Digital Medicine and the Scripps Translational Science Institute

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Originating in 2007, the Scripps Translational Science Institute (STSI) had a principal objective to leverage the remarkable progress being made in human genomics. It was conceived that this would be an ideal way to bring together basic scientists and clinical investigators, and accelerate research to favorably impact human health. With a science team incorporating individuals from The Scripps Research Institute (TSRI), Scripps Health, Sanford Burnham Institute, the Salk Institute, the San Diego Supercomputer Center (SDSC), San Diego State University, the J.C. Venter Institute, the Neuroscience Institute, and Children's Hospital of Philadelphia's Applied Genomic Center, we were well positioned to execute this goal. Funded by the Clinical and Translational Award (CTSA), NIH program in 2008, two examples of our first round pilot studies included understanding the pharmacogenomics of clopidogrel, the second largest prescription drug in the world, and in determining modifier genes in Friedrich's ataxia to explain the marked variability in penetrance of this devastating neurodegenerative condition. Both of these projects were remarkably successful. The first study enhanced our understanding of the link between clopidogrel and both specific gene variants and platelet function. It led, in 2009, to our center being the first in the United States to initiate systematic genotyping (for variants of the gene CYP2C19) in all patients undergoing coronary stenting procedures. The second study has identified key modifier gene variants that appear to largely explain the variable phenotype and temporal course of individuals who carry the risk alleles for Friedrich's ataxia. All told, through 2010, there have been more than 240 applications and 40 such pilot studies funded through STSI, many of which have been centered on genomics, and all required clinicians and basic scientists to work together for transformative projects that had no identifiable source of funding. To potentiate our access to cutting edge technology, we set up meaningful collaborations with San Diego based life science companies, including the two largest genome science companies in the world—Life Technologies and Illumina. We have many of the next-generation DNA sequencing platforms, as well as mass spectrometry for proteomics and metabolomics, and our collaborators at the Salk Institute successfully sequenced the first human methylome to accelerate our understanding of epigenomics.

The number one form of commerce in San Diego, however, is wireless technology and the largest company, among over 600 that work on wireless products and applications, is Qualcomm. In putting together our CTSA application in 2007, we highlighted a section that described our planned joint venture with Qualcomm. This joint venture was set up to educate and nurture the careers of young physicians with an interest in wireless medicine. There was remarkable enthusiasm for this goal reflected by the reviews of our application, which helped reinforce our plan to move forward.

In late 2008, we had the fortune of meeting Gary West and Mary West, who became interested in philanthropically supporting a new institute dedicated to wireless medicine. By April 2009, the

West Wireless Health Institute (WWHI) became a reality with a \$100 million donation and governmental recognition of a new nonprofit medical research organization, with Scripps Health as the institutional sponsor, located nearly adjacent to STSI (*Figure 1*). The main goal of WWHI is to accelerate the research of innovative wireless health technologies and reduce the costs of health care. Notably, many noninvasive wearable sensors that continuously measure physiologic metrics, such as blood pressure (BP), heart rhythm, respiratory rate, oxygen concentration in the blood, blood glucose, and other phenotypes were rapidly evolving and yet need to be exploited in clinical research and practice. Many of the companies that were working in this space were located in San Diego.

While this was a fortuitous and somewhat serendipitous coupling of STSI and WWHI, it exposed many synergies and a potential convergence of genomics and wireless medical capabilities in research and clinical initiatives. For example, new phenotypes could be quantified and defined, such as continuous BP monitoring that could provide insight into BP variability, which has recently been shown to be a key driver of adverse outcomes of stroke and heart attack. The genetic basis of these BP phenotypes may shed light on the pathogenesis of heart disease. Similarly, continuous monitoring of glucose may help to both expose hitherto hidden pharmacogenomic relationships among the various drugs used to treat diabetes (e.g., acute postprandial response, subtle weight changes, delays in intervention, compliance) that could only come to light with more intensive phenotypic monitoring, along with helping understand even more subtle phenomena, such as the epigenomic effects that are induced by abnormal glucose homeostasis. With the leveraging of data-intensive genomic and wireless-monitoring technologies and research paradigms one could imagine a future involving a "digital medicine" revolution that would truly be rooted in individualized clinical practice and disease prevention.

In *Table 1*, the parallels between genomics and wireless technologies are laid out. While genomic understanding involves making sense of four nucleotides in DNA sequence (the "code of life") and how they impact biological function, wireless monitoring relies on the 0|1 digital code. Both of these technologies are already capable of exabyte flooding and are well on their way to generating terabytes of data in routine applications, as more whole human genomes are sequenced and thousands of people undergo multimetric physiologic continuous monitoring. Our link to the SDSC has proven especially important with respect to handling this data tsunami. Each of genomics and wireless monitoring features networks and, while the components of these networks are different, the science behind networks implicated in each is critical to relevant research efforts; consider, for example, systems biological interpretations of genetic networks from whole transcriptome or methylome studies or the comprehensive processing of signals from multichannel wireless body sensors and area networks. The issues of privacy and security are vital

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Figure 1. The (STSI) and the (WWHI) are located within 300 yards of each other overlooking the Torrey Pines South golf course and the Pacific Ocean.

	Genomic medicine	Wireless medicine
Basis	Genetic code(A,T,C,G)	Digital code (0,1)
Time of assessment	Measure once	Intermittent/continuous measuring
Core technology	Nextgen sequencers	Microelectronics
Data generated	Terabytes (10 ¹²)	Terabytes (10 ¹²)
Individuality	Molecular biology	Physiology
Networks	Systems biology	Body area, Internet
Primary concern	Security/Privacy	Security/Privacy
Who owns it?	The consumer's DNA	The consumer's cell phone

Table 1. Comparison of genomic and wireless medicine.

for the exploitation of both genomics and wireless technologies in next-generation medicine, which will be both quantitative and individualized (i.e., “digital medicine”). Both genomics and wireless technologies are exceptionally useful and essential to help define the individuality of patients needing care, with genomics (and omics in general) providing unique molecular biologic information about a patient, and the wireless sensors yielding idiosyncratic physiologic patient insights. Of particular note, the two areas share the theme of consumer empowerment. It is the individual consumer who can decide whether he or she wants to have DNA sequencing (or other biomarker data determined), and most of the wireless sensor data will ultimately be provided via an individual's cell phone.

With the two fields of digital medicine, we are now training clinician scholars in both tracks, and it is fascinating to see the transdisciplinary convergence. Not only are we bringing together basic scientists and clinicians for projects, but also now engineers and clinical researchers are working together for the first time on designing or validating new wireless sensors. Such synergies will not only accelerate a transition to future digital medicine, but will undoubtedly lead to greater efficiencies in clinical research and practice. Genomics can help circumscribe groups of

patients most likely to benefit from particular therapies, leading to more efficient, small sampling burden, clinical trials, and continuous time monitoring of those patients will allow decisions about the ultimate value of those therapies to be reached in a minimal amount of time. In fact, one can imagine scenarios in which possible treatments, approved or experimental, for an individual patient are determined based on genomic profiling and then those treatments are refined and vetted on that patient using sophisticated wireless monitoring, leading to routine “N-of-1” trials which reflect true individualized medicine. However, genomic medicine and wireless medicine are each independently, and more so in concert, driving a critical need for maturation of a third capability, that being bioinformatics on a grand scale. For in the end, the value of digital medicine will be less in the specific genome or in the specific stream of physiologic data, but more in the contextually derived learning and actionable information, which may only be discerned by multidimensional analysis of the superset of data constructed at the intersection of these two data streams. Just as particle physicists use the high-energy super-collider to reveal the origin of the universe, cutting-edge medical researchers will need to become savvy at the intersection of

genomics and wireless medicine, if we are to unlock the secrets of truly personalized medicine.

In the national consortium of over 50 CTSA sites, Scripps is quite distinct and this is not only related to its digital medicine orientation. It remains as the only site that is not centered in a university and does not have a medical school associated with it. Perhaps not being encumbered by the typical hierarchical and bureaucratic structure of a university, STSI had the advantage of agility and velocity to build out its overarching goal of fostering individualized medicine, and by engaging industry collaborations that may be uncomfortable in traditional academic settings.

In order to override our current practice of population medicine, resulting in such problems as the annual \$300 billion cost of prescription drugs and the use of mass screening for risk of a disease that most individuals have no chance of ever developing, we need innovative, smarter, and less-expensive approaches. We believe that they will most likely come about by elucidating our biologic and physiologic individuality. STSI working closely with WWHI hopes to build on its early successes of promoting human health. Were it not for the CTSA program, it is unlikely that STSI or WWHI would exist today.

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