Early Clinical Experience With Networked System for Promoting Patient Self-Management

Kit Yee Au-Yeung, PhD; Greg D. Moon, MD, MBA; Timothy L. Robertson, PhD; Lorenzo A. DiCarlo, MD; Michael S. Epstein, MD; Stephen E. Weis, DO; Randall R. Reves, MD; and Gregory Engel, MD

Objective: To gain early experience with a networked system designed to assess a patient's adherence to oral medication and physiologic metrics in an ambulatory, at-home setting.

Study Design: Prospective, observational studies.

Materials and Methods: This networked system for patient self-management consists of ingestible markers and a wearable, personal monitor. When a marker is ingested, it communicates to a monitor that time-stamps the ingestion and identifies the marker as unique. The monitor also records heart rate and activity. Data from third-party monitoring equipment (eg, sphygmomanometer, weight scale) can be integrated into the system. Collected data are summarized for patient and physician review. Directly observed ingestion (DOI) of placebo tablet markers was used to assess the system's technical performance. Markers were also coencapsulated with drugs to capture at-home adherence. A performance criterion of ≥95% was set as the objective for system performance.

Results: A total of 111 subjects ingested 7144 ingestible markers; 3298 were DOIs. The system's positive detection accuracy and negative detection accuracy in detecting ingested markers were 97.1% and 97.7%, respectively. It differentiated 100% of multiple drugs and doses taken simultaneously by type and by dose. Medication adherence was >85%. The most common adverse effect was mild skin rash from the monitor's electrodes. No definitive marker-related adverse effects were reported.

Conclusion: The system appears to be safe and effective in capturing and integrating adherence and physiologic data. Efforts are under way to enhance system functionalities and refine user interfaces. By providing context-rich information, this system may enhance patient-provider collaboration.

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For author information and disclosures, see end of text.

The World Health Organization has characterized poor adherence to treatment as a worldwide problem affecting developing as well as developed countries. In the United States, it is estimated that one-third to one-half of all patients do not take their medications properly.[1] Patients who do not take their medications as prescribed cost the US healthcare system an estimated $290 billion in avoidable medical spending annually.[2] The World Health Organization considers adherence to be the single modifiable factor that compromises treatment outcome across diseases. It has called for an evolution of the health systems to provide patient-tailored interventions to address poor adherence and to consider the patient's family, community, and affiliated organizations to be key contributors to success in improving medication adherence.[1]

Barriers that patients face in taking their medications have been studied extensively.[3-7] Typical reasons cited by patients for not taking their medications include forgetfulness (30%), other priorities (16%), deliberate decision to omit doses (11%), lack of information (9%), and emotional factors (7%).[7] These barriers to adherence oftentimes can be improved upon or overcome by patient efforts independent of providers or other members of the healthcare system. Thus, a necessary and important first step in improving adherence is to provide attention and aid to patients.

Barriers to adherence are also related to poor interactions and/or communication between the patient, the healthcare providers, and the healthcare system. Traditionally, physicians and designated healthcare workers have played a key role in achieving adherence by providing the rationale for treatment to their patients, and involving family and caregivers whenever possible. However, it is time and resource intensive for providers to assess and influence adherence alone on a timely and ongoing basis. There remains an unmet need for a reliable and broadly utilizable means to accurately assess and manage a patient's medication adherence.

An ideal system for improving adherence would not only engage the patients themselves, but also leverage their selected health providers, caregivers, and communal support network. The system would also allow a secure exchange of reliable and robust information among patients and clinical decision and support systems.[2] By utilizing the latest medical technol-

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Early clinical experience with a networked system consisting of ingestible markers (integrated with oral medications to capture at-home adherence patterns) and a wearable, personal monitor indicates that this system appears to be safe and effective in capturing, integrating, and presenting medication adherence and physiologic information.

- Compared with directly observed ingestion, the system's ability to detect ingested markers was 97.1% and 97.7% for positive and negative detection accuracy, respectively.
- Adherence was juxtaposed with physiologic data for a comprehensive report.
- Sharing of context-rich information between patient, providers, and caregivers may enhance collaboration to achieve and sustain patient wellness.

ogy, patients could be empowered in a novel way to promote self-management of their chronic conditions, beginning with better management of their adherence.

The purpose of this report is to discuss the early clinical experience with a networked system for promoting patient self-management. This system is designed to utilize unique ingestible markers that confirm the ingestion of individual oral medications and doses, to integrate this adherence data with physiologic parameters and wellness metrics, to offer patient-directed sharing of health information with caregivers and providers, and to incorporate individualized behavioral support tools. Some of the above-mentioned functionalities have been implemented and evaluated in 4 separate clinical studies of 4 populations; early safety and technical performance results are presented.

MATERIALS AND METHODS

A Networked System

A networked system has been developed to electronically confirm adherence to oral medication, to acquire physiologic metrics periodically and remotely, and to gather and present this information in a comprehensive, centralized manner[8-15] (**Figure 1**). Briefly, upon ingestion, the ingestible marker dissociates from the medication or carrier within the stomach and is activated by stomach fluids. The marker then begins communicating its unique signature to the wearable, personal monitor. This data communication scheme is similar to what a heartbeat does in transmitting an electrocardiogram to the surface of the body. The communication process is unnoticed by, and not detected beyond, the system user. The personal monitor interprets the information from the marker, identifies it as unique, and stores the marker ingestion event to the memory of the monitor. Periodically, the personal monitor transfers the collected data to a mobile phone, which relays the data to a secure server. Once validated at the server level, adherence and physiologic data can be viewed via a Web browser on a computer or a mobile phone. The system components are described in detail below.

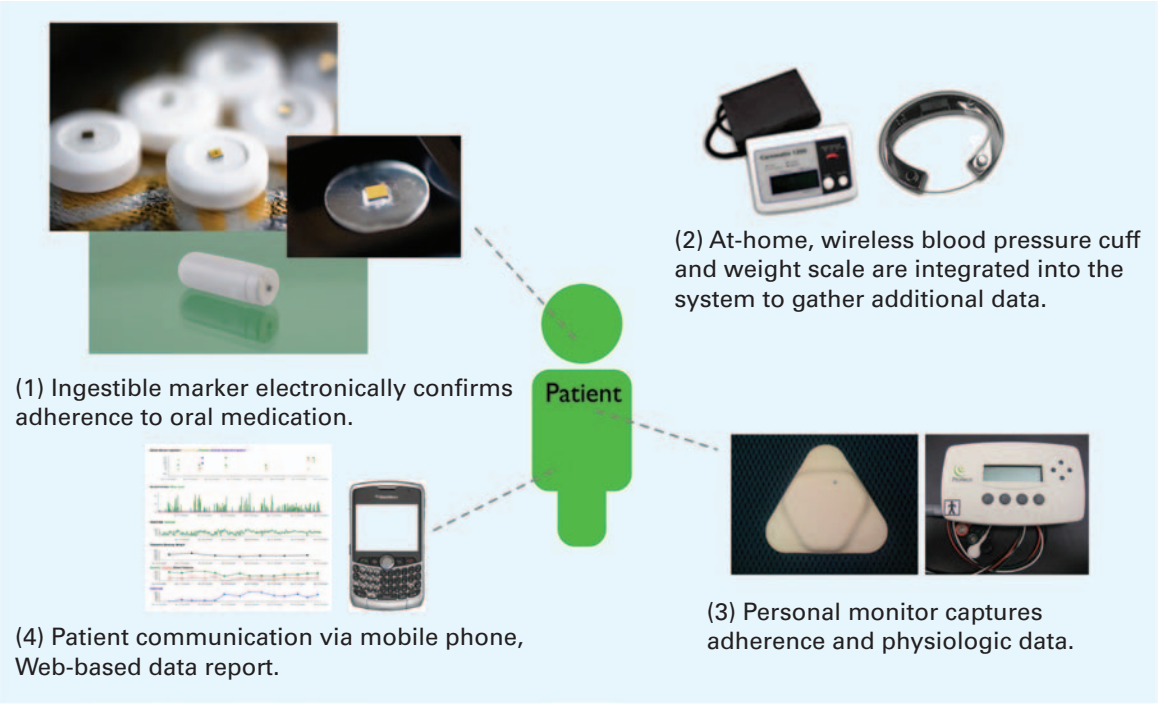
Ingestible Marker-Enabled Medication. The system utilizes ingestible markers that are incorporated into oral medication to electronically confirm medication adherence. The ingestible marker is considered biocompatible and toxicologically safe. It is 1 mm × 1 mm in size, and it is coated with a copper salt on one side and magnesium on the other. The levels of silicon, copper, magnesium, minerals, and cellulose present in the marker are far below the levels commonly present in the diet. The ingestible marker is also designed to be compatible with the formulation of oral pharmaceuticals. Upon ingestion, the marker is activated by gastric fluids and communicates a unique identifying signature to the personal monitor. The marker is currently designed to communicate for approximately 7 minutes. After that, the communication ceases and the marker becomes completely inactive; it goes through normal gastric transit and is eliminated from the body via fecal elimination.

Personal Monitor. The personal monitor serves 2 purposes. First, it records the identifying signatures from the ingestible marker-enabled medications and time-stamps the drug taken, its dose, and its time of ingestion. Second, it has internal markers that are capable of reporting metrics such as heart rate, respirations, activity, body position, and monitor-wearing compliance. The current iteration of the personal monitor is a miniaturized, soft foam, skin-patch device measuring 5 cm × 11 cm × 1 cm. It is capable of recording a variety of physiologic parameters and periodically transmitting stored data to a computing device via Bluetooth telemetry. It adheres to the torso of a subject in a similar fashion to an adhesive bandage.

Peripheral Wireless Devices. In addition to adherence and physiologic data collected by the ingestible markers and the personal monitor, other metrics can be collected and integrated into the networked system using peripheral wireless devices. A wireless sphygmomanometer, weight scale, and base station can be set up at a patient's home. When a blood pressure or weight measurement is made, it is sent to the base station and subsequently to a centralized, secure data server via a phone or Internet connection. At the server level, data from these peripheral wireless devices are integrated with those from the ingestible markers and the personal monitor, to provide a comprehensive view of a patient's physiologic and wellness profile. Data from other telemetric devices (eg, glucometer) may also be integrated with the system in this manner.

Mobile Phone, Web-Based Patient Communication. Once data are aggregated, they can be disseminated to ap-

■ **Figure 1.** Overview of a Networked System and Its 4 Components



propriate stakeholders. Data can be securely viewed using a Web-based platform. Summary reports can be generated and shared with the patients. In the next-generation system, data could be sent to the patients directly, discreetly, and securely via a Web-based or mobile phone platform. With the patient's permission, the same set or a subset of the gathered data could be shared with the persons they designate, including family members, caregivers, and/or healthcare providers.

Study Design

To gather comprehensive information regarding system use, 4 separate small-scale, prospective, observational studies were conducted in 4 populations over a course of 19 months. Each of the 4 studies targeted a specific patient subject population including healthy volunteers and patients with tuberculosis (TBC), heart failure (HF), and hypertension (HTN). Studies were conducted at 5 clinical sites in the United States: 2 were clinical research organizations and 3 were outpatient clinics. Studies were approved by institutional review boards at Chesapeake Research Review, Inc, Western Institutional Review Board, University of North Texas Health Science Center, and Independent Review Consulting, Inc. Studies were routinely monitored by the sponsor according to Good Clinical Practice guidelines.

Study Population

Study candidates were recruited through advertisement and referrals. In general, candidates identified for inclusion in the study were those who were willing to adhere to study procedure, had the capacity to provide informed consent, and for women of childbearing age, had a negative urine pregnancy test. Study candidates were excluded if they had acute or chronic gastrointestinal symptoms, terminal illness, known allergies that could preclude safe participation in the study, or current presence of an electronically active implanted medical device (except in the HF population study), or if they were participating or had participated in any clinical trial (drug or device) ≤30 days prior to study start.

Since each study targeted a particular subject population with specific procedural requirements, additional inclusion and exclusion criteria were implemented. Table 1 summarizes these specific subject selection criteria. Study subjects were enrolled after providing written, informed consent per the International Conference on Harmonisation Guideline for Good Clinical Practice.

Study Objectives

Two main objectives were common to all 4 studies. First, the networked system safety, including ingestible marker ingestion and personal monitor wearing, was evaluated. Sec-

Table 1. Subject Selection Criteria by Study

Criteria	Healthy	Tuberculosis	Heart Failure	Hypertension
Inclusion	Age 21 y or above	Age 18 y or above	Age 18 - 80 y	Age 18 - 80 y
	In general good health	Received at least 10 days of active TBC treatment	NYHA class II or III HF	Outpatient in stable condition
			Outpatient in stable condition	Taking medications for HTN for ≥6 months
			Taking furosemide once or twice daily, ≤40 mg/day	Taking valsartan once daily, either 80 or 160 mg/day
			Implanted with a CRT or ICD device for ≥2 months	Current valsartan dosage has been unchanged for ≥2 months
Exclusion			HF hospitalization within past 2 months	Hospitalization for any reason within past 3 months
			Chronic paroxysmal atrial fibrillation, active at the time of enrollment	NYHA class III-IV HF
				Unstable angina
			Myocardial infarction within past 3 months	Myocardial infarction within past 3 months
			Serum creatinine >2.0 mg/dL	Cerebrovascular accident within past 3 months
			Cerebral vascular accident within past 3 months	History of cognitive impairment
			History of cognitive impairment	

CRT indicates cardiac resynchronization therapy; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; TBC, tuberculosis.

ondly, the technical performance of the networked system was characterized. Namely, the reliability of the system in detecting ingestible marker ingestions was compared with a gold standard: directly observed ingestion.

In addition to the main objectives described above, a number of corollary aims were unique to each study and subject population. The purpose of including these study aims was to expand the scope of the technical assessment of the networked system. The study aims and the population(s) that these aims were evaluated in were (1) to assess the effect of body mass index (BMI) on ingestible marker detection in all studies, (2) to assess the effect of meal type on ingestible marker detection in healthy users, (3) to characterize the effect of the ingestible marker carrier form factor on marker detection in all studies, (4) to characterize the unsupervised, at-home adherence pattern using marker-enabled medications in HF and HTN patients, and (5) to demonstrate the use of peripheral wireless devices for additional physiologic monitoring in HF and HTN patients.

Study Procedures

To achieve the main objectives described above, several procedures were implemented and repeated in each study. First, a safety assessment was conducted in each protocol by evaluating the frequency and nature of the adverse events (AEs) occurring during the active and the follow-up phases of the study. An AE was defined as "any undesirable medical event occurring in a subject, whether or not the event is considered related to the investigational device." Study investigators were asked to document and classify all AEs based on severity and relatedness to the study device and procedure.

Second, investigators periodically conducted direct observation of marker ingestions to assess the system's accuracy in detecting marker ingestion. While at the clinic, subjects were instructed to ingest 2 to 4 markers in the presence of research personnel, who would observe and log each ingestion. Both functional and some nonfunctional markers were administered, to evaluate the positive detection accuracy and negative detection accuracy of the system, respectively. The system's identification accuracy—the ability to correctly identify the unique identifier of the ingested device—was also assessed.

To address the corollary study aims, specific procedures were conducted. Subjects' height and weight were recorded at enrollment to assess the effect of BMI on marker detection

Table 2. Outcome Measures

Name	Definition
Positive detection accuracy	The number of detected ingestible markers divided by the number of functional, ingestible markers administered; assessed in conjunction with directly observed ingestion; assume independent observations
Negative detection accuracy	The number of nondetected, nonfunctional, ingestible markers divided by the number of nonfunctional markers administered plus any incidence of false-positives; assume independent observations
Identification accuracy	The number of correctly identified (by unique signature) ingestible markers divided by the number of ingestible markers detected
Taking adherence	The number of marker-enabled medications detected by the system divided by the number of marker-enabled medications prescribed (in heart failure and hypertension studies only)
Scheduling adherence	The percentage of doses taken within a predetermined time window collectively determined by the study subject and the coordinator before the study; a marker-enabled medication was considered taken "on-time" when ingested within ±1 hour and ±2 hours of the specified time for a twice-daily and once-daily dosing regimen, respectively (in heart failure and hypertension studies only)
Weight taking	Once daily, body weight reported by the wireless weight scale that is integrated into the networked system
Blood pressure taking	Twice daily, systolic and diastolic blood pressure reported by the wireless sphygmomanometer that is integrated into the networked system

accuracy. Healthy subjects were given meals and beverages designed by a dietician prior to marker ingestion, to evaluate the effects of meal composition on system performance. Markers were delivered on a placebo tablet ingested alone, on a placebo tablet coingested with medication, or attached to a capsule body containing medication in these studies, to assess the impact of the marker carrier form factor on detection. In the HF and HTN studies, subjects' prescribed furosemide and valsartan were marker enabled to capture subjects' unsupervised, at-home medication adherence pattern using the networked system. Wireless devices including blood pressure cuff and weight scale were distributed to the subjects for use, to evaluate the system's ability to integrate peripheral health monitoring equipment.

In these 4 studies, the active study participation duration varied from 2 to 42 days with periodic visits at the clinic with the study coordinators. The safety follow-up period ranged from 5 to 21 days, depending on the duration of study participation.

Outcome Measures

To characterize the technical performance of the networked system, a number of outcome measures were defined and assessed. The key outcome measures are summarized in Table 2.

Moreover, to focus primarily on ingestible marker in vivo activation and detectability in these early feasibility studies, the technical evaluation of positive detection accuracy (PDA) and negative detection accuracy (NDA) excluded instances where (1) data were collected from subjects during training prior to the observation phase, (2) there were user errors in properly activating monitor prototypes prior to marker ingestion, (3) there were malfunctions in prototype software or hardware, or (4) placement or location of the monitor prototype was unsatisfactory, as indicated by a measured electrode impedance of 1000 ohms or greater.

Statistical Analysis

The system's PDA, NDA, and identification accuracy were calculated for ingestible marker ingestions administered at directly observed ingestion across all subjects. All measurements were assumed to be independent. A 95% confidence interval (CI) was determined using the method of Clopper-Pearson (an exact method). When appropriate, descriptive statistics including number, mean, median, standard deviation, minimum, maximum, and 95% CI were presented. The association of a covariate of interest and the PDA was assessed by using the Wald χ^2 from the mixed model for repeated measures. The level of statistical significance was set at .05.

RESULTS

Demographic Characteristics

A total of 111 subjects, including 30 healthy volunteers, 30 patients with TBC, 8 patients with HF, and 43 patients with HTN, were enrolled in a series of 4 clinical studies.

Table 3. Demographic Characteristics of Study Populations

Characteristic	Population				Overall
	Healthy	TBC	HF	HTN	
Number of centers	1	2	1	1	5
Number of subjects					
Enrolled in study	30	30	8	43	111
With complete data for analysis[a]	25	30	8	40	103
Sex, No. (%)[b]					
Male	9 (30)	16 (53.3)	7 (87.5)	26 (60.5)	58 (52.3)
Female	21 (70)	14 (46.7)	1 (12.5)	17 (39.5)	53 (47.7)
Age, y					
Mean (SD)	33.4 (10.3)	44.9 (14.1)	67.9 (13.3)	61.7 (8.8)	49.8 (16.8)
Minimum, maximum	21.5, 62.8	22.5, 79.5	46.0, 85.0[a]	44.0, 79.0	21.5, 85.0
Body mass index, kg/m^2					
Mean (SD)	27.2 (7.1)	23.5 (4.1)	28.2 (5.5)	31.6 (5.8)	28.3 (6.6)
Minimum, maximum	17.8, 44.6	16.0, 31.1	21.0, 34.2	21.2, 47.0	16.9, 47.0
Race, No. (%)[c]					
White	23 (76.7)	3 (10.0)	6 (75.0)	33 (76.7)	65 (58.6)
White/Hispanic	0	6 (20.0)	0	0	6 (5.4)
Hispanic	1 (3.3)	7 (23.3)	1 (12.5)	0	9 (8.1)
Black	6 (20)	9 (30.0)	0	2 (4.7)	17 (15.3)
Black/Hispanic	0	1 (3.3)	0	0	1 (0.9)
Asian	0	3 (10.0)	0	8 (18.6)	11 (9.9)
Eurasian	0	0	1 (12.5)	0	1 (0.9)
American Indian	0	1 (3.3)	0	0	1 (0.9)

HF indicates heart failure; HTN, hypertension; TBC, tuberculosis.
[a]There was no difference in characteristics between subjects who completed the data set and those who did not. Reasons for incomplete data sets were either training-phase participation or early withdrawal from the study.
[b]Study compliance deviation in inclusion criteria: subject age >80 years at enrollment. This deviation had no effect on the primary end points or patient safety.
[c]Percentage was calculated based on the number of enrolled subjects.

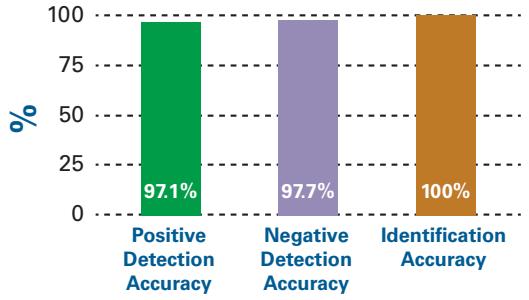
Results from all 111 subjects were used in the safety assessment of the networked system. Of the 111 subjects, data from 103 (92.8%) met protocol specification and were used in the technical assessment of the system. Study subjects' demographic and baseline characteristics are summarized in Table 3.

A total of 7144 ingestible markers were ingested by this 111-subject cohort. The number of days that personal monitors were worn per study ranged from 2 to 42 days per protocol. The number of markers ingested per day ranged from 2 to 36 markers per protocol. Of the 7144 ingestible marker ingestions, 604 (8.5%) ingestions were excluded from technical evaluation of PDA and NDA based on the criteria defined above. A total of 6540 marker ingestions were analyzed: 3298 (50.4%) were administered in a directly observed ingestion setting, and 3242 (49.6%) were taken by the subjects in an unsupervised at-home setting, using a marker-enabled medication form.

Safety Assessment of the Networked System

A safety assessment was conducted per protocol. Records from 111 enrolled subjects were reviewed; 69 AEs were reported by 45 subjects. Of the 69 AEs, 67 (97.1%) were nonserious, and the 2 (2.9%) serious adverse events were both unrelated to the study procedure or device. No unanticipated device AEs were observed. The majority of the AEs (82.6%) were mild in nature. About 55% of the reported AEs were deemed by the study investigators to be either related or possibly related to the device. The most commonly observed device-related AEs were described as mild skin rash associated

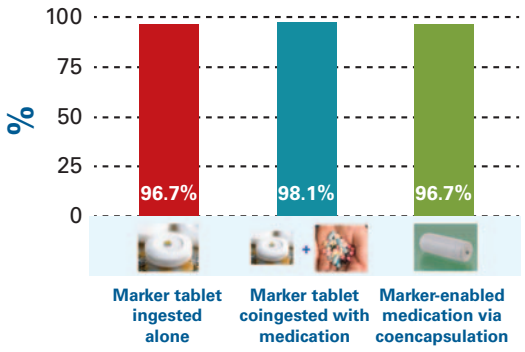
■ **Figure 2.** Networked System Technical Performance Compared With Directly Observed Ingestion



Mean	97.1%	97.7%	100%
No. markers	3298	221	2641
95% CI	96.5%-97.7%	94.8%-99.3%	99.9%-100%

CI indicates confidence interval.

■ **Figure 3.** Networked System Positive Detection Accuracy as a Function of Marker Ingestion Method[a]



Method	A	B	C
Mean	96.7%	98.1%	96.7%
No. markers	1670	1046	582
95% CI	95.7%-97.5%	97.1%-98.8%	95.7%-97.5%

CI indicates confidence interval.
[a] *P* values of pairwise comparisons using the χ^2 test: A – B = .03; A – C = .97; B – C = .09.

with the adhesive electrodes of the personal monitor placed on a subject's body. No definitive ingestible marker-related AEs were observed.

Technical Assessment of the Networked System

Directly Observed Ingestion. Using the results from directly observed ingestion, the overall networked system's PDA in detecting ingestible markers was 97.1% (95% CI 96.5%-97.7%, n = 3298 marker ingestions by 103 subjects). The system's NDA was 97.7% (95% CI 94.8%-99.3%, n = 221 marker ingestions by 55 subjects). The unique identifiers of the detected markers were verified against those of the actual ingested device. The system's identification accuracy was 100% (95% CI 99.9%-100%, n = 2641 marker ingestions by 55 subjects). The networked system technical performance results are summarized in Figure 2.

In each of the 4 study populations, BMI was consistently found to be not significantly associated with PDA. In the study conducted in healthy volunteers, 4 meal types were evaluated, including liquid/no food, carbohydrate-rich, protein-rich, and lipid-rich diet. They were found not to be significantly associated with PDA (P = .151). Three methods of marker ingestion were utilized in the studies: (1) ingestible marker on a placebo tablet ingested alone, (2) ingestible marker on a placebo tablet coingested with medication, and (3) ingestible marker attached to a capsule body containing medication inside. The system demonstrated high PDA of 96.7% or above across ingestion methods, as shown in Figure 3.

Unsupervised, at-Home Ingestion. In the study with HF and HTN patients, the networked system was used to capture the subjects' unsupervised, at-home medication adherence pattern using marker-enabled drugs. The system was successful in identifying the medication ingested by analyzing the unique identifiers of the detected markers. The system detected, time-stamped, and differentiated the ingestion of one 20-mg furosemide capsule from two 20-mg capsules, ingestion of an 80-mg valsartan from a 160-mg valsartan, and also the ingestion of up to 3 simultaneously ingested marker-enabled capsules. In the 8-subject HF patient cohort, the mean taking adherence (see Table 3; taking adherence is also known as "dose count") and scheduling adherence (see Table 3; scheduling adherence is also known as "dose time") were 85.4% (median, minimum, and maximum were 86.0%, 67.0%, and 98.5%) and 68.5% (median, minimum, and maximum were 82.5%, 10.8%, and 89.3%), respectively. In the 40-subject HTN patient cohort, the mean taking and scheduling adherence were 90.0% (median, minimum, and maximum were 92.5%, 44.1%, and 100%) and 82.8% (median, minimum, and maximum were 88.6%, 12.7%, and 100%), respectively.

In addition to using marker-enabled medication, subjects in the HF and HTN studies were asked to take 2 blood pressure measurements (morning and nighttime) and 1 weight measurement (morning) daily, utilizing the wireless sphygmomanometer and weight scale provided. On average the subjects took 83.8% and 92.0% of the blood pressure and weight measurements prescribed, respectively. Data collected by these peripheral wireless devices were successfully integrated into the networked system, to be displayed side-by-side with the subject's medication adherence behavior characterized via

Figure 4. Example of a Subject's Comprehensive Data Set Over Days Collected by the Networked System, Integrating Medication Adherence, Physiologic Data, and Measurements From Wireless Health Monitoring Devices

ingestible markers. An example of a subject's comprehensive 7-day data report is shown in Figure 4.

DISCUSSION

Having improved knowledge of a patient's adherence is advantageous to healthcare providers, because it could potentially influence clinical decision making. When providers are able to distinguish between pharmaceutical underdosing, low pharmaceutical concentrations, ineffectiveness despite being adherent, and misleadingly acceptable pharmaceutical concentrations related to periodic adherence, they can determine whether ongoing therapeutic management should focus upon improving medication adherence, dose adjustment, drug substitution, or polypharmacy. Objective and accurate adherence data could have a critical impact on a patient's treatment road map for his or her chronic condition.

Of the methods currently used to improve adherence to medication treatment, the most reliable has been directly observed therapy: namely, watching a patient swallow each dose of medication. Directly observed therapy has been widely used in the treatment of TBC and HIV.[16,17] Although highly reliable when performed appropriately, directly observed therapy is resource intensive, time consuming, and costly, incurring an average incremental cost of about $1400 over that for self-administered therapy.[18] Alternative, indirect methods such as patient questioning, pill counts, and prescription refill rate monitoring have been used for assessing adherence. However,

data obtained with these methods have been shown to be subjective and inaccurate.[19] Electronic monitors that record the opening of a medication bottle cap could be used as a surrogate measure for drug dosing. However, this methodology does not offer a direct association between electronic cap opening and actual drug intake, particularly in situations where more than 1 dose or no dose is taken per each electronic cap opening event, or when a patient opens the medication bottle for refilling purposes. Moreover, no adherence data are captured when a patient uses medication from a bottle without the electronic monitor cap.[20-23] The use of multiple electronic caps to confirm adherence to multiple drugs has also been shown to be too burdensome to be practical.[24]

Some clinical studies have considered rates of more than 80% to be acceptable for pharmaceutical adherence, whereas others consider rates of more than 95% to be mandatory for adequate adherence, particularly among patients with serious conditions such as HIV infection.[7] The networked system described in this report exceeded the minimum performance criterion of 95% that was set for the PDA and NDA of detecting pharmaceutical ingestion when compared with directly observed therapy. This novel system represents a significant improvement on existing methods for confirming adherence. System usage, particularly ingestible marker ingestion, appears to be safe, with very few minor adverse events reported. The current system iteration demonstrated an overall 97.1% reliability in ingestible marker detection when compared with direct observation. The system also showed 100% accuracy in decoding the marker's unique identifier.

While further system refinements are under way to improve PDA and NDA, the current achievement indicates that the networked system could be a valuable tool capable of reporting actual medication ingestion date, time, and drug information including type, dose, and manufacturing details. The current system could be useful in characterizing a patient's adherence trend and pattern. As the system matures over time, it could provide more sophisticated features such as pill-by-pill monitoring, and reminders could be sent to a patient when a medication dose is not detected by a set time.

One of the novel features of using the ingestible markers to capture oral medication ingestion is that the communication is private. The method of marker communication to the personal monitor is similar to that of electrocardiography, where the individual is the communication pathway and communication of a heartbeat to the electrocardiograph is confined to the body. The unique signature of the ingestible marker is not broadcast in any way; the communication process is unnoticed by and not detectable beyond the system user. Furthermore, the adherence data gathered by the ingestible markers can be juxtaposed with physiologic and behavioral information collected by the personal monitor, peripheral wireless devices, and any other data source with a time stamp. The comprehensive data set offered by the networked system may provide new insights to the patients about their health and lifestyle, and may empower them to find new ways to achieve and sustain wellness.

Fundamentally, the information gathered by the networked system belongs to the patient user; he or she has the right to determine whether or not and with whom to share this information. To maintain privacy and to mitigate the risk of accidentally disseminating these health-related data to unintended parties, high-quality data exchange infrastructure must be implemented to allow individuals to discreetly and securely share their information. Such infrastructure could be modeled after financial and social systems, where credit card and social networking Web sites are now ubiquitous and allow millions of individuals to conduct transactions and share personal information with selected parties. Similar approaches should be feasible for care and wellness systems. Information sharing is powerful and could elicit support and new insights. A patient sharing information with family members, caregivers, and friends may gain communal encouragement in achieving wellness. A patient sharing information with healthcare providers may allow providers to truly individualize care.

The studies presented had some limitations. These were pilot investigations with small sample sizes and were of short duration; the system usability and user acceptability of the networked system for long-term, repeated use remain unknown, and these are areas of ongoing work. An early clinical trial version of the system was utilized in these studies, which led to some user errors and subsequent exclusion of data from analysis. A more mature version of the system shall be evaluated to further validate and confirm the performance of the system. Moreover, the study protocol required patient subjects to attend weekly clinic visits for study material replenishment and data collection. The study procedural requirements along with the potential Hawthorne effect might bias the results regarding medication adherence and system use compliance. Finally, the system PDA and NDA were assessed via repeated observations of the same subjects. To accurately quantify these metrics, additional independent observations from a wide range of user subjects are needed.

Despite these limitations, the networked system was demonstrated to be capable of capturing adherence electronically and acquiring physiologic data in an ambulatory, at-home setting. System enhancements are under way to increase the functionality of the system and to optimize it for everyday use. The unique identifier field of the ingest-

ible marker will be expanded such that every dose of any medication will be given a globally unique signature, allowing true unit-level identification of pharmaceuticals. Additional sensing modalities are also being developed for the ingestible marker. These additions will transform the ingestible marker from a simple marker of ingestion to a multifunctional data collection platform. The functionality of the personal monitor is also being expanded to further increase physiologic measurement. The future personal monitor will resemble a small, disposable electronic bandage.

CONCLUSION

A networked system has been developed to document actual ingestions of oral medications, to differentiate the types and doses of drugs simultaneously, and to provide these data along with physiologic information to patients and their designated persons as a potential aid for tailoring individual care. Early clinical studies have demonstrated that system safety appears to be satisfactory; gathering, integrating, and communicating of multiple data streams appear to be feasible. Perhaps the most exciting area for future system enhancement lies in data visualization, utilization, and user experience optimization to allow patients to gain insights into their own wellness and to provide them with useful tools to achieve and sustain health. Building upon current trends in behavioral research, self-actualization, and human-centered design, the networked system has the potential to become a comprehensive platform for exploring the relationship between objective health data and individual wellness.

Author Affiliations: From Proteus Biomedical, Inc (KAY, GDM, TLR, LAD), Redwood City, CA; Digestive Disorders Associates (MSE), Annapolis, MD; University of North Texas Health Science Center (SEW), Fort Worth; Denver Public Health TB Clinic (RRR), CO; Cardiovascular Medicine & Cardiac Arrhythmias (GE), Palo Alto, CA.

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Address correspondence to: Kit Yee Au-Yeung, PhD, Proteus Biomedical, Inc 2600 Bridge Parkway, Suite 101, Redwood City, CA 94065. E-mail: kauyeung@proteusbiomed.com.

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