Bionic Technologies Transforming the Science of Healthcare Delivery

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Individualization of patient care is creating an envisioned future in which practitioners wield a new doctor's bag deploying individual molecular, genetic, cellular, and systems profiles.[1,2] These emerging tools are refining traditional paradigms of disease palliation into nuanced patient management algorithms employing prognostic risk stratification, therapeutic response prediction, and adverse event avoidance.[3,4] Advancing technologies are enabling a shift to more proximal nodes along the continuum of pathobiology. Innovations in biomarker platforms, genomic profiling, and molecular imaging reveal the earliest stages of pathophysiology,[5–7] limiting systems disruption to cells and tissues while preserving integrated organ function, enabling risk mitigation and disease prevention.[8–10] At even earlier stages, the interplay of genetics, epigenetics, environmental exposures, nutrition, and lifestyle define a roadmap to the clinical nonpareil of disease avoidance.[11] Broad dissemination of these principles into global healthcare paradigms changes the dynamics and economics of health across populations.[11–13] Realization of these algorithms transforms healthcare from the tradition of relieving pain and suffering to a future maintaining longitudinal wellness and healthy aging.[12,14,15]

While coevolution of emerging technologies offers unprecedented opportunities for risk mitigation and disease prevention, their impact on the science of healthcare delivery is restricted by the stochastic nature of disease evolution. Symptomatic disease rises to medical attention because disruption of integrated organ function produces physical manifestations, initiating the reactive palliative model of healthcare delivery. In contrast, early evolution of disease confined to cells and tissues, often the stage most amenable to cure, evades medical attention because it is asymptomatic and, consequently, silent. The time course of progression from asymptomatic to symptomatic disease states, a critical element in therapy lag, reflects individual genetic and environmental parameters and their impact on disease-specific pathobiology; organs affected and their functional reserve; and kinetics of disease progression. These elements conspire to produce uniquely individual profiles of disease progression whose temporality often defies prediction, relegating healthcare delivery to reactive palliation, rather than proactive anticipatory risk mitigation and prevention.[4,14,15]

This paradigm is exemplified by cardiovascular disease, the leading cause of morbidity and mortality worldwide, afflicting 15% of the global population.[16] This is the principle cause of coronary artery disease, which underlies the 10 million myocardial infarctions that occur each year worldwide.[17] In the United States, 18 million Americans live with coronary artery disease that produces more than 1 million myocardial infarctions and 0.5 million deaths each year at a cost of $36 billion, an economic burden that will escalate to more than $100 billion by 2030.[18] The pathobiology includes critical progressive narrowing of coronary arteries by expanding atheromatous plaque, which limits blood flow to downstream myocardium.[17] The erratic kinetics of progression of atheromatous growth and vessel narrowing reflect genetic, environmental, lifestyle, and other unknown factors whose interactions remain undefined. The acute event at the center of morbidity and mortality, myocardial infarction, is precipitated by the unpredictable rupture of these plaques, creating a thrombogenic surface precipitating clot formation and acute vessel obstruction.[17,19] The severity of organ damage, in part, reflects the reservoir of collateral circulation to at-risk myocardium downstream from the occlusion. An essential therapeutic paradigm minimizing mortality is treatment by clot lysis or angioplasty at the earliest time after the onset of a myocardial infarction.[20] Here, "time is muscle," and delays in treatment result in irretrievable loss of myocardium associated with diminished cardiac function.

This example highlights the essential contribution of the stochastic nature of disease progression to morbidity and mortality. Even in the context of established risk factors, for example hypercholesterolemia, hypertension, or diabetes, and the associated certainty of the presence of coronary artery disease, the temporal kinetics of disease progression and plaque rupture remain unpredictable in individual patients. If there was certainty to the timing of myocardial infarctions in the minutes to hour time scale, clot lysis, or angioplasty could be initiated at the earliest possible moment, minimizing myocardial damage and maximizing cardiac function.[20] Beyond optimizing the timing of acute interventions, if plaque rupture could be predicted on the hours to day time scale, myocardial infarctions and the associated morbidity and mortality could be eliminated. The ability to predict and prevent myocardial infarctions in real time could transform the science and economics of healthcare delivery globally.

This discussion underscores the clinical management gap for diseases whose progression is individualized and stochastic and whose culmination is catastrophic, for example coronary artery disease, heart failure, graft rejection, cancer, or stroke. This gap specifically encompasses the dimension of time, illustrated by the availability of effective therapeutic interventions that interrupt, reverse, or prevent permanent organ damage but the inability to predict the kinetics of the catastrophic event. Management of these conditions could be transformed by technologies providing continuous longitudinal surveillance that identify the earliest stages in evolution of acute events in a time frame facilitating effective therapeutic interventions. This unmet clinical need, in which application of advances in individualized medicine are limited by unpredictable kinetics of pathobiology, can be addressed by the emerging science of implantable biosensors, a disruptive technology that can bridge the temporal gap in disease management.

Implantable biosensors are moving from the realm of science fiction (Star Trek tricorder, Six Million Dollar Man) into mainstream healthcare. Sensors that detect cardiac arrhythmias are integral to automatic implantable defibrillators.[21] Implantable glucose monitors can assess glycemia in real time in diabetes.[22] Pacemakers

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deconvolute the cardiac cycle to maintain adequate perfusion.[21] The evolution of these first generation applications into complex systems-level devices that transform healthcare from palliation to prevention is enabled by the convergence of exponential advances in prognostic and predictive biomarker discovery, nanodevices, material sciences, wireless data transfer, medical informatics, and microscale energy technology.[23] The intersection of these disparate scientific communities has been catalyzed by the revolution in biology, which is providing healthcare solutions that must be actualized at the interface of science, medicine, engineering, and informatics.

The dimensionality of implantable biosensors encompassing axes of time, disease, and therapy, provides a context for their evolution and application. The time dimension comprises elements of stability, periodicity, and kinetics. Continuous monitoring could benefit processes that are highly dynamic, for example electrical activity underlying epilepsy. Similarly, longitudinal surveillance could identify imminent exacerbations in conditions with oscillating progression, for example relapsing and remitting diseases like multiple sclerosis. Also, it could benefit diseases that evolve slowly and asymptomatically over long durations, like coronary artery disease and cancer. In the disease dimension, elements include damage, reversibility, and severity. Conditions in which damage is initially silent, progressive and cumulative, for example the sequelae of microvascular disease including neuropathy, nephropathy, and retinopathy in diabetes, might benefit from continuous monitoring. Also, disease processes that are reversible, in which outcomes can be influenced by therapeutic intervention, are candidates for longitudinal monitoring. Of course, the severity of disease and its impact on end organ function, quality of life, and productivity is a key element in considering the value proposition of continuous monitoring. Finally, the dimension of therapy considers the elements of efficacy, therapeutic index, and interindividual variability. Resource allocation for developing and deploying biosensors advances healthcare management only within the context of the availability of highly effective therapeutic interventions that alter the course of the disease. Also, continuous monitoring could facilitate the application of drugs with narrow therapeutic indices, replacing intermittent *ex vivo* therapeutic drug monitoring that can miss the window of toxicity. Finally, drugs in which there is genomically based broad interindividual variability in either therapeutic responses or adverse reactions could benefit from longitudinal monitoring that optimizes therapy.[24,25]

Current models for continuous biosensor monitoring specifically focus on applications that bridge the temporal gap between disease progression and acute exacerbation, an extension of the established reactive paradigm of disease palliation. For example, automatic implantable defibrillators detect the earliest stages of an arrhythmia and deliver therapeutic cardioversion to interrupt what could be a catastrophic event.[21] Here, the sensor is dedicated to detecting a single output (electrical), there are minimum external data handling requirements in this closed-loop system, and the downstream actions entrained by sensor activation (cardioversion) are stereotypic, obviating complex clinical response protocols. However, as biosensor platforms advance in sophistication at the biology–engineering interface, they will drive coevolution of healthcare to a proactive paradigm of risk mitigation and disease prevention. On the immediate horizon, the next-generation bionic pancreas will encompass closed-loop biosensor systems that continuously monitor serum glucose and, through an informatics interface with complex response algorithms, automatically deliver insulin, to maintain steady state euglycemia and prevent microvascular disease in diabetic patients.[22] At the next level, complex biosensor systems strategically deployed in multiple anatomical compartments that integrate panels of physiological and biochemical parameters will create a data-driven management paradigm for complex life-long conditions, for example cancer, obesity and metabolic diseases, and cardiovascular disease. These higher order biosensor systems will demand innovation in data integration and reporting, wireless data transfer and telemetry, and clinical response algorithms.[23] Beyond disease risk mitigation and prevention, one envisioned future includes complex integrated biosensor architectures that enable longitudinal wellness and healthy aging. These systems will incorporate physiological, as well as disease diagnosis, prognosis, and prediction, analytic capabilities. They will have hierarchical data response algorithms that address physiological and pathophysiological deviations.[23] Moreover, these systems will permit the evolution of decentralized healthcare delivery, where health maintenance and disease management occur outside the boundaries of traditional healthcare structures like hospitals, facilitated by innovations in medical informatics, including electronic data transfer, integration, storage, and management.[12]

While this envisioned future incorporating continuous biosensor monitoring is poised to transform healthcare delivery, the hurdles to actualization are formidable and should not be underestimated. For example, there is an essential dependence on identifying and validating biomarkers of disease risk and early disease detection. The revolution in the new biology has provided unparalleled biomarker discovery platforms, evidenced by the near-daily identification of unique biomolecules associated with pathophysiology.[7] Yet, there continues to be a paucity of disease biomarkers that are analytically validated, qualified in their association with disease and proven in their prognostic or predictive utility.[26] Substantial bioengineering challenges focus on biocompatibility, durability, and performance in biosensors for diseases that may require life-long monitoring. Energy scientists will need to develop enduring sources of power at micro, nano, or atomic scale, compatible with long-term residence in vivo. Informatics engineers must create algorithms that assemble and integrate longitudinal data collected over vast arrays of (patho) physiological, cellular, and biochemical analytes to produce systems-level profiles of health and disease that are actionable. Wireless data transfer algorithms will need to be mapped to provide data at appropriate intervals that hierarchically subserve maintenance of longitudinal wellness, longitudinal monitoring of disease progression, or acute prevention of unpredictable catastrophic events. Moreover, clinical algorithms for effectively responding to these data will need to be established, accompanied by systems that can deploy response resources to patients.

Beyond biology, engineering, and clinical challenges, there are regulatory and policy considerations surrounding this disruptive innovation. While clinical development and regulatory approval strategies are well established for traditional drugs and devices, complex implantable biosensor systems represent an amalgamation of technologies cutting across many disparate domains, and new paradigms to evaluate their safety and efficacy will be necessary. Fully implemented, these complex biosensor systems will generate prodigious volumes of longitudinal clinical data that qualify as Personal Health Information. Structures will be required to securely warehouse, and policies established to define legal entities that control and have access to, this confidential HIPAA

(Health Insurance Portability and Accountability Act)-protected health information. Biosensor systems will produce clinically actionable data driving patient management, and the science of healthcare delivery will need to create new methods to effectively and economically operationalize and deploy this information. Moreover, Payors will have to develop policies and procedures that quantify the value proposition of this new technology to determine whether this approach to disease prevention and wellness maintenance economically unburdens the healthcare system, to define reimbursement strategies.

Technology that anticipates heart attacks before they happen, predicts the occurrence of strokes, and identifies the earliest stages of cancer before it comes to clinical attention would truly transform global health. Emerging tools in the clinical armamentarium to accelerate that transformation include implantable biosensors that bridge the temporal gap in disease management. This revolution in disruptive innovation will evolve at the interface of biology, engineering, and clinical medicine. It will require parallel innovations in regulatory science, health policy, and the science and economics of healthcare delivery. Moreover, it will require the combined efforts of diverse communities of practice, which have traditionally remained independent silos. Although the challenges are great, implantable devices have the potential to fully realize the benefits of individualized medicine, and drive the evolution of healthcare from palliation to prevention, shifting the focus from disease mitigation to maintenance of longitudinal wellness. CTS

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