 3D fetal imaging, and elective corneal surgery. This raises the intriguing possibility of bypassing to some degree the clinical approval process established by regulatory bodies such as the U.S. Food and Drug Administration. With increasing awareness of and demand for personalized healthcare solutions following the advent of genetic mapping of the patient, customized diagnostic and

therapeutic modalities may become the norm in the near future. Implantable biosensors may therefore be ideally positioned to tap into this opportunity.

3.1 Potential Drivers of Implantable Biosensors Technology

The proposed study aims to help piece together and elucidate the different forces driving the commercialization of implantable biosensors technology in healthcare and its potential for successful adoption and diffusion with respect to four broad dimensions:

1. *Winning technology platform(s)*
2. *Meeting patient's needs*
3. *Political and Regulatory barriers*
4. *Economic consideration*

While these four dimensions were used to set the framework for the discussions with the subject matter experts, they were not intended to limit the scope of discussions or insights into the subject in any way.

4 STRATEGY FRAMEWORK: SCENARIO PLANNING

Strategic planning that is based on assessment of risk associated with specific outcomes that can be identified is well known to and widely used by corporate managers with regards to efficient allocation of resources to attain specific organizational objectives. However, in the context of emerging technologies particularly in a longer-term frame of reference, the evolution of the technology is impacted by numerous complex, highly volatile, and often inter-related and interacting forces, around which there usually is considerable uncertainty. As a consequence, specific scenarios of the future, driven by these forces, are not easily identifiable. Sometimes the forces are so weak and barely observable that they are not even recognized. The *inability to envision* all vitally important potential futures in the face of uncertainty, as improbable as they might be, puts a firm at risk of being blind-sided and potentially losing any competitive advantage that it had[2]. Put succinctly, when considering emerging technologies, the issue is not as much about how well a firm is engaging in a particular game (i.e. competitive situation) but rather more fundamentally 'does the firm even know *what game* the firm is playing?'[3]. An unanticipated scenario may completely upend any meaningful short-term strategy on which the firm may have relied until then[4].

At issue fundamentally is the decision to either bet big on risky projects, hedge using real options, or just wait and watch. Ideally, a decision should be based on an assessment of the degree of uncertainty that besets an issue. Strategy scholars have argued for a stratification of uncertainty in terms of (a) trends, such as market demographics, that are clearly identifiable, (b) factors that are currently unknown but are *knowable* provided the right analysis were done e.g. measuring

[2] P. J.H. Schoemaker and V. M. Mavaddat, "Scenario Planning for Disruptive Technologies" in *Wharton on Managing Emerging Technologies*, ed. G. S. Day and P. J. H. Schoemaker, Wiley, New York, 2000.
[3] E. K. Clemons, article in *Financial Times*, March 2006.
[4] E.g. Porter's Five forces analysis.

elasticity of demand, and (c) *residual uncertainty* e.g. technological disruption. This residual uncertainty can be classified per four broad categories[5]:

Level I: Predictable future – Managers anticipate one outcome and can essentially develop a single point forecast of the future, albeit a risky one due to general inherent unpredictability in all businesses.

Level II: Multiple discrete futures – The increased uncertainty manifests itself here in multiple outcomes, each with a different objective probability. The *risk* associated with a decision in this case is the likelihood that one of the alternate scenarios emerges rather than the one on which the firm bets. This is the realm of *contingency planning*.

Level III: A Range of Futures – This is the level of uncertainty by which most emerging technologies are characterized. A future scenario will be defined by a set of forces whose outcomes may lie on a continuum e.g. the penetration rate for a new medical device may be anywhere in a range between 10% and 50%, leading potentially to distinctly different resources and capabilities required by the firm. While *sensitivity analysis* and even *computer simulations* lend themselves to understanding a situation that is affected by a *single or few drivers* assuming a range of possible outcomes, these tools are not useful when multiple, possibly interacting, drivers are simultaneously changing, with variability over a large range.

Level IV: Total Ambiguity – Very few situations are characterized by complete ambiguity and even when this is the case, the level of transitory uncertainty reduces over time so that one can systematically classify and address these situations under the previous three broad categories of uncertainty. The mistake that most managers make however is that they inappropriately classify most

[5] H. Courtney, J. Courtney, and P. Viguerie, "Strategy under uncertainty", Harvard Business Review, November – December 1997.

situations in a binary fashion as either Level I or Level IV uncertainty and throw up their hands when faced with Level IV uncertainty.

Scenario planning is a relatively recent strategic framework that has been successfully applied to situations characterized by *Level III uncertainty*, to add clarity through a disciplined imagination of future outcomes[6,7,8]. This technique is based on a broad assessment of a variety of forces that drive and influence a technology or issue so that a better picture of the future can be identified. Central to scenario planning is the focus not just on trends, for which outcomes may be more easily predictable, but also on those forces about which little is known. While the range of uncertainty is not mitigated by just examination of these forces, one can still judiciously speculate specific outcomes along these dimensions based on input from other supporting trends. One can then begin to build strategies around these potential scenarios.

For example, while few may have expected that *e-Commerce* was even possible 10-15 years ago, one could have speculated that online business-to-consumer transactions might evolve in one of two different and extreme ways. At one limit, B2C interactions might involve spot transactions, where consumers seek out the best online merchant for each good that they wish to procure, and in the other limit, the merchant may become a one-stop-shop because online transactional security concerns may confer a higher value to an Internet merchant with an established reputation for secure transactions processing[9]. When one considers such outcomes for several intertwined forces, it becomes increasingly more complex, but it is still possible to paint a picture of how the future might evolve.

[6] P. J. H. Schoemaker, "Scenario Planning: A New Tool for Strategic Thinking," *Sloan Management Review*, Winter 1995.
[7] P. J.H. Schoemaker and V. M. Mavaddat, "Scenario Planning for Disruptive Technologies" in *Wharton on Managing Emerging Technologies*, ed. G. S. Day and P. J. H. Schoemaker, Wiley, New York, 2000.
[8] E. K. Clemons and M. C. Row, "Alternative Futures for Electronic Customer Interaction: Market Structures and Competitive Strategies," *The Wharton School—Information: Strategy, Systems and Economics*, June 1999.
[9] E. K. Clemons and M. C. Row, p. 6 in "Alternative Futures for Electronic Customer Interaction: Market Structures and Competitive Strategies," *The Wharton School—Information: Strategy, Systems and Economics*, June 1999.

This is, in essence, scenario planning. Other recent examples of dramatic shifts in the competitive paradigm are the attacks on broadcast television. Both content delivery and advertising revenue generation in broadcast television have been threatened by digital distribution technology i.e. *time- and place shifted* content delivery[10] using Podcasts, Web TV, and Digital Video Recording technology (e.g. *Tivo*, *Inc.*).

It is important to distinguish that strategies such as large firms' alliances with startups to gain a *window* into new, potentially disruptive technologies[11], or even equity investments in startups to gain *real options*[12,13], are decisions a firm takes *after* it has gained an understanding of potential future scenarios that may emerge. Thus, scenario planning accelerates the process of recognizing which scenario is likely to unfold, while real options provide for both delay and rapid response when future events resolve the current strategic uncertainty[14].

The goal in using scenario planning is to reveal and organize the uncertainty underlying emerging technologies. While experts from a broad stakeholder group are consulted to gain insight into the key drivers that will influence future outcomes, the uncertainty is not resolved simply by consulting technical experts. In fact, technical experts can be too close to the subject so that an independent and collective assessment based on multiple perspectives can often surprise the same experts. The drivers that influence outcomes in emerging technologies are also not necessarily technological factors alone, although these are often the focus of most strategic planners. It is crucial to account for non-technological

[10] "Prime-Time No More: The Television Industry struggles against Digital Distribution Upstarts," *Knowledge @ Wharton*, April 5, 2006.
[11] J. H. Dyer and H. Singh, "Using Alliances to Build Competitive Advantage in Emerging Technologies" in *Wharton on Managing Emerging Technologies*, ed. G. S. Day and P. J. H. Schoemaker, Wiley, New York, 2000.
[12] M. Amram and N. Kulatilaka, *Real Options: Managing Strategic Investment in an Uncertain World*, Harvard Business School Press, Boston, 1999.
[13] T. A. Luehrman, "Strategy as Portfolio of Real Options" Harvard Business Review, September-October 1998.
[14] E. K. Clemons, "Dealing Effectively with Strategic Uncertainty" in *Information Technology Investments*, book manuscript (version 1.7) under preparation.

factors such as economic, social, political and environmental. Even from a technology perspective, it is not just modular changes in the component technologies but rather the re-architecting of technological modules, in unanticipated combinations, which poses the greatest disruption and hence technological uncertainty[15].

The result of scenario planning is the articulation, in vivid, concrete, narrative form, of more than one potential future based on an assessment of a few key drivers[16]. While the scenarios should be credible and internally consistent with the other forces acting on the subject of interest, the scenarios should *challenge* managerial beliefs by highlighting vitally important outcomes that are *possible even if highly improbable*. This essential value of scenario planning – the process by which to detect weak but vital signals in the midst of clutter or on the periphery of a firm's vision – is the framework we will employ to better understand the commercialization of implantable biosensors technology in healthcare. It enables any investor in risky projects associated with this technology to balance commitment and flexibility by focusing on the immediate term as well as preparing for the longer term[17].

[15] R. Henderson and K. Clark, "Architectural Innovation: The Reconfiguration of Existing Product Technologies and the Failure of Established Firms," *Administrative Science Quarterly*, v. 35, p. 930, March 1990.
[16] While more scenarios offer a richer picture of the future, one often restricts the analysis to consideration of 4-8 potential scenarios to ensure manageability of the process.
[17] H. Courtney, J. Courtney, and P. Viguerie, "Strategy under uncertainty", Harvard Business Review, November – December 1997.

5 RESEARCH METHODS

The following represents the Scenario Planning methodology that we have adopted in this study. Our initial research was based on secondary sources (published literature), which often address current trends more than uncertain forces. This process was then followed by interviews of thought leaders and subject matter experts from the relevant stakeholder group including academics, technologists, managers, VCs, and entrepreneurs.

5.1 The Scenario Planning Methodology

The Scenario Planning process consists of the following steps:

1. Define scope of issues and set a relevant timeframe (5-10 years) over which the decision variables have influence on the technology.
2. Identify key stakeholders – corporate managers, investors, entrepreneurs, academics/technologists – who have to make decisions regarding investments of time and/or money in new projects associated with this technology. In addition, the stakeholder group could be broadened to include patients (consumers), provider groups (physicians, surgeons), payer groups (e.g. CMS, HMOs, and other Health Insurance companies), the U.S. Food and Drug Administration (FDA), and even lawyers who get involved in case of medical malpractice liability.
3. Identify strategic drivers or forces, and classify them broadly per social, technological, economic, environmental, and political categories. The identification of key drivers is aided by the interviews of experts.
4. Among these 20-30 strategic drivers, distinguish trends from forces that exhibit significant uncertainty, and rank-order them in order of importance with the help of the experts.
5. After identifying the key 2-3 drivers of the technology, aggregate other forces around these key uncertainties on the basis of internal consistency and inter-relatedness i.e. Can the drivers co-exist in a scenario? Would presumed actions of stakeholders be consistent with their interests?

6. Then, create narrative 'learning' scenarios by choosing specific outcomes or states for the key uncertainties, and refine the scenarios with the assistance of the experts.
7. Finally, test the scenarios among a subgroup of the experts to examine if the scenarios enable better mental models to understand the uncertainty surrounding the situation or issue and to assess the associated risk.

6 BACKGROUND: IMPLANTABLE BIOSENSORS

6.1 Context

The forces driving the commercialization of implantable biosensors were segmented into four major categories for analysis: (1) technological drivers (2) economic considerations (3) social and patient issues, and (4) political and regulatory factors. The drivers were initially identified through a review of secondary sources[18]. These drivers (trends and uncertainties) were then used to frame the interviews that were conducted with the subject matter experts.

6.2 Key Strategic Drivers

Medical devices have advanced on many fronts, resulting in instruments that can be implanted within the body for periods ranging from a few days (e.g. catheters) to several years (e.g. cardiac pacemakers).

6.2.a Winning Technology Platform(s)

Clinical safety and efficacy. Biosensors fall under the category of medical devices[19] according to the definition set by the U.S. Federal Drug Administration (FDA) and as such are bound by the regulations for medical testing and approval[20]. Clinical safety and efficacy are therefore necessary for successful translation of a biosensor technology through the pre-market approval process (PMA), or the less stringent 510(k) pre-market notification process for devices with equivalents already in the market. However, the benefits gained from implanting a device or sensor, directly at the site of the disease or injury, is sometimes outweighed by poor clinical efficacy when compared to an existing standard of care (gold standard). A good example of this would be implantable

[18] Standard & Poors Industry Surveys; MIT Technology Review; The Economist, etc.

[19] Per the U.S. F.D.A., a medical device is defined as "an instrument, apparatus, implement… intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease… intended to affect the structure or any function of the body… and which does not achieve any of its primary intended purposes through chemical action within or on the body… and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

[20] (U.S.) Federal Food, Drug and Cosmetic of 1938 (The Act); Medical Device Amendments of May 28, 1976; Safe Medical Devices of 1990; FDA Modernization Act (FDAMA) of 1997; Medical Device User Fee and Modernization Act of October 26, 2002.

blood glucose sensors technology, which has yet to match the performance of blood glucose testing performed outside the body using small samples of blood, even though implantable technology affords other benefits such as (1) continuous *in situ* monitoring for improved glucose regulation, (2) eliminating patient error with respect to accurate, regular, and timely monitoring, and (3) relief from the pain associated with needle pricks. Thus imposition of a standard that is based on a non-equivalent technology may be either unachievable or extremely costly to satisfy. Sometimes novel technologies promise benefits that cannot be adequately compared to and measured against existing standards, thereby creating challenges for gaining approval because they face tougher regulatory scrutiny. Finally, the limitations of the FDA approval process, in terms of the required funding for training in effective device regulation and quality control/ quality assurance programs[21], may inadvertently impose a bottleneck in the approval process, discouraging commercialization of novel, high-risk technologies.

Miniaturization. While modular technological improvement generally drives products to become "better, faster, and cheaper", there is a wave of miniaturization that is being enabled by parallel advances in cellular device technology. Historically, technical advances in other parallel fields have been readily accepted by the medical device industry, examples of which include fiber-optic endoscopy, surgical lasers, and novel polymer materils. With reduction in size and correspondingly power consumption, the threshold requirements for long-term implantation and sustainability are more likely to be exceeded. Nanoscale technologies or nantotechnologies, where feature size is on the order of a millionth of a millimeter, promise unique size-dependent physical and material properties not available in the macro scale. Examples of nanoscale miniaturization include carbon nanotube sensors for extremely sensitive CO2,

[21] Recommendations of the Secretary of the Department of Health and Human Services in "Report to Congress on the Timeliness and Effectiveness of Premarket Reviews", August 2003.

virus, and DNA detection[22]. Other micrometer-scale miniaturization technologies include micro-electromechanical systems (MEMS), which borrow fabrication techniques from the semiconductor chip industry. MEMS technology has already established itself in applications ranging from telecommunications devices to industrial sensors and is now making inroads into biosensors applications[23].

Minimally invasive device implantation and removal. Recent advances in laparoscopic (or minimally invasive) surgery, particularly with remote navigation and robot-assisted instrument control, surgical incisions have become less invasive and resulted in quicker post-operative recovery. This is a key enabler for the proliferation of embedded sensors given that barriers associated with surgical cost, risk, and even inconvenience e.g. lost productivity at work, are significantly lowered[24].

Remote monitoring. Wireless telemetry advances made possible by cellular technology have untethered devices and consequently increased patient mobility during continuous sensor operation. Examples include wireless logging of data and reporting of alarms by embedded devices such as cardiac rhythm management systems[25], where sensors monitor patient data that is then encrypted and transmitted securely to medical staff on call. In some cases, data from weighing scales and blood pressure arm cuffs (weight and blood pressure) is also linked to the heart data for a complete description of the patient's heart condition. This enables medical staff to pre-empt worsening heart conditions or perhaps detect a malfunctioning device before it is too late.

Autonomous operation. User management or operation of a device is often cumbersome and prone to error, often requiring intervention by a clinician. Systems that function autonomously through a well-tested and regulated mode of

[22] See for example Nanomix, Inc. (www.nano.com)
[23] See for example MicroCHIPS, Inc. (www.mchips.com)
[24] M. Andrews, "A Guiding Hand", *U.S. News & World Report*, July 31, 2006.
[25] "Patients with Defibrillators take wireless technology to heart, home", Associated Press, August 8, 2006.

operation can therefore provide significant flexibility and effectiveness to disease management. A striking example of this potential is the concerted effort to bring to market an implantable blood glucose monitor that communicates wirelessly with an implantable pump to regulate the delivery of insulin autonomously for more effective diabetes management.

Reliability. The opportunities afforded by novel technologies also raises the specter of unanticipated and sometimes unmeasurable risk of failure. While device manufacturers put new device technology through rigorous and extensive testing in anticipation of high hurdles during the approval process, device failures can and do occur after acceptance for marketability, and can be costly to the firm's reputation and value e.g. Johnson and Johnson's potential acquisition of Guidant[26]. Even if these are isolated cases due to tremendous heterogeneity in patient populations and unforeseen risk factors, such inherent technical risk associated with revolutionary advanced biosensor technology could therefore impede commercialization and cause technological improvements to be made at a much slower albeit less risky pace. The risk and cost associated with gathering sufficient data on device reliability can slow or even halt adoption. Sources of reliability failures include electromagnetic interference, current leakage, and material fatigue. Wireless telemetry for example runs the risk of electromagnetic interference from the plethora of wireless devices around us[27]. Effective adoption therefore necessitates regulatory guidelines and standards to be in place to ensure patient safety[28].

[26] *The Economist*, "Nothing but heartache", June 30, 2005. Guidant's well-publicized problems with its malfunctioning drug eluting stents caused its pending acquisition by Johnson and Johnson to be re-evaluated, with Guidant's subsequent valuation dropping sharply.
[27] Mitchell Shein (U.S. FDA) was quoted as saying 'the electronic environment is only going to become more complex' in "Patients with Defibrillators take wireless technology to heart, home", Associated Press, August 8, 2006.
[28] Medtronic for example uses a dedicated communications frequency band set aside by government regulators for medical implants. "Patients with Defibrillators take wireless technology to heart, home", Associated Press, August 8, 2006.

Biocompatibility. Implants have to be designed so as to not induce an undesirable immune response while the device performs its function. Typically, the immune response is an occlusion of the device by scar tissue overgrowth. For short-term implants, the undesired response might be simply the avoidance of undesired obstruction of blood or other flows. The ability to safely and reliably deploy sensors for diverse applications and at multiple sites therefore requires materials and structures that do not trigger an adverse autoimmune response. While materials that are biocompatible in a broad context are not currently available, there has been progress in engineering application-specific biomaterials based on compounds or materials drawn from natural systems, a concept known as *biomimetics*. Examples of biomimetic applications include drug-device combination products such as (1) recombinant protein-based drug coatings on tissue scaffolds to stimulate tissue healing and regeneration[29], and (2) drug-eluting stents (DES) which release drugs to prevent scar tissue-like growth that can re-occlude stented arteries.

Distributed Sensor Networks. Biological systems are replete with models of primitive structures, with simple behavior or limited intrinsic functionality, but the extraordinary ability to self-organize to exhibit complex global biological behavior that cannot be achieved by the individual entities alone. The individual entities interact utilizing only local information, and they lack any sort of "master plan" or centralized leadership[30]. Analogous to such biological systems, multi-sensor or distributed sensor networks, consisting of interacting nodes with minimal power and complexity, have emerged in mobile communications systems[31] and wide-area environmental monitoring[32]. Applications include multi-point dynamic tracking to identify the location of mobile objects. There is ongoing research to understand the potential and challenges of implantable biomedical *smart*

[29] See for example BioMimetic Therapeutics, Inc. (www.biomimetics.com).
[30] M. Pirretti et al, "Biological Primitives", Ch. 46 in S. S. Iyengar and R. R. Brooks ed., *Distributed Sensor Networks*, Chapman & Hall/ CRC, Boca Raton, FL.
[31] J. M. Kahn et al, "Mobile Networking for Smart Dust" in ACM/IEEE Intl. Conference on Mobile Computing and Networking (MOBICOMM 99), Seattle, WA, August 17-19, 1999.
[32] D. Steere et al, "Research Challenges in Environmental Observation and Forecasting Systems", Proceedings of MOBICOMM, 2000, pp. 292-299.

sensors, with respect to scalable, biocompatible, fault-tolerant, and energy-efficient wireless networks in a biological system[33]. Such systems could significantly enhance the quality of the information that is gathered from complex biological systems, at multiple sites in the body, and would represent a significant departure from the present localized, or focal, sensing strategies.

Computing Power. Computing power has been doubling every 2 years over the last three decades[34], only slightly slower than the rate suggested by Moore's Law[35], according to which computing power is likely to double every 18 months. Furthermore, because the cost of computing power has grown substantially more slowly, high performance computing devices have become ubiquitous. A striking example is the wireless telephony device, which has also driven more efficient chip designs through a tremendous demand for miniaturization. In addition to ever-diminishing feature size of transistors to achieve higher density chips, a significant new trend is the advent of *multicore* chip sets for better use of device real estate and lower power consumption at high data rates. Such processors were previously available only for high end computing servers but increasingly multicore processors are making their way into consumer electronics such as embedded networking devices and set-top boxes[36]. A result of this trend is the proliferation of more powerful computing systems in the home, driving sophisticated home electronics. All this computing power is likely to enable a new breed of implantable sensors that will provide mobile and home-based monitoring of patient health. With advances in communications, inexpensive wireless and wireline connectivity may enable transport of large volumes of sensor data back and forth between the patient and remote (medical) data processing centers.

[33] L. Schwiebert et al, "Research Challenges in Wireless Networks of Biomedical Sensors", in Proceedings of the 7th Annual MOBICOMM, 2001, pp. 151-165.
[34] J. Bond, "The Drivers of the Information Revolution – Cost, Computing Power, and Convergence", Public Policy for the Private Sector, The World Bank Group, Note No.118, July 1997.
[35] A law, commonly attributed to Gordon Moore, legendary founder of Intel Corporation, postulating that transistor count per microprocessor, and hence computing power, is likely to double every 18 months.
[36] Tom Krazit, IDG News Service, "ARM crafts Multicore Chip", in PC World, May 17, 2004.

Powering of Devices. Power to drive implantable medical devices has been derived primarily from batteries. Battery technology has evolved considerably in the recent past, again driven by unrelated consumer technologies such as cellular telephony. Traditional battery configurations have consisted of the cylindrical bobbin cell, the cylindrical wound cell, the button cell, and the prismatic cell, each providing different tradeoffs with respect to energy capacity, power delivery, compact form factor, and suitability for large volume production[37]. Battery technology has been largely defined by battery chemistry, cell design, size, and shape. The energy capacity until recently was directly proportional to the size of the battery but this paradigm may change with innovations in materials, battery chemistry, as well as designs based on thin and flexible form factors. For example, new *fuel cell* technology, based on disposable or replaceable cartridges containing methanol, promises up to 10 times (theoretically, 40-60 times) the energy efficiency of conventional batteries such as the Lithium Ion battery[38]. Others are exploring hybrid devices consisting of conventional batteries as well as fuel cells, where the latter may be used complementarily for example to recharge the former. Industry analysts expect fuel cell technology to make headway into consumer applications, with pricing, form factor, and weight becoming very competitive with that of current battery technology. However, concerns remain with respect to the flammability of methanol. Finally, the advent of inductive coupling technology can now enable remote powering or charging of implanted medical devices so that invasive battery replacement could potentially be eliminated[39]. Other forward-looking technologies to power implantable biosensors include potentially biomechanical, biochemical, and biothermal energy sources within the body itself. For example, natural or even genetically modified microorganisms could be used to produce hydrogen as part of biological energy production cycles, and offer the potential

[37] H. Y. Cheh, "Battery Technology Overview", in National Science Foundation Workshop on Prospects for Miniaturization of Mass Spectrometry.
[38] Lincoln Spector, "Bye-Bye Batteries? Long-lasting Fuel Cells favored to (eventually) power Portable Devices", PC World, April 3, 2003.
[39] See for example, Splashpower Limited (www.splashpower.com) and Edison-GE (subsidiary of Edison Electric Corporation, www.edisonge.com).

for continuously operating systems for biological energy conversion[40]. Some startups exploring biothermal energy sources suggest that biothermal energy sources could last up to 30 years compared to the 5-7 year life of current Lithium-based batteries[41].

6.2.b Economic Considerations

Cost containment and cost effectiveness. The Centers for Medicare and Medicaid Services (CMS) estimates the U.S.' healthcare bills reached $1.9 trillion in 2004, up 7.9% from $1.7 trillion in 2003. This rate of increase in spending was more than twice as fast as that of the Consumer Price Index (CPI), which grew at the rate of 3.3% during the same period. The healthcare spending accounted for 16% of the U.S. GDP, or about $6,280 per capita. While the overall rate of growth of healthcare spending was the slowest in a decade, there is considerable motivation to contain costs throughout the system, largely driven by CMS, according to a Standard and Poor's healthcare industry survey[42]. Emerging from this context is the thrust towards preventative care in lieu of more costly therapeutic intervention. A Task force report on Preventive Services[43], published in 2002, outlines a healthcare policy where effective preventive care will be driven by an 'evidence-based' assessment of intervention procedures[44], followed by a partnership with Medicare, to ensure that these services are delivered and utilized, and with CMS, to ensure that there is adequate reimbursement for such procedures. While these reports indicate a tilt towards preventive care technologies with regards to changes in funding allocations, notwithstanding the

[40] "Grow a biological *in vitro* power source on a chip", The National Academies Keck Futures Initiative Designing Nanostructures at the Interface between Biomedical and Physical Systems: Conference Focus Group Summaries.
[41] M. Rice, "Emphasis on Miniaturization: Miniaturization driving medical device innovation", www.reedlink.com.
[42] R. Gold and W. Diller, Standard & Poor's Industry Surveys—Healthcare: Products and Supplies, February 23, 2006.
[43] C. M. Clancy, Acting Director, Agency for Healthcare Research and Quality (AHRQ), Department of Health and Human Services (HHS), "AHRQ's role in evidence-based preventive healthcare services", report to House Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, May 23, 2002.
[44] Evidence-based medicine is a systematic approach to evaluating the best evidence for making decisions about patient care, consumer-driven healthcare, step therapy, and high-deductible health plans.

validation of clinical efficacy of screening technologies prior to adoption and reimbursement, they also seem to suggest that biosensors may be adopted commercially sooner rather than later. The reason is that biosensors not only promise early-stage diagnostic capabilities but also potentially enable the collection of stronger, comprehensive clinical data to better assess preventive and therapeutic interventions.

Private payers typically follow CMS reimbursement guidelines and also use evidence-based medicine to control spending. However, they can and do go further to offer 'incentive-alignment' plans to encourage preventive care, with lower-cost programs based on risk, responsibility and cost sharing with the consumers and their employers[45]. Cost containment by payers may also limit reimbursement for new technologies, particularly when there is competitive pricing pressure. The risk of limited reimbursement or threats to sustainable high unit pricing can diminish future investments by medical device manufacturers in healthcare innovation. Nevertheless, even high-cost preventive technologies could be readily adopted provided a comprehensive view of cost containment is assumed, with potential savings in procedure and equipment costs over time.

Understanding the provider's economics. A key and perhaps often-overlooked fact is the economic impact of a new healthcare technology on the provider, who is an integral part of the 'distribution system' for healthcare products. Medical devices technologies that create new procedures are attractive to the provider who can consequently bill for services provided in the current 'procedure- or process-based model of reimbursement'. For example, an MRI scan or a minimally invasive biopsy may be billable, regardless of whether the intervention was beneficial or even necessary. A new trend towards 'outcomes-based reimbursement model' may shift the focus to preventive care strategies thereby impacting the prescription of specific clinical procedures that are currently

[45] Examples of such programs include Consumer Driven Healthcare Plans (CHDP) and Health Savings Accounts (HSA).

prevalent. A process-based reimbursement model is also an incentive for primary care practices to increasingly specialize and adopt technologies to deliver high-margin procedures. Similarly, an outcomes-based model may encourage even primary care providers to recommend and deliver technological solutions such as implantable sensors to facilitate preventive care and hence improved clinical outcomes. However, a broad assessment of outcomes based on the clinical evaluation of new technologies can also be skewed by the direct or indirect influence of the equipment supplier. This practice known as' gainsharing', where the care provider is *paid* or influenced to use certain procedures or suppliers, however well intentioned, is arousing considerable controversy. For example, physicians and hospitals could be convinced to work with fewer vendors in order to obtain better pricing, thereby limiting competition. In response, less powerful device manufacturers have sought legislative protection to prohibit gainsharing and consequently level the playing field[46]; however such legislation has not yet been passed. Providers also have the power to occasionally block the adoption of new technologies, particularly when the new technological procedure involves retraining or new equipment that could render obsolete existing equipment in which the provider has already invested heavily. The positron emission tomography (PET) imaging is an example of a technology that apparently faced considerable resistance to adoption by neurologists even when clinical efficacy data and usage costs were superior to that of existing MRI technology. Key backers of PET technology argued that the reason was that neurologists had made significant prior capital investments in MRI systems and had not yet recouped their investments[47].

Medical malpractice liability. Risk of medical malpractice liability can also thwart the adoption of innovative technologies. Healthcare cost inflation has been attributed as one reason for escalating medical malpractice awards in jury

[46] R. Gold and W. Diller, Standard & Poor's Industry Surveys—Healthcare: Products and Supplies, February 23, 2006.
[47] C. Curran, "Dollars and Sense: The Economics of PET", Medical Imaging magazine, June 2003, quoting Senator Ted Stevens (Alaska), ranking member of U.S. Senate Health Committee.

verdicts. However, the high inflation in healthcare costs is largely due to heavy investments in research and development of innovative technologies with potentially high returns in terms of clinical outcomes. As malpractice costs and insurance escalate, equipment suppliers and providers may become excessively risk averse, choosing to restrict themselves to accepted technology and treatment methods[48]. This is precisely the policy goal of the malpractice regime but the unfortunate outcome could be that technologies with immense clinical promise do not find an outlet to commercialization and technological innovation may be stunted.

Employer-subsidized healthcare programs. Preventive healthcare options, such as those potentially offered by continuously monitoring implantable biosensors technology, may find a path to commercialization even in the absence of reimbursement assurances from CMS. Private employers may choose to include such treatments on the grounds of overall improvements to employee productivity or even as novel benefits that differentiate them from other competing employers. The business case for managing employee health and productivity is increasingly the subject of active debate, with particular focus on (1) ROI metrics with regards to health-related investments, (2) the enabling tools and resources for improved employee health and productivity, and (3) specific actions to most effectively advance wellness and productivity in the workplace.

Direct-to-consumer marketing. Direct to consumer marketing is a tactic employed commonly by pharmaceutical companies to drive or influence the consumer to create a 'marketing pull' for branded drugs. Such approaches may find their way into the medical devices industry as well, particularly when targeting consumers is easier than ever before thanks to the open and widespread access to medical information on the internet. An example of a medical device technology that is driven by consumer marketing efforts is the 'total (whole, full) body scan', which

[48] S. Seabury, "Does liability for medical malpractice drive healthcare costs and technology adoption?" American Society of Health Economists (ASHE) inaugural conference on Economics of Population Health, June 6, 2006.

is a 3-D X-ray or computed tomography (CT) scan. While critics such as the American Association of Physicists in Medicine (AAPM) argue that there is at most marginal clinical benefit when used in patients without symptoms[49], aggressive marketing on the basis of a promise of preventive medicine and implied peace-of-mind, has captured the attention and interest of some consumers.

6.2.c Meeting Patient's Needs

Individualization of care. With gene-expression profiling contributing to the evolving realization that biologic heterogeneity of diseases has implications for treatment[50], there is a growing awareness that clinical therapy is most effective when it is targeted, perhaps not only with respect to disease phenotype but also disease site and even the individual body's metabolic response to therapy[51]. There is now a proliferation of drugs based on monoclonal antibodies that bind to receptors on diseased cells and do not damage nearby healthy cells[52], but effective delivery of these drugs to the disease site still remains a challenge. Some researchers are developing cancer 'targets' based on metallic nanoscale structures for non-invasive photo- or radio-ablative therapy[53]. However, concerns still remain as to how non-biocompatible targets and markers can be safely flushed from the body after therapy.

Tracking patient care. As with targeted therapies for improved clinical efficacy, given the variability in an individual patient's response to treatments, there is also a need for pre- and post-market surveillance of adverse reactions to drugs and

[49] Inside Science News Service, American Institute of Physics (AIP), "Whole-body scans more marketing than science, say medical physicists", August 26, 2002.
[50] J. O'Shaughnessy, "Molecular signatures predict outcomes of breast cancer", New England Journal of Medicine (editorials), v. 355;6, pp. 615-617, August 10, 2006.
[51] D. Christensen, "Targeted Therapies: will gene screens usher in personalized medicine?" Science News Online, The weekly magazine of Science, v. 162, no. 11, p. 171, September 14, 2002.
[52] Targeted Cancer Therapies, National Cancer Institute (NCI) Fact Sheet, U.S. National Institutes of Health (NIH) (www.nci.nih.gov/cancertopics/factsheet/Therapy/targeted).
[53] See for example, Nanospectra Biosciences, Inc. (www.nanospectra.com).

implanted devices[54]. A few companies are already developing biosensors to assess adverse drug reactions (ADR) in patient populations[55], using for example microfluidics-based assay systems to detect changes in biochemical markers directly induced by the drug, and then wirelessly relaying the results to medical personnel.

Medical data privacy. The Health Insurance Portability and Accountability Act (HIPAA) of 1996[56] is the key legislative framework that now guides the protection of private patient medical information. While the act was originally designed to protect the portability of insurance for continued medical coverage, the component of the act that seeks to "…combat waste, fraud, and abuse in health insurance and health care delivery…" has become the most visible purpose of this legislation. This legislation is particularly relevant to the commercialization of implantable biosensors because the mining of biological data from patients is likely to create private patient data that could be vulnerable to abuse. The HIPAA regulations provide the patient with rights to access to, ownership of, and authorized release of personal medical information. However, authorized release of specific medical data, for example biomarker levels pertaining to cardiovascular disease (CVD), could potentially lead to unintended extraction of additional information about other potential disease conditions present in the patient.

Patients' risk aversion. Consumers in the U.S. appear not to have a sense of risk aversion to new healthcare technologies, given the implicit trust in the U.S. Food and Drug Administration's ability to effectively regulate safety and clinical efficacy of drugs and medical devices before introduction into the market. The solid foundation laid down by the FDA's efficacy standard, based on well-controlled clinical trials, is one of the main reasons that there is a strong confidence in the

[54] D. Christensen, "Targeted Therapies: will gene screens usher in personalized medicine?" Science News Online, The weekly magazine of Science, v. 162, no. 11, p. 171, September 14, 2002.
[55] See for example, Theranos, Inc. (www.theranos.com)
[56] Public Law 104-191, Health Insurance Portability and Accountability Act, August 21, 1996 (http://aspe.hhs.gov/admnsimp/pl104191.htm).

healthcare products that are on the market today. However, this confidence could be undermined by practices such as off-market labeling[57], which is currently prevalent in drugs prescription but which could extend to medical device usage as well. Bypassing of FDA controls could therefore inadvertently shift the burden of risk management at least in part to the patient, thereby affecting which, and how quickly, new medical products enter the market.

6.2.d Political and Regulatory Barriers

Universal healthcare access and coverage. There has been considerable debate through the years over the potential creation of a universal healthcare insurance program in the U.S. Universal healthcare is a healthcare system in which all residents of a geographic or political entity have their healthcare paid for, regardless of medical condition or financial status. The majority of universal health care systems are funded primarily by tax revenue. Some nations, such as Germany, France, and Japan, employ a multi-payer system in which health care is funded by private and public contributions. Others, such as Canada, Sweden, and Denmark, have opted for a single-payer system, in which a single entity, typically a government-run organization, acts as the administrator (or "payer") to collect all health care fees, and pay out all health care costs. Some advocates of universal health care assert that single-payer systems save money that could be used directly towards health care by reducing administrative waste and inefficiencies in the delivery of healthcare. Critics of universal coverage voice concerns about the high potential cost of providing government-funded universal coverage particularly during times of tight budgets, arguing that there is “not enough money to cover all uninsured Americans”[58]. Furthermore, health insurance companies have strong lobbying connections to both political parties in Congress and have fought any attempt to regulate or eliminate their business.

[57] C. M. Clancy, Acting Director, Agency for Healthcare Research and Quality (AHRQ), Department of Health and Human Services (HHS), “AHRQ’s role in evidence-based preventive healthcare services”, report to House Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, May 23, 2002.

[58] Newshour with Jim Lehrer Extra, “Who should pay for healthcare?” Public Broadcasting System (PBS) Television, January 19, 2004.

Meanwhile, proponents of a universal healthcare program in the U.S. have proposed several variants of a universal coverage plan: universal care for all children, universal care for all citizens under age 25, universal care for all those who are employed, and in the extreme case universal care for all with complete elimination of private insurance. Some have even argued for the purchase of prescription drugs from Canada where they are cheaper, much to the dismay of pharmaceutical companies in the U.S. and despite the FDA's safety qualms. Purchasing prescription drugs from foreign countries is presently a violation of federal law.

There have been several unsuccessful attempts at creating a universal healthcare program in the U.S., but more recently popular sentiment about universal coverage has turned a corner, with more Americans disappointed with the high cost of profit-driven medical care and favoring a universal insurance program, managed in principle by the government and funded with higher tax dollars. In an extensive ABC News/ Washington Post poll, "Americans by a 2-1 margin, 62-32 percent, prefer a universal health insurance program to the current employer-based insurance system"[59], with the support conditional upon choice of doctors without excessive restriction, and access to non-emergency treatments without excessive waiting lists. While the majority of Americans (54%) are dissatisfied with the overall quality of health care in the U.S. for the first time since 1993, this dissatisfaction is counterbalanced by a broad satisfaction amongst those who currently have some sort of insurance coverage. This schism between the haves and the have-nots is precisely the problem according to the healthcare policy researchers, who argue that the U.S. healthcare 'system' is more of a "patchwork of public and private programs with widely differing eligibility criteria"[60] leading to incomplete and uneven coverage. Furthermore, these multiple systems operate on the basis of widely varying principles of design

[59] G. Langer, "Health care pains: growing health care concerns fuel cautious support for change", ABC News, August 29, 2006.
[60] S. M. Butler, "Laying the groundwork for universal health care coverage", testimony before the Special Committee on Aging, U.S. Senate, March 10, 2003.

and economics. Existing models such as employment-based private insurance coverage, while generally successful, create challenges for small businesses, which simply do not have the economies of scale to provide insurance subsidies. While government subsidizes insurance coverage through tax exclusion of employer-sponsored programs, the subsidies are highly inequitable because upper-income workers receive the most help whereas the lower-paid uninsured receive little or no help; hence, those who most need assistance the most are the ones who get neglected. Finally, the Medicare program, although intended originally to be a social insurance program, is likely not the appropriate model for a universal care system because it faces huge financial liabilities, it provides outdated coverage that includes for example only limited prescription benefits, it it depends on a complex formulaic system for payments, and it is plagued by bureaucratic decision making. Some policy researchers therefore recommend an approach known 'creative federalism', in which the federal government and the states enter into covenants where federal funds are available to assist states to experiment with a chosen strategy for arranging health insurance and services at the state level[61]. These federal-state covenants would operate within policy constraints designed to achieve national goals for achieving universal coverage.

We may already be migrating towards such a program, but with leadership from the states rather than the federal government. Basically, insurance costs are high because medical care is expensive. High medical care costs are partly attributable to the current dependence on late stage interventional care, as opposed to less costly preventive care approaches. The challenge then is to perhaps include as many people as possible in a mandatory health insurance program so that illnesses are diagnosed and treated early and at lower cost. A watershed event was the passing of a universal coverage program by Massachusetts, which requires that all its citizens obtain mandatory insurance[62];

[61] S. M. Butler, "Laying the groundwork for universal health care coverage", testimony before the Special Committee on Aging, U.S. Senate, March 10, 2003.
[62] D. A. Fahrenthold, "Mass. Bill requires Health Coverage: state set to use Auto Insurance as a model" Washington Post, April 5, 2006.

the program would require all uninsured adults purchase some kind of insurance policy by July 1, 2007, or face a fine. The cost of insurance would then be subsidized for those in financial need through a combination of public-private partnerships. The fundamental idea behind the plan therefore is to require adults to become accountable for seeking healthcare protection, with the help of the state. Proponents of the plan argue that a 'complete medical coverage' of its citizens would reduce waste and inefficiencies and thus lower costs. Other states such as Maine and Hawaii are also offering near-universal access to health insurance, and Illinois is set to widely increase coverage for needy children. Most recently, California passed a bill[63] that would cover every California resident with comprehensive health insurance including a guarantee of the right of each resident to choose the doctor. The plan is expected to save the state, its businesses, and its working families about $8 billion in the first year alone through more efficient administration of services[64].

Still challenges remain for universal healthcare, with respect to: challenges from drug and device manufacturers, funding and efficiently managing universal care programs, and ensuring access to all legal residents. The impact on newer healthcare technologies like implantable biosensors will likely be the push for solutions that enable preventive care. However, device manufacturers may not invest in such technology development, arguing that pricing pressures that will erode the high margins that they claim are needed to fuel innovation.

Consumer advocacy and activism. Grass roots activism and advocacy for healthcare, while influencing how care is regulated and delivered, is yet to significantly influence the commercialization of healthcare technology. Grass-roots advocacy organizations such as Health Care for All (HCA), National

[63] California Senate Bill 840, authored by State Senator Sheila Kuehl, passed August 28, 2006.
[64] A. Ricchiazzi, "SB 840 passes California Assembly", Health Care for All (HCA) California—Working for High Quality, Universal, Single Payer Health Care, August 28, 2006 (http://www.healthcareforall.org/blog/?p=73).

Alliance on Mental Illness (NAMI), and Consumers Union[65] are however becoming visible and vocal with respect to informing consumers about health conditions, supporting educational programs, and pushing for action on key social and health issues with donor support. These organizations for example have raised awareness about healthcare spending issues such as cuts in state Medicaid budgets, and fraudulent use of medical information. Recently, a consumer advocacy group known as Public Citizen lobbied CMS to limit or deny reimbursement coverage for a new, and purportedly unproven, device for electrical stimulation of the vagus nerve to treat depression[66]. Whether or not the voices of advocacy groups are heard where it matters remains to be seen. As technology becomes more pervasive and people become less empowered to understand the ramifications of technology's impact on society and their lives, they will seek support from and consequently empower advocacy groups further. If for example a medical technology such as implantable biosensors raises concerns about potential abuse of medical data, and loss of ownership/ control of medical data, these organizations are likely to get involved and may significantly influence outcomes. The influence arises from effective control and management of information channels such as television, newspapers, and increasingly informally organized Internet 'blog' (weblog) sites as well. Lawyers could also get involved in the discussion if technology issues become central to medical malpractice litigation.

Medical data ownership and control. Data ownership refers to both the possession of and responsibility for information. Ownership implies power as well as control. The control of information includes not just the ability to access, create, modify, package, derive benefit from, sell or remove data, but also the right to assign these access privileges to others[67]. As patient medical data is

[65] Health Care for All societies in various states (www.healthcareforall.org, www.njshca.org, www.hcfama.org, www.vthca.org), National Alliance on Mental Illness (www.nami.org), Consumers Union (www.consumersunion.org).
[66] B. J. Feder, "Battle Lines in Treating Depression", New York Times, September 10, 2006.
[67] Loshin, D., Knowledge Integrity: Data Ownership (Online) July 19, 2002 (http://www.datawarehouse.com/article/?articleid=3052).

increasingly becoming computerized to facilitate data access to health care professionals for diagnostic and research purposes, unauthorized reception and disclosure of medical information may compromise patients' right to privacy. Hence, legislation such as HIPAA 1996 has been enacted to protect patient privacy. However, it is not clear whether medical data is 'owned' by the patients when the data may have significance and applicability to all people and therefore comes under societal protection. A case in point is the data generated from the human genome-sequencing project, in which the status of genetic material and genetic information is unclear[68]. While many hospitals consider the records in their systems to be their property, many patients argue that their medical information is their own[69, 70]. While information ownership can be ceded to the hospitals with assurances that information is released to third parties on a 'need to know' basis for the provision of appropriate care[71], unrestricted access must still generally be permitted to the patients. However, whether control and ownership are retained by the hospitals or by the patients, issues of access, control, and liability (for not acting appropriately upon the data) may become entangled. For example, data generated by biosensors may be subject to such limitations in the absence of clear protocols on how to act upon the data.

[68] de Witte, J. I. & Welie, J. V. (1997). The status of genetic material and genetic information in The Netherlands. *Soc Sci Med* (*Social Science & Medicine (1982)*, 45(1): 45-9.
[69] Annas GJ. A national bill of patients' rights. N Engl J Med 1998; 338: 695-699[Medline].
[70] Stanberry B. The legal and ethical aspects of telemedicine. 1: Confidentiality and the patient's rights of access. J Telemed Telecare 1997; 3: 4[Medline], 179-87.
[71] R. Schoenberg and C. Safran, "How to Use an Internet-Based Medical Records Repository and Retain Patient Confidentiality", Center for Clinical Computing, Beth Israel Deaconess Medical Center, Harvard Medical School (online—http://www.hipaadvisory.com/action/patientconf.htm).

7 ANALYSIS OF INTERVIEWS

The experts who were interviewed for this study represent a broad cross-section of relevant stakeholders: (1) high-level corporate managers, who control or influence both internal and external investments in healthcare technology, (2) venture capitalists, who invest in early-stage ventures in the healthcare space, and (3) technologists, who are directly involved in investment of effort in next generation healthcare technologies. The interviewees were provided with the list of potential strategic drivers from Section 6, which served as the starting point for discussions. The one-on-one interviewees clarified the above drivers and also added new strategic drivers of the commercialization of implantable biosensors technology in healthcare. The original drivers, gathered from secondary sources, as well as the new ones are listed in Table 7.1 below, in the left and right columns respectively. Where the new drivers are closely related to the original ones, they are listed in the same row.

Table 7.1 A listing of 48 strategic drivers of the commercialization of implantable biosensors technology, gathered from interviews with the experts (right column) as well as from review of secondary sources (left column). The drivers are categorized per (1) technological factors, (2) economic factors, (3) social factors, and (4) political and regulatory factors. Where drivers in the left and right columns are closely linked, they are listed on the same row.

DRIVERS COLLECTED FROM SECONDARY SOURCES	DRIVERS IDENTIFIED FROM EXPERT INTERVIEWS
Technological	
Clinical safety and efficacy	
Miniaturization	Handling miniaturized devices effectively
Minimally invasive device implantation	
Remote monitoring	External communications interference
Autonomous operation	Reliable integration into clinical care delivery
Reliability	
Biocompatibility	Biocompatible materials; biological interference
Distributed Sensor Networks	Synchronizing inter-related measurements
Computing Power	
Powering of Devices	Power management and probability of catastrophic failure

	System Infrastructure & Interdependencies
	Data overload for Doctors
	Scope of Functionality/ Application
Economic	
Cost containment and cost effectiveness	Outcomes-based capitation driven by Payers
Understanding the provider's economics	Retraining costs & Resistance to change
Medical malpractice liability	
Employer-subsidized healthcare programs	
Direct-to-consumer marketing	Consumer influence on technology adoption
	Who gets reimbursed for responding to sensor data—capitation formula
	Identifying where care will be delivered
	Commercialization path—route to Market
Social	
Individualization of care	
Tracking patient care	
Medical data privacy	Privacy vs. convenience & efficacy
Patients' risk aversion	Trust in the regulatory system
	Personal convenience vs. social cost limits
	Value of terminal care
Political/ Regulatory	
Universal healthcare access and coverage	Organizing providers for Outcomes-based care
Consumer advocacy and activism	Awareness/education of technology's value
Medical data ownership and control	
	(Sensor Data) Response processes & protocols
	FDA's mandate vs. Truth-in-labeling practices
	Broad adoption of Biosensors platform for preventive screening

7.1 Assessment of Strategic Drivers based on Discussions with Experts

The following is an assessment of the new strategic drivers that emerged from discussions with experts and seasoned investors in the medical devices industry.

7.1.a Additional Technological Drivers

While miniaturization is recognized as a clear trend facilitated by advances in parallel technologies such as cellular telephony handsets, one expert noted that reducing the size of medical sensors and devices too much may pose a problem,

noting that there may be a minimum size limited by the practicality of effectively handling such devices.

External communications interference from other wireless devices, which are now quite ubiquitous, poses a potential challenge to reliable operation, noted another expert, in spite of the use of dedicated medical device communications channels.

With the announcement of development efforts leading to closed loop systems such as the artificial pancreas, some believe that the protocols for effectively integrating the closed loop system into conventional clinical care delivery may face reliability issues; care providers may not be fully trained to interpret the results of the closed loop systems.

Others observed that the unavailability of broadly biocompatible materials would impede sensor deployment. They also recognized that another form of bio-incompatibility might be the interference from other biological markers and analytes in the body, leading to erroneous sensor measurements.

Some of the experts recognized that synchronizing data from multiple inter-dependent sensors would challenge the successful operation of multi-node sensor networks or clusters, thereby possibly limiting application to standalone modular sensors.

Power management and the catastrophic impact to human life, in the case of a power failure, was viewed as a serious challenge to long-term deployment of implantable sensors.

Another significant challenge may be the ability of doctors to manage the massive amounts of data that might arise from the biosensors, and the potential

liability fallout in case the doctors were found not to have responded to crucial biosensor data.

Perhaps the two most noteworthy new technological drivers that were discussed were: (1) system infrastructure and interdependencies, and (2) scope of functionality and application. The former suggests that the effectiveness of implantable biosensors technology may critically depend on the parallel deployment of supporting infrastructure such as sensor data recorders, analyzers, and a network of adopters, as well as appropriate protocols for processing and responding to the data. The latter suggests that while the scope of sensor functionality depends on the specified application, wide application will be determined by a host of factors such as the type of disease, the reliability of components, the availability of risk capital, and the needs of the customer that companies are trying to fill; in one case, the customer may be a mature medical devices company that is seeking sensors to monitor pre-existing implanted device performance rather than pure biological sensing.

7.1.b Additional Economic Drivers

Preventive care might lead to wider adoption of biosensors technology. Some experts noted that while outcomes-based reimbursement models may follow a wholesale paradigm-shift to preventive care, driven by payers to reduce cost of care, it is not at all clear when such a reimbursement model would be adopted. Some countries such as the UK, which is at the leading edge of the outcomes-based movement, are following a gradual transition into outcomes-based medicine in parallel with the current process (procedure)-based approach[72].

Doctors and other care providers are also highly resistant to change particularly if retraining is a cost that they have to bear. The resistance is even greater if the

[72] L. Roner, editor, *eyeforpharma* briefing, "Selling prescription drugs in an outcomes-based world", March 25, 2005 (http://www.eyeforpharma.com/search.asp?news=45464).

innovative technology supplants the providers, or if the technology follows earlier investments in older technology.

An interesting observation was the potential for consumer influence on technology adoption and the indirect dis-intermediation or undermining of CMS's influence on payers. CMS and healthcare insurers have focused thus far on treating disease but consumers and even businesses (as a benefit to employees) may drive the adoption of technology that has the potential to provide preventive, prophylactic, or even cosmetic value.

One of the experts noted the potential challenges involved in identifying a 'data response' protocol and network to monitor and respond to the volume of data likely to emerge from a cluster of sensors or even a single sensor. With touch points to a network of care providers, reimbursement issues need to be carefully worked out so that incentives of all involved are aligned to the goal of prompt, safe, and efficacious care delivery. This network of people and services, which would have to be seamlessly integrated for efficiency, could include for example: secure data processing and archival services; messaging and information delivery services; safety and regulatory compliance management; a first-responder team; triage services; a primary care physician; consultant specialists; ambulatory services in the case of critical care; billing services; and hospitalization and pharmacy support.

Point of care for minimally invasive implantation, servicing, and removal of biosensors also emerged as a major driver. Ubiquitous adoption and periodic servicing would require skilled staff at specialized centers within easy access to the patient population. These procedures would necessarily have to be in an outpatient setting, with perhaps even primary care physicians or technical support staff trained to deliver the services within safety controls.

An interesting observation made by some of the experts was that the form and scope of such technologies would inherit the characteristics – risk profile, functional scope, etc. – that the likely 'consumers' would impose upon them. It is noteworthy that most of the current innovation in medical device technology's route to market is via one of 3 or 4 of the major device manufacturers, whose risk profile – willingness to commit risk capital and invest in new technologies whether at seed stage or even when generating revenues – varies significantly across the major firms. These 'consumers' of new innovation could therefore inadvertently limit the rate at which new technology is developed and adopted.

7.1.c Additional Social Drivers

Experts noted that while medical data privacy is a concern, consumers may permit limited compromises to personal privacy in order to increase convenience, comfort, and even peace of mind. For example, medical records may be entrusted to a third party such as a medical data management repository if it is recognized that such private storage of records facilitates immediate access by multiple care providers during an emergency. While there may be risk of privacy violation, such a risk may potentially be accepted by the patient in exchange for a significant benefit.

Experts also noted that 'fear' of having an object implanted inside the body, with potentially risk of harmful effects, is largely tolerated by consumers today. The reason is that there is an implicit trust in the ability of the regulatory system (FDA) to effectively screen technologies and products on the basis of both safety and efficacy. If evidence of post-market approval product failures increases, the confidence in the FDA may be undermined, leading to unregulated use of new implanted medical technologies based solely on the consumer's risk profile and awareness. Additionally, efforts to implement practices such as truth-in-labeling could have the unintended effect of making the consumer not just the final, but the sole arbiter of product efficacy; after all, one could argue that with clear

identification of risk in labels, 'what you (the consumer) see is what you get' (WYSIWYG).

Another expert observed that as a society, we often choose personal convenience over social cost perhaps until we reach a crisis situation when we are forced to make sacrifices. For example, obesity-related diabetes and heart disease and smoking-related lung cancer are attributable to poor lifestyle choices by some individuals in society, and the bailout is a technological solution at a high social cost, subsidized by others either through higher insurance or additional tax dollars. Sometimes these poor choices are exacerbated by the security that insurance is available to cover the medical costs. When the non-poor with health insurance over-use medical resources, insurance costs are driven up and the poor can no longer afford insurance[73].

Similarly, a disproportionate amount of insurance and tax payer dollars are spent in this country on medical care for the last 6 weeks of a person's life, relative to the expenditures over the rest of the person's life. This imbalance may change under crisis conditions as society begins to revalue care for the terminally ill.

7.1.d Additional Political and Regulatory Drivers

The likelihood of a universal healthcare program depends to some extent on which political party – republican democrat or some other – is in power. Some experts noted that the potential shift to a universal healthcare policy might force healthcare providers (doctors) to subscribe to an outcomes-based model but they recognized that organizing providers for the outcomes-based capitation model might be very difficult and protracted, given the complexity of the current system and the embedded system of incentives for the various stakeholders.

[73] G. Langer, "Health care pains: growing health care concerns fuel cautious support for change", ABC News, August 29, 2006.

Another observation was that it is not clear whether the average consumer will gain sufficient awareness and understanding of the impact and risks of new healthcare technologies such as implantable biosensors. However, as noted earlier, grassroots advocacy groups are increasingly organizing to influence consumers, using the Internet to break down the information imbalance.

For wide-scale deployment of implantable biosensors, data response protocols are essential. Central to the issue of data management and response is identification of individuals who will clearly be accountable for the care delivery or face liability. Unless medical malpractice liability issues are resolved to the satisfaction of providers, there may be an unwillingness to assume responsibility, and hence risk, for responding to the large volume of new biosensor data that is likely to be generated.

Finally, an expert noted that perhaps under a universal healthcare program with a stronger preventive care mandate in light of skyrocketing medical costs, government may be able to curb individual rights and force broad use of implantable biosensors technology by consumers. An example in present times is the threat and challenges to individual privacy civil liberties under the pretext of a crisis situation such as a war. Whether such policies could continue unchallenged over time remains to be seen.

7.2 Separating Trends from Uncertainties

We note again that the objective of scenario planning is to gain insight into the future by envisioning various scenarios that are likely to be driven by key uncertainties. The list of drivers that we compiled, through review of secondary sources and discussions with experts, was further reduced. We separated the forces that were trends from those that exhibited true uncertainty. As discussed earlier, trends are forces that are clearly identifiable or knowable with the right analysis e.g. market demographics and changing consumer behavior. Uncertain forces on the other hand are drivers about which little can be predicted, given the

wide range of possible outcomes. We classified the 46 forces that were compiled into 20 trends and 26 uncertainties, based on information from review articles and the interviews with the experts. The result of this subjective assessment is shown in Table 7.2 below.

Table 7.2 List of strategic drivers likely to impact commercialization of implantable biosensors technology, separated into trends (left column) and uncertainties (right column).

TRENDS (20)	**UNCERTAINTIES (26)**
Technological	
Miniaturization	Clinical safety and efficacy of Biosensors
Minimally invasive device implantation	Handling miniaturized devices effectively
Remote monitoring	External Communications Interference
Autonomous operation	Reliable integration of Closed-loop systems into clinical care delivery
Immune-response suppression during implantation	Broad Biocompatibility; biological interference
Computing Power	Component Reliability
Powering of Devices	Synchronizing of data from distributed Sensor networks
	Power management and probability of catastrophic failure
	System Infrastructure & Interdependencies
	Data overload for Doctors
	Scope of Functionality/ Application
Economic	
Cost containment and cost effectiveness	Identifying where care will be delivered
Understanding the provider's economics	Medical malpractice liability
Payer-driven Outcomes-based capitation	Employer-driven dis-intermediation of CMS role in defining reimbursement levels
Retraining costs & Resistance to change	Consumer influence on technology adoption
Employer-subsidized healthcare programs	Who gets reimbursed for responding to sensor data—capitation formula
Direct-to-consumer marketing	Commercialization path—route to Market
Social	
Individualization of care	Privacy vs. convenience & efficacy
Tracking patient care	Trust in the regulatory system
Medical data privacy	Personal convenience vs. social cost limits
	Value of terminal care
Political/ Regulatory	
Universal healthcare access and coverage	Organizing providers for Outcomes-based care
Consumer advocacy and activism	(Sensor Data) Response processes &

	protocols
Awareness/education of technology's value	FDA's mandate vs. Truth-in-labeling practices (WYSIWYG)
Medical data ownership and control	Broad adoption of Biosensors platform for preventive screening

7.3 Rank Ordering of Key Uncertainties

The uncertainties were further rank ordered, for ease of analysis, within the four main categories (Table 7.3) – technological impact, economic impact, social impact, and political/ regulatory impact. After this initial prioritization, the list was further ordered on a general basis, independent of category (Table 7.4). The ranking was subjective but primarily based on concurrence from the experts on which drivers exhibited significant uncertainty and not necessarily on just the degree of importance or weight the drivers carried. For example, while component reliability is critically important, sufficient testing could limit the risk of catastrophic failure, whereas very little can be predicted about the broad range or nature of interdependencies and infrastructure that may be required for successful adoption of implantable biosensors.

Table 7.3 Rank ordering of 26 uncertainties influencing implantable biosensors technology within the four broad categories: technological, economic, social and political/ regulatory factors.

Rank within category	**UNCERTAINTIES (26)**
	Technology
5	Clinical safety and efficacy of Biosensors
10	Handling miniaturized devices effectively
11	External Communications Interference
6	Reliable integration of Closed-loop systems into clinical care delivery
4	Broad Biocompatibility; biological interference
9	Component Reliability
7	Synchronizing of data from distributed Sensor networks
8	Power management and probability of catastrophic failure
1	**System Infrastructure & Interdependencies**
3	Data overload for Doctors

2	**Scope of Functionality/ Application**
	Economic
3	Identifying where care will be delivered
4	Medical malpractice liability
6	Employer-driven dis-intermediation of CMS role in defining reimbursement levels
5	Consumer influence on technology adoption
2	**Who gets reimbursed for responding to sensor data—capitation formula**
1	**Commercialization path—route to Market**
	Social
4	Privacy vs. convenience & efficacy
3	Trust in the regulatory system
1	**Personal convenience vs. social cost limits**
2	**Value of terminal care**
	Political/ Regulatory
2	**Organizing providers for Outcomes-based care**
1	**(Sensor Data) Response processes & protocols**
4	FDA's mandate vs. Truth-in-labeling practices (WYSIWYG)
3	Broad adoption of Biosensors Platform for preventive screening

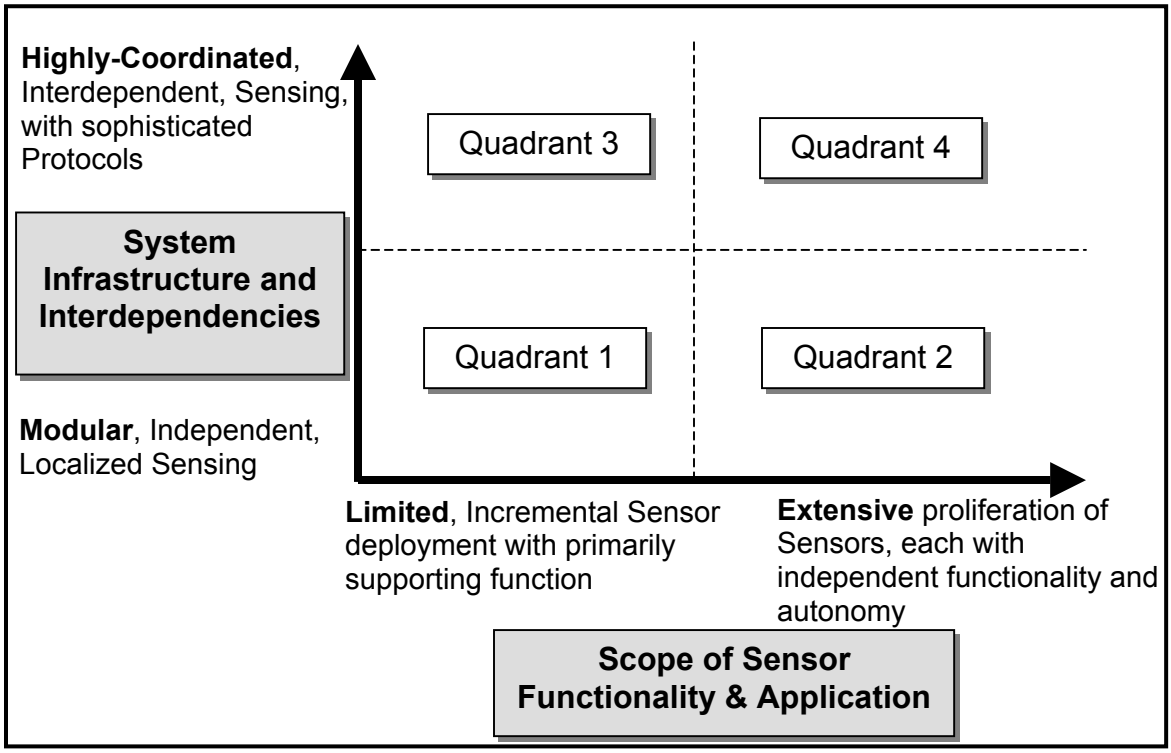
Table 7.4 Generalized rank ordering of the 26 uncertain forces.

Generalized Rank	TOP (9) UNCERTAINTIES (in bold)
5	**Clinical safety and efficacy of Biosensors**
	Handling miniaturized devices effectively
	External Communications Interference
	Reliable integration of Closed-loop systems into clinical care delivery
4	**Broad Biocompatibility; biological interference**
	Component Reliability
	Synchronizing of data from distributed Sensor networks
	Power management and probability of catastrophic failure
1	**System Infrastructure & Interdependencies**
3	**Data overload for Doctors**
2	**Scope of Functionality/ Application**
	Identifying where care will be delivered
	Medical malpractice liability
	Employer-driven dis-intermediation of CMS role in defining reimbursement levels
	Consumer influence on technology adoption
	Who gets reimbursed for responding to sensor data—capitation formula
8	**Commercialization path—route to Market**
	Privacy vs. convenience & efficacy
	Trust in the regulatory system
7	**Personal convenience vs. social cost limits**
9	**Value of terminal care**
	Organizing providers for Outcomes-based care
6	**(Sensor Data) Response processes & protocols**
	FDA's mandate vs. Truth-in-labeling practices (WYSIWYG)
	Broad adoption of Biosensors for preventive screening

7.4 Aggregation of Inter-related Drivers under the Two Principal Uncertainties

From the assessment in Table 7.4, we arrived at the two principal uncertainties that will have broadest impact on future scenarios for commercial implantable biosensors in healthcare. The two key uncertainties are: (1) the system infrastructure and interdependencies to support commercial implantable biosensors, and (2) the scope of functionality and application that these biosensors will realize. These two drivers then formed the two dimensions on which the uncertainty was characterized. Restricting the outcomes of these two uncertain drivers to simply two possible, extreme states, we arrived at a manageable 2 x 2 matrix (Figure 7.1) that would capture four potential scenarios of the future of commercial implantable biosensors in healthcare.

Figure 7.1 Key strategic dimensions of uncertainty driving the commercial implantable biosensors in healthcare: (1) "what will the sensors do" (scope of sensor functionality & application), and (2) "how will the sensors operate" (infrastructure & interdependencies).



The four scenarios, represented in the four quadrants in Figure 7.1, would emerge not only from an assessment of the possible states that the two drivers could take, but also from the possible states that other inter-related drivers could assume (e.g. data overload concerns, commercialization path, etc.). We therefore aggregated the 26 key drivers in Table 7.4, to the extent possible, under the two principal dimensions in Figure 7.1. The aggregation of drivers (Table 7.5) was performed on the basis of: (1) internal consistency, (2) inter-relatedness, and (3) significance. The assessment was necessarily subjective but reflects the comments and views of the experts interviewed in this study.

Table 7.5 Aggregation of various drivers under the two primary drivers of uncertainty regarding commercial implantable biosensors.

System Infrastructure and Interdependencies	**Scope of Sensor Functionality and Application**
Data overload management	Broad biocompatibility for wider sensor application
Biological interference	Personal convenience vs. social cost: cost-driven sensor-based preventive care
Clinical safety and efficacy with biological/ systemic interdependencies	Commercialization path—route to market:
Data response processes and protocols	Value of terminal care
Handling miniaturized devices effectively	Component reliability
External communications interference	Power management and catastrophic failure
Reliable integration of sensor networks into care delivery	Liability-limited proliferation of new sensor technologies
Synchronized data from distributed sensors	Employer (productivity)-driven proliferation of new sensing technologies
Single point of failure in sensor network	Consumer influence on wider adoption of sensor technology
Identifying where care will be delivered	Privacy vs. convenience and efficacy: tradeoffs for wider sensor proliferation
Liability from negligence within interdependent support systems	Continued consumer confidence in the FDA regulatory system
Reimbursement model for care providers in for sensor technology infrastructure	Dis-intermediation of the FDA through Truth-in-labeling practices
Organizing providers for outcomes-based care	Broad adoption of Biosensors in multiple applications for preventive care

The scope of functionality and application has embedded in it significant uncertainty through the influence of other inter-related forces. For example, the number and variety of commercial implantable biosensors at different body sites – e.g. blood glucose monitors, drug efficacy sensors, arterial occlusion monitors, etc. – is likely to depend on uncertain technological drivers such as broad biocompatibility, implantable component reliability, overall power management within the body, and reliable signal telemetry between components within the body and to the outside world. In addition, socio-economic drivers that are likely to constrain the pace at which new biosensors technology is rolled out include: medical malpractice liability barriers, the ability to secure adequate reimbursement for radically new technologies, consumers' influence on channels to market, and the products functionality as defined by the needs of mature medical device firms which might seed and later acquire the innovators. Finally, political and regulatory factors include: the likelihood of a universal healthcare program that will be driven by the goal of preventive care, the role and power that the FDA will continue to have to regulate new device technologies, and the tradeoffs between privacy of medical data and convenient and efficacious care delivery.

The system infrastructure and interdependencies has emerged as the other major driver of uncertainty in this study, with indirect and direct influence on and from the following drivers. For example, the ability for implantable biosensors to effectively diagnose a specific disease, or even a broad range of diseases, would depend on perhaps sensing a complex system of parameters (bio-analytes) and synchronizing, processing, and interpreting the different biological data effectively, and even managing the biological interference between them. Once the data has been collected and processed and a diagnosis or prognosis has been made, there still remains the issue of archiving, protecting, and sharing the data efficiently and effectively. Identifying the network of individuals and teams that will have access to the data and how they will respond to it in light of accountability for health management will be crucial. This infrastructure will

perhaps have to be highly integrated to ensure that there is no single point of failure in the larger 'biosensors' supporting ecosystem'. The devices themselves will also impose additional requirements on specialized handling procedures, depending on their size, how and at what types of healthcare centers they will be implanted within the body and also serviced. Finally, the care delivery ecosystem for implantable biosensors will have many players who will have to be adequately reimbursed for their contributions to ensure that everyone is focused on safe and efficacious delivery of care.

8 CREATING SCENARIOS

8.1 Scenarios in a 5- to 10-year Reference Timeframe

With the aggregation of the drivers under the two principal dimensions of uncertainty, we then proceeded to construct four scenarios by imposing two specific states for future outcomes along each of the two key dimensions. Thus, we assumed that scope of functionality and application could be either limited or extensive, and similarly the system infrastructure and interdependencies could be either modular or highly integrated. Under these specific states, we subjectively compiled a list of self-consistent characteristics that the scenario in each quadrant would likely exhibit (Figure 8.1). The four scenarios are elaborated below.

Figure 8.1 Identification of the characteristics of four scenarios (quadrants 1-4). The characteristics emerged from an analysis and aggregation of key drivers of uncertainty under the two principal dimensions: (1) system infrastructure and interdependencies, and (2) scope of functionality and application.

Quadrant 1—Modular Adjunct Sensors supporting Implanted Devices	**Quadrant 2—Proliferation of Multiple, Stand-alone Sensor Applications**
1. Relatively simple sensors to monitor implanted device performance & reliability. 2. Limited direct interaction with biological host 3. Sensors with narrow biocompatibility, potentially shielded within implanted device. 4. Sensor safety/ efficacy linked closely to host implant device. 5. Data response protocols limited to assessment of implant performance, with link to device monitoring system. 6. Miniaturization requirements set by size constraints of pre-existing implant. 7. Wireless link between sensor and	1. Broadly biocompatible materials and structures enable sensors at multiple sites in the body. 2. Proliferation/ deployment of many varieties of modular Biosensors, targeting prevention of multiple diseases e.g. Insulin deficiency/ resistance, arterial occlusion, retinal damage, obesity, sleep apnea. 3. Independent, new Sensors companies developing Biosensors for standalone monitoring function rather than supporting performance monitoring of Implants. 4. De-emphasis of funding allocation on high-cost terminal care, with new focus on preventive care. 5. Increased component reliability

control system based on dedicated communications spectrum. 8. Sensors co-implanted with medical device at the same point of care. 9. Sensor applications constrained by exits via 3-4 major Medical Device firms and their narrow technological needs. 10. FDA continues to regulate new 'intelligent' implantable devices with assessment of pre/post-market data including device's internal monitoring.	(batteries, microchips) drives proliferation of Biosensors 6. Medical malpractice caps limit liability and increase available risk capital for innovative biosensors technology. 7. Productivity-driven proliferation of Biosensors to monitor many varieties of disease. 8. Wider adoption of Biosensors by consumers to facilitate personal convenience and unhealthy lifestyle choices. 9. Medical privacy compromised to enable greater convenience and efficacy in broader preventive care policy. 10. Lack of safety/ efficacy controls due to dis-intermediation of FDA by direct to consumer practices, without alternative regulatory system. 11. Wireless link architecture and response protocols similar even across distinctly different Biosensors.
Quadrant 3—Coordinated Health Management based on targeted Biosensor applications 1. Multi-sensor data fusion and management. 2. Coordinated multi-point sensing to account for biological complexity of diseases e.g. cancer, heart disease, and mental disorders. 3. Complex interdependent sensor systems for targeted diseases, with broad data accumulation for improved clinical efficacy. 4. Specific data response protocols, including integration of closed loop monitoring with traditional clinical care delivery e.g. "artificial pancreas" systems. 5. Fault-tolerant data links in sensor system to mitigate risk of single point of failure and communications interference. 6. Implantation of sensor system at	**Quadrant 4—Broad Preventive Care based on Autonomous Integrated Biosensor Networks** 1. Autonomous sensor nodes mine "human biological data", working in tandem to monitor total health of patient for coordinated care of multiple diseases. 2. Deployment motivated by cost-efficient strategy for managing terminal care, for patients with multiple advanced diseases e.g. AIDS and advanced-stage cancer. 3. High cost of care creates healthcare crisis and drives wider government-mandated adoption of biosensors for broad disease prevention under universal healthcare policy. 4. Biological data comes under purview of FDA, with limitation of individual rights to medical privacy. 5. Specialized highly coordinated new services for sensor implantation and

specialized facilities, including specialty primary care centers. 7. Medical malpractice caps limit liability and increase availability of experimental biosensors systems, which gain acceptance with good post-market surveillance. 8. Reimbursement model rewards single principal care provider and supporting care network for total disease management. 9. Well positioned for outcomes-based capitation model.	response protocols, as well as for patient biological data management. 6. Novel biocompatible/ resorbable materials and structures enable near-ubiquitous use of nano-scale, self-assembling, distributed biosensors for intelligent sensing in aggregate. 7. Sensor functionality broadly includes monitoring of physiological condition, disease diagnosis, prognostic indication, and therapeutic intervention. 8. FDA charged with implementing wide-scale testing platform for total body sensor mesh networks for 'pervasive sensing'. 9. Biosensors technology innovation driven by specialized Sensor companies forming new industry segment with special federal mandate to develop integrated sensor-based care systems. 10. Liability constraints eased/limited in controlled fashion to spur technological innovation. 11. Outcomes-based reimbursement model grows out of preventive care paradigm, with integrated care provider network supporting total patient health.

8.1.a Scenario 1: Modular Adjunct Sensors supporting Implanted Devices.

The first scenario describes a potential outcome in which the scope of application and functionality is expected to be limited, and the system infrastructure and interdependencies are expected to be modular and minimally coordinated. The sensors are likely to be relatively simple, primarily to provide a supporting role for monitoring the performance and reliability of implanted medical devices. For example, such sensors could monitor pressure and abrasion of knee or hip implants, and track refill status for drugs in the internal chambers of drug-eluting devices. The sensors need not have extensive interaction, if at all, with the host

biological system and may be restricted to sensing the specific operating parameters in the implanted 'parent device'. As such, the biocompatibility requirements for such sensors may be narrow, given that the sensor may be shielded within the compartment of the parent device. The safety and efficacy standard of such sensors may be tightly linked to that of the parent device. Furthermore, the efficacy standard for the parent device may even be eased given that the adjunct sensor's role is precisely to monitor, *in situ* and in real time, safety and efficacy of the parent device. Given this role, data response protocols may be relatively light, limited to communicating data about specific parameters to an external monitoring/ control station. The encrypted communication between the sensor and the control systems will likely use a wireless link across a private spectral band. Also, such adjunct sensors may have miniaturization requirements set by size constraints in the parent device.

These modular adjunct sensors will likely be co-implanted with the primary medical implant at the same point of care, probably at specialized or tertiary healthcare institutions. This restricted use of biosensors will likely be due to the domination of the market by a small, select group of mature medical device makers with specific technological needs in support of existing products. Given the marginal role that the sensors will likely play, the technological risk that the 'end-user firms' will accept may also be comparatively low. Finally, the FDA will likely continue to regulate the new class of 'intelligent implants', with assessment of not only pre-market safety and efficacy data but also prost-market surveillance of the same, utilizing in fact the implant's internal monitoring capabilities. Pre-market approval should not become any tougher, provided the sensors are eased in as beneficial accessories to the primary implanted device without imposing any additional risk.

8.1.b Scenario 2: Proliferation of Multiple, Stand-alone Sensor Applications

The second scenario describes a potential outcome in which the scope of application and functionality is expected to be extensive, but the system infrastructure and interdependencies are expected to remain modular and minimally coordinated. There will likely be a proliferation of a variety of modular sensors for multiple, stand-alone applications at multiple sites in the body, monitoring problems such as insulin deficiency, arterial occlusion, retinal damage, obesity, and sleep apnea. Broad biocompatibility, based on thin surface coatings of biomimetic polymers to make the sensors essentially transparent to the autoimmune response system, will likely enable sensing applications in organs, tissue, as well as blood vessels. The proliferation will also be made likely by the improvements in the reliability of components – batteries, microchips, micro-motors, etc. – beyond the 'tipping point' for widespread adoption. Standards for wireless telemetry between the implanted sensors and external systems will likely emerge to regulate communications protocols broadly used by a variety of sensors, so that safe operation with minimal interference can be ensured.

This biosensor technology will likely be shepherded to market by a new breed of independent sensor companies, developing biosensors for standalone monitoring applications rather than as adjunct devices for specific implants i.e. the sensory information provided by the new biosensors may not require the co-implantation or co-operation of another implantable medical device such as a stent, cardiac defibrillator, or neural stimulator. The push towards broader biosensing capabilities will be driven in large part by cost-containment efforts, with a general shift in funding allocations (by CMS and private payers) from high cost critical and terminal care to lower average-cost preventive care. The drive for cost effectiveness will likely have to be matched by containment of other cost-escalating factors such as medical malpractice liability, essentially through creative legislation of caps for malpractice awards. Limits on penalties for risk

taking will likely increase the available risk capital and spur technical innovation. Some of the biosensor innovation may be driven by a desire for increased employee productivity and reduced liability risk at businesses, with applications such as sleep apnea monitoring garnering interest initially in high-stress professions such as among surgeons and pilots. Consumer choice and convenience may also drive adoption of biosensor technologies such as 'gastric monitors' to enable automatic, controlled release of diet drugs *in vivo* in high-risk obesity patients on as-needed basis.

While standards for communications and biomaterials will likely be adopted unilaterally by the biosensors industry to ensure safe and efficacious operation of the devices, the broader regulatory influence of the FDA may be weakened. The undermining of FDA authority may result from the rapid proliferation of sensor technologies and the consequent inability of the FDA to effectively manage the safety and efficacy control checks. Furthermore, inherent controls for safety and efficacy within the new sensor technologies may empower firms to argue that their products be permitted to essentially bypass the FDA process. However, this could also serve to weaken the influence of the FDA over time. Without an effective alternative regulatory body, the dis-intermediation of the FDA could undermine, over the longer term, people's confidence in the safety and efficacy of healthcare technology in general, and medical devices and sensors in particular.

8.1.c Scenario 3: Coordinated Health Management with Targeted Biosensor Applications

The third scenario describes a potential outcome in which the scope of application and functionality is expected to remain limited, but the system infrastructure and interdependencies are expected to become highly coordinated. One is likely to see a deployment of highly coordinated 'sensor systems' with sophisticated data fusion, processing, and management. The sensor system concept will emerge as it becomes more evident that the most effective way to

cure, or even manage, complex diseases such as cancer, heart disease, and mental disorders may be to sense several sites and 'analytes' in the body simultaneously, to correctly account for the inherent complexity and interdependence in biological interactions. An example of such diverse sensing for improved clinical efficacy could be the management of heart disease by simultaneously tracking: arterial blockage, cholesterol levels, arterial blood pressure, body weight, and even hormonal changes associated with stress. The first generation of such multi-parameter sensing systems may already be emerging, with wearable sensors measuring for example calories consumed, calories burned, carbohydrates consumed, and blood glucose levels for improved metabolic assessment and management of diabetes[74]. Specific data response protocols will likely be developed for the management of a given disease, including effective integration of closed loop systems with conventional healthcare delivery processes. An example of a closed loop system might be the 'artificial pancreas' where it is hoped that implanted insulin delivery pumps will communicate effectively with implanted blood glucose sensors[75]. The data from the closed loop system will likely be downloadable and presentable to an endocrinologist for further assessment of any aberrant glycemic 'patterns', even with the closed loop glucose monitoring system, so that if necessary the patient can be brought in to the hospital for emergent care. Efficacy improvements notwithstanding, multi-site sensor systems present additional challenges in terms of potential single-point-of-failure situations arising in a specific component or even a data link. Fault-tolerant architectures will likely emerge, either through notification using alarms or through use of redundant components and links.

However, such biosensors for coordinated health management may still be limited in scope of application by the availability of broadly biocompatible structure and materials. For example, structural and material limitations may

[74] See for example, BodyMedia, Inc. (www.bodymedia.com).
[75] For example, Medtronic's Minimed division has announced that it will attempt to bring to market by 2008 an implantable glucose sensor and insulin pump system. See: http://www.jdrf.org.au/research/newsitem.asp?newsid=98.

dictate how the sensor attaches itself to the biological host without interfering with the ongoing biological processes of the host, e.g. an intra-arterial sensor that will not obstruct blood flow or accidentally cause tissue overgrowth to get dislodged, leading to a pulmonary embolism[76] and possibly death. Some sensors may be deployed in tissue but not in blood vessels, or in arteries but not in tiny blood capillaries. Therefore, under this scenario, it is anticipated that limitations in broadly applicable materials and structures for implantation will likely restrict the biosensors technology to specific applications, at least until major breakthroughs in biomaterials are achieved.

On the regulatory and legislative front, medical malpractice liability awards may have to be restricted in order to increase availability of experimental biosensor systems, but it is likely that that these systems will gain increasing acceptance with good post-market surveillance from the data logged by the systems themselves. In fact, the long-term continuous monitoring of biological data using these biosensor systems will very likely usher in a new era of data gathering capability for the validation of the next generation of medical devices. The reimbursement model may very well migrate to an outcomes-based approach simply because for the first time, outcomes will become 'measurable', not just in terms of the number of days of hospitalization for each patient treated (the lower the better), but additionally in terms of monitoring the patient's vital statistics and health parameters in a more sophisticated way. For example, the physician in charge will be reimbursed for his prescription of the most efficacious drug for a given patient, and the drug company will be reimbursed accordingly for the same efficacious outcome, but the difference is that the clinical efficacy may be measured by assessing specifically how the body metabolizes the drug and how the disease responds to it overall, accounting for adverse drug reactions. The healthcare delivery network to be reimbursed will likely include supporting

[76] A pulmonary embolism (PE) is a blockage of an artery in the lungs by a blood clot, fat, air or clumped tumor cells. The most common form of PE is thromboembolism, which occurs when a blood clot dislodges from its site of formation and embolizes to the arterial blood supply of the lungs. Symptoms can include breathing difficulty, circulatory instability, and even death.

technical staff that will capture, process, manage, and share the data among the team of doctors, with a single physician assuming total accountability.

8.1.d Scenario 4: Broad Preventive Care with Autonomous Integrated Biosensor Networks

The fourth scenario describes a potential outcome in which the scope of application and functionality is expected to be extensive, and the system infrastructure and interdependencies are expected to become highly coordinated. One is likely to see autonomous biosensor nodes, working interdependently in a mesh network to mine human biological data. These sensors will monitor the total health of the patient for coordinated care of multiple diseases and will provide unprecedented 'aggregated intelligence' (AI) about the patient's body. The deployment of such sensors will be motivated by the goal of cost effectiveness in the delivery of healthcare, particularly critical and terminal care. For example, patients with advanced diseases such as AIDS or advanced-stage cancer are likely to benefit from such systems.

We envision sensor network functionality that will broadly include: monitoring of physiological condition, disease diagnosis, prognostic indication, and therapeutic intervention. The implantation and servicing of the physical devices, as well as the response to and management of data, will likely require a new class of specialized, highly coordinated services. As discussed in Section *7.1.b*, this network of people and services, which would have to be seamlessly integrated for efficiency, could include for example: secure data processing and archival services; messaging and information delivery services; safety and regulatory compliance management; a 24/7 first-responder team; triage services; a principal care provider; consultant specialists; ambulatory services in the case of critical care; billing services; and hospitalization and pharmacy support. Resources such as 'biotags' for locating targets within the body, ubiquitous data readers, and a network of users to build critical mass for the effort, will likely become prevalent. Secure and efficient management of this complex biological data network, both

within and outside the body, will require truly redundant, fault-tolerant, mesh network architectures. If one biosensor node fails, other nearby nodes will likely be able to reorganize to seamlessly recover the operation of the network. Such architectures are already in existence in wide-area wireless communications. Context awareness may be another characteristic of such networks, with each sensor having the ability to sense not only biological changes but also the presence of other nearby sensors and even its specific role in a new biological environment. The biosensors will likely be delivered to the target sites by direct, minimally invasive insertion at the site. Alternatively, the biosensors, if sufficiently small e.g. nanoscale sensors, could be inhaled, infused through the skin, or even ingested; in the latter case, the sensors will likely be attached to binding agents targeting specific receptor sites, in much the same way as targeted drug delivery to disease sites in the body is designed today. Thus, such sensors could become effectively hybrid devices, combining device technology with drug coatings before dispersion into the biological system. With the ubiquity of data and control links between sensors and the external control station, the communications would have to be secure. It is likely that some form of bio-security protocol will emerge as a standard to encrypt data from each individual, with this data being accessible only using a unique identifier or 'key' available to the patient and authorized personnel.

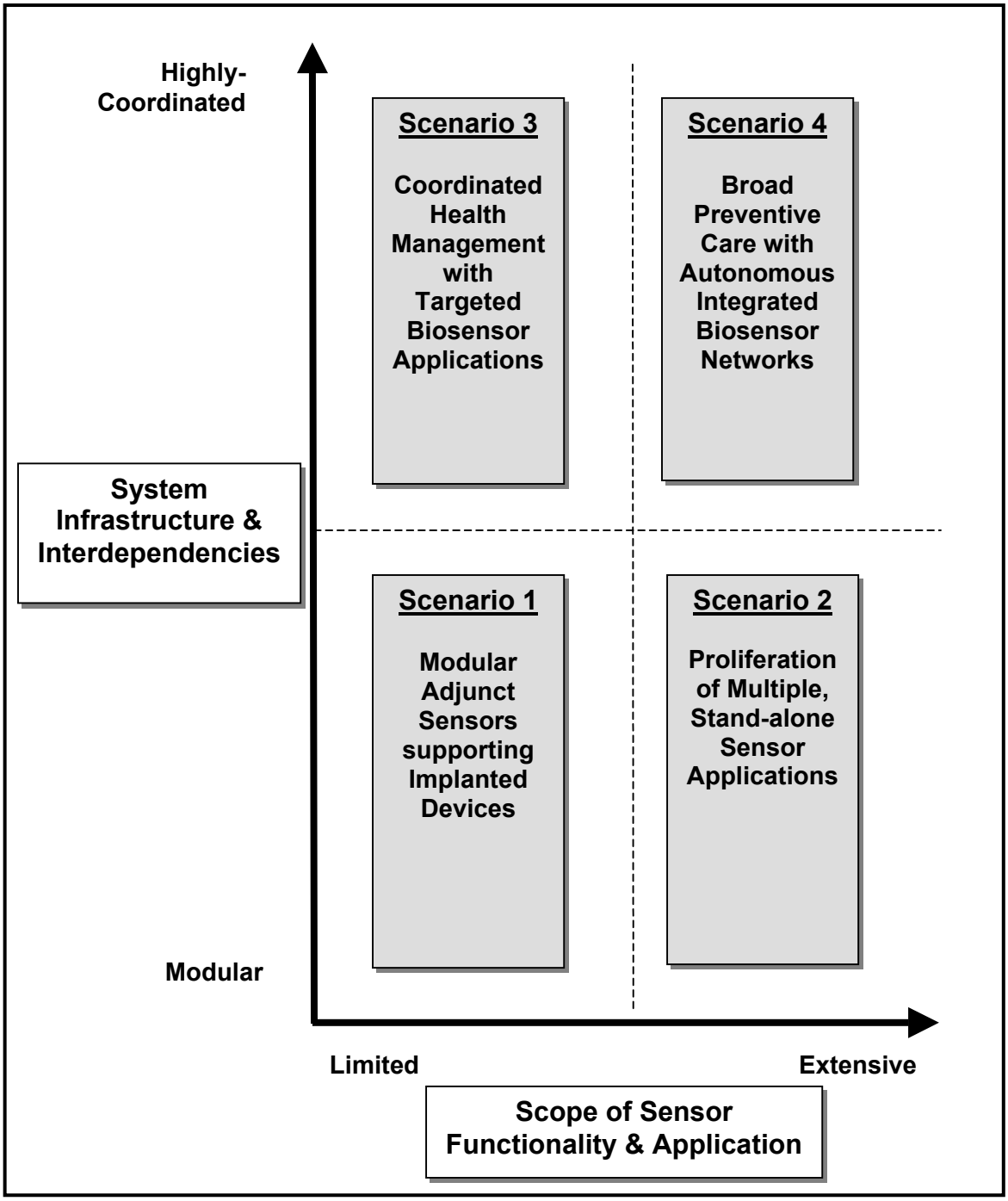
The high cost of healthcare today will likely create an acute crisis in this country at which point preventive care will truly take center stage. Under this scenario, the FDA is likely to emerge as a stronger, even more influential body. All biological data from U.S. citizens will come under the jurisdiction of the FDA, which will 'own' the data but will permit access to all authorized parties including the patient. We envision government support for biosensors technology for broad disease prevention under a universal healthcare coverage policy, with a combination of state and federally mandated incentives and penalties, in the form of personal and business tax shields and other creative mechanisms, to encourage adoption. To counter concerns about safety and efficacy and to

overcome the consumer's fear of having pervasive continuously-active implants within the body, the FDA or equivalent body will likely be charged with developing and managing a wide-scale testing platform, in partnership with research institutions and industry, to evaluate these 'total body sensor mesh networks' for pervasive sensing within the body. At the same time, there will likely be legislative efforts to limit risk from medical malpractice liability for biosensor manufacturers, at least for a limited period of time, to spur innovation.

Finally, it will be a new group of specialized sensor companies that will drive the biosensors technology innovation. They will likely create a whole new industry segment, with a special federal mandate and perhaps even licenses to develop integrated sensors-based healthcare monitoring and delivery systems. Within this unique sheltered environment of technology development with sufficient controls for a high degree of product safety, we will likely see remarkable technical innovations, and perhaps even some significant breakthroughs in curing, or effectively managing, one or two major diseases such as diabetes or a specific cancer.

The four scenarios are shown in Figure 8.1 below.

Figure 8.1 Key strategic dimensions of uncertainty driving commercial implantable biosensors in healthcare: (1) "what will the sensors do" (scope of sensor functionality & application), and (2) "how will the sensors operate" (infrastructure & interdependencies), including the four scenarios that are likely to emerge.



9 DISCUSSION OF RESULTS AND FUTURE WORK

The exercise of creating the scenarios has been based on a disciplined imagination of how the various uncertain forces could interact to shape outcomes. The first scenario suggests incremental advances in implantable biosensor technologies in an environment largely similar to the status quo. In the second scenario, we see a wider proliferation of implantable sensor technologies, enabled primarily by the availability of broadly biocompatible materials and structures. However, in this scenario, we envision that scope expansion without greater coordination may result in an uncontrolled and perhaps haphazard development and adoption of technology, fraught with greater personal risk for the patient. In the third scenario, while greater coordination is predicted to accurately account for and manage the inherent interdependencies in sophisticated biosensing systems, applications will still be limited by the availability of biomaterials and biostructures broadly compatible with a variety of biological environments in the body. Finally, under the fourth scenario, we predict scope expansion as well as a high degree of coordination. We anticipate significant regulation and control by designated federal and state agencies to foster a sheltered environment for innovation while also protecting consumer safety.

We address below several noteworthy observations on the specific scenario outcomes that were reached. One astute remark was that our scenarios are characterized by what could really be deemed ‘phases of technological sophistication’ rather than truly orthogonal outcomes. Orthogonality between the final scenarios is an important property because the scenario planner is attempting to uncover and prepare for as many distinct and dissimilar scenarios as possible through this multi-perspective assessment of the future. However, one has to recognize that each of these ‘technological scenarios’ is a product of a variety of other factors such as economic, social, and regulatory drivers. While all four of our technological scenarios *can emerge perhaps sequentially* (phases), *only one may actually emerge* because each needs unique conditions and

environment to foster it, and if the conditions are right, we might leapfrog one or more these 'phases'. For example, if legislation is passed to judiciously limit medical malpractice liability risk and the FDA pre-market approval process is eased in return for increased surveillance of implanted medical devices, companies may invest in crucial enabling technologies such as biomaterials and biosensor networks. The end result might be a much more rapid and wider proliferation rather than an incremental evolution of implantable biosensors technology.

Another comment was that the scenarios have a distinctly technological flavor, and that perhaps the primary drivers of uncertainty should have included non-technological factors as well e.g. economic, political/ regulatory, etc. Again, it is true that the scenarios are the product of forces from dissimilar categories (technological, social, political/regulatory, economic), but there is no requirement that the primary drivers of uncertainty emerge from these orthogonal categories i.e. the scenarios can be formed from considering two *technological* drivers. In this study, the primary drivers emerged naturally from the discussions with the experts. However, it must be recognized that the self-consistent aggregation of forces under this umbrella of 'primary drivers' also accounts for the other important factors such as reimbursement and healthcare policy; these other forces, while now in a supporting role, are certainly not ignored.

The technological flavor also emerged because the time horizon for these scenarios was reasonably long (5-10 years). The majority of the experts in our panel felt that other important and uncertain issues such as reimbursement could eventually be worked out provided the efficacy and complexity of biosensors technology could be sorted out first. Interestingly, Wharton's Mack Center is pursuing another scenario planning study (ongoing) to gain insights into the

future of implantable medical devices[77]. The medical device's function would of course be broader than that of a biosensor, including not only monitoring/sensing but also therapeutic intervention. In the new Mack Center study, the time horizon is shorter (5 years) and as a result many experts felt that reimbursement would be more critical. The primary drivers of uncertainty in that study emerged as *information* (quality, type, reliability, etc.) and *reimbursement* (who gets paid, how much, and for what). Furthermore, information has to be broken down into: patients' personal identity data, medical device data, and clinical Information/ data e.g. blood pressure and heart rate, but also possibly deeper physiological and biochemical data. This study on implantable biosensors does attempt to address the complexity of and coordination required to manage some classes of biosensor information, including but not limited to reimbursement for physicians and support staff who will respond to the data.

Whether the monitoring of patient health or disease condition using biosensors will be *recognized* as actually creating value, in view of the complexity and challenges in remote monitoring and its adequate reimbursement, remains to be seen. Nevertheless, there are certainly early indications that there is growing awareness of its potential value. With the new emphasis on post-market surveillance, product information at minimum – from tracking product serial number and patient identity to ensuring normal device operation – would be important from economic and safety perspectives. Perhaps the clearest indicator of this trend is the recent legislation submitted to the U.S. Congress for increased reimbursement of remote health care monitoring (Remote Monitoring Access Act of 2006, Sept. 13, 2006, HR 6063). Under this new legislation, we note specifically[78]:

[77] P. Schoemaker et al, "Scenarios for Implantable Medical Devices: U.S. view through 2012", Decision Strategies International, Inc. in partnership with the Wharton School's Mack Center for Technological Innovation, December 2006.
[78] See for example, http://www.theorator.com/bills109/hr6063.html.

"…Despite these innovations, remote management technologies have failed to diffuse rapidly. A significant barrier to wider adoption is the relative lack of payment mechanisms in fee-for-service Medicare to reimburse for remote, non-face-to-face management… This Act will eliminate this barrier to new technologies by requiring Medicare to reimburse doctors for time spent analyzing data transmitted to them by remote patient management technologies. "

"…The Secretary (of HHS), in consultation with appropriate physician groups, may develop guidelines on the frequency of billing for remote patient management services. Such guidelines shall be determined based on medical necessity and shall be sufficient to ensure appropriate and timely monitoring of individuals being furnished such services… the Secretary, in consultation with appropriate physician groups, shall take into consideration-- (A) costs associated with such services, including physician time involved, installation and information transmittal costs, costs of remote patient management technology (including devices and software), and resource costs necessary for patient monitoring and follow-up (but not including costs of any related item or non-physician service otherwise reimbursed under this title); and (B) the level of intensity of services provided, based on-- (i) the frequency of evaluation necessary to manage the individual being furnished the services; (ii) the amount of time necessary for, and complexity of, the evaluation, including the information that must be obtained, reviewed and analyzed; and (iii) the number of possible diagnoses and the number of management options that must be considered…"

While our assessment of the degree of uncertainty in the drivers of commercial biosensor implants was largely subjective in this study, we believe that a quantitative analysis of correlation between interacting drivers, using correlation matrices, could potentially lead to a better estimate of the degree of uncertainty. Going forward with this assessment of future scenarios, stakeholders such as investors, technologists, and corporate managers still need to address the questions: (1) how do firms decide which biosensor technologies to pursue

(strategic evaluation of technologies using real options reasoning), (2) when they should pursue them (estimation of the maturity of the technology, market creation vs. market penetration objectives, risk profile), and (3) in what way should they position their businesses to take advantage of opportunities at the right time (strategic alliances, seed investments in startups, acquisition of startups, internal R&D). We hope the above will be the subject of a future study.

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11 BIOGRAPHICAL DATA OF EXPERTS INTERVIEWED

Steven Dow is a General Partner at Sevin Rosen Funds, a top-tier early stage venture capital firm with extensive operating, technology and investing experience. SRF has invested in the information technology, telecommunications, enterprise software, and life sciences sectors. Notable successes from their investment portfolio include: Compaq, Lotus, Silicon Graphics, Electronics Arts, Ciena, Citrix, Arqule, and Cypress Semiconductor. Since joining Sevin Rosen in 1983, Steve has helped entrepreneurs refine their great ideas and turn them into thriving realities, serving as an advisor and counselor during incubation periods. Dow is currently serving on the boards of two public companies funded by SRF, Cytokinetics and Citrix. He also sits on the boards of Airgo Networks, Green Border Technologies, Kabira, ProactiveNet, Reactive Nanotechnologies, and Silicon Alley.

Steven Shaya is Vice President of the Corporate Office of Science and Technology (COSAT) at Johnson & Johnson, which, through its operating companies, is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, medical devices and diagnostics markets. Steven has been with COSAT for 12 years, helping J&J companies evaluate and access emerging technologies in academic and early commercial stages. More than 230 Johnson & Johnson operating companies employ approximately 116,000 men and women in 57 countries and sell products throughout the world. With worldwide revenues in excess of $50 billion in 2005, Johnson & Johnson is committed to the advancement of healthcare through science and innovation targeting unmet clinical needs.

Peter Nicholas is Co-founder and Chairman of the Boston Scientific Corporation. He served as Chairman and Chief Executive Officer from the Company's founding in 1979 until 1999. Under Pete's vision and leadership,

Boston Scientific has grown from a start-up company with 38 employees to a global corporation with approximately 16,000 employees and revenue of $5.5 billion in 2004. Boston Scientific is the world's largest medical device company dedicated to less-invasive therapies. Before co-founding Boston Scientific with John Abele, Pete served as General Manager of the Medical Products Division of Millipore Corporation. From 1968 to 1978, he held a variety of positions both domestically and internationally at Eli Lilly in sales, marketing and general management.

Robert Langer is Robert S. Langer is one of 14 Institute Professors (the highest honor awarded to a faculty member) at the Massachusetts Institute of Technology (MIT). Dr. Langer has written over 860 articles. He also has over 500 issued or pending patents worldwide, one of which was cited as the outstanding patent in Massachusetts in 1988 and one of 20 outstanding patents in the United States. Dr. Langer's patents have been licensed or sublicensed to over 100 pharmaceutical, chemical, biotechnology and medical device companies; a number of these companies were launched on the basis of these patent licenses. He served as a member of the United States Food and Drug Administration's SCIENCE Board, the FDA's highest advisory board, from 1995 - 2002 and as its Chairman from 1999 - 2002. Dr. Langer has received over 140 major awards. In 2002, he received the Charles Stark Draper Prize, considered the equivalent of the Nobel Prize for engineers and the world's most prestigious engineering prize, from the National Academy of Engineering. He is the also the only engineer to receive the Gairdner Foundation International Award; 65 recipients of this award have subsequently received a Nobel Prize. Forbes Magazine (2002) selected Langer as one of the 15 innovators worldwide who will reinvent our future. He received his Bachelor's Degree from Cornell University in 1970 and his Sc.D. from the Massachusetts Institute of Technology in 1974, both in Chemical Engineering.

Ellen Koskinas is a Partner at Interwest Partners, a top-tier early-stage venture capital firm investing in the information technology and life sciences sectors. Ellen focuses on life sciences investing, with an emphasis on medical devices. She is a board member of Applied Spine Technologies, Apsara Medical, CardioMind and Neuronetics. She has also been an active observer on the boards of Corgentech, Epicor (acquired by St. Jude Medical), NeuroPace and Paracor Medical. Prior to InterWest, Koskinas held a number of key roles in marketing and business development at Guidant Corporation, where she built a new business in minimally invasive cardiac surgery and then led Guidant's acquisition of CardioThoracic Systems. Koskinas has also served as an Engagement Manager for McKinsey & Company, managing projects for a broad range of pharmaceutical, healthcare delivery and medical device clients. At the outset of her career, she worked in corporate finance at Morgan Stanley in New York and London. Koskinas received her M.B.A. from the Stanford Graduate School of Business and her B.A. in economics, with honors, from Harvard College.