UNIVERSITY OF CALIFORNIA SAN DIEGO

Smart Eyedrop Bottle Using Rigid-flexible Electronics for Unobtrusive Monitoring of Glaucoma Medication Adherence

A Thesis submitted in partial satisfaction of the requirements for the degree Master of Science

In

Bioengineering

By

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The Thesis of Vincent Wu, and it is acceptable in quality and form for publication on microfilm and electronically:

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ABSTRACT OF THE THESIS

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by

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Master of Science in Bioengineering

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Professor Todd P. Coleman, Chair

Glaucoma, the leading cause of irreversible blindness, affects more than 70 million people worldwide. Lowering intraocular pressure, the most common method of delaying both the development and progression of glaucoma, is typically done

with daily topical administration of therapeutic eye drops, which has notoriously high non-adherence rates ranging from 30% to 80%. The advent of smart phone enabled technologies creates an opportunity to address the non-adherence problem. However, previous eyedrop electronic monitoring solutions had awkward medication bottle adjuncts and crude software design for monitoring the administration of a drop, which adversely affected their ability to foster significant and, sustainable improvements in adherence. Here we present our prototype, the “smart drop” bottle, that is capable of detecting each eyedrop medication administered while maintaining the shape or size of the eyedrop bottle. This is achieved by developing a smart-phone application that interacts with a small rigid-flexible electronics circuit beneath the bottle and bottle label respectively. We have shown we can achieve wireless communication close to 100 feet with 0% false positive rates, thus providing a potential solution for adherence monitoring of glaucoma patients.

INTRODUCTION

Reduced adherence with prescribed systemic and topical medications (such as eyedrops) for treating chronic illness has long been identified as a key obstacle to delivering successful treatment. Complications from poor adherence result in huge waste in medical resource utilization, with cost estimates approximating $100B/year in the United States alone.[1] More importantly, poor adherence often leads to failed treatment regimens and subsequently poor patient outcomes. As former United States Surgeon General C. Everett Koop, MD, stated, “Drugs don't work in patients who don't take them.”[2] In a similar vein, the World Health Organization (WHO) has declared, “Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.”[3]

Reduced adherence is a prominent issue in the management of glaucoma, a chronic eye disease that is the leading cause of irreversible blindness globally,[4] projected to affect more than 80 million people worldwide by 2020.[4,5] Glaucoma incurs more than $3 billion in direct healthcare costs in the US alone.[6] Lowering intraocular pressure (IOP) is the only proven method of delaying both the development and progression of glaucoma.[7] The most common first line therapy for IOP reduction is achieved by topical administration of a series of eye drops.[8,9]

While eye drops can be effective in lowering IOP, they require patients to administer medication daily or often multiple times a day. Unfortunately, adherence

with eye drops has been reported to range from 30% to 80%,[10,11] failing to consistently meet the 80% threshold recognized as an acceptable standard of adherence for many systemic medications.[1] Moreover, patients tend to overestimate their own adherence compared to device-measured or pharmacy refill data.[12] Medication non-adherence is a critical barrier to glaucoma management, as it can hasten disease progression and lead to worsening visual impairment and eventual blindness.[13–16] Visual impairment due to glaucoma is associated with decreased quality of life,[17–19] psychiatric disorders such as depression and anxiety,[20–23] and increased costs to patients, caregivers, and the health system.[24–26]

While no single factor fully predicts poor medication adherence, some contributors to non-adherence in the context of glaucoma include the lack of visual symptoms in the early and intermediate stages of the disease, lack of information or education regarding the disease process and the irreversibility of vision loss from glaucoma, need for lifelong treatment, and the cost of treatment.[27–29] Poor adherence has been established across a wide array of ethno- and socioeconomic demographics and age groups,[27,28,30–34] indicating the pervasiveness of this issue. Taken together, interventions to improve medication adherence must not increase burden, be timely with personalized reminders, and provide accurate adherence data to patients and providers.

Early evidence indicates a potential role for the use of alerts or reminders at drop-taking times, bolstered by the widespread use of smart-phone enabled technologies.[35–38] However, previous electronic monitoring solutions for eye drops have design drawbacks that have impaired their ability to foster significant, sustainable improvements in adherence. For example, the Alcon TRAVATAN dosing aid[39] had awkward medication bottle adjuncts and crude software for monitoring the administration of a drop, contributing to this not being a viable product. More recently, Nemera has developed an ophthalmic drug delivery system, e-Novelia, which entailed customized eyedrop bottles containing sensors and electronics for wireless signaling of adherence patterns to smart phones for reminders.[40] However, this system utilizes custom bottles of larger size than typical eyedrop bottles and cause further inconvenient to the patients. As such, there is an unmet need for seamlessly integrated technology that can register a successful drop delivery to the eye and communicate this information to both patients' providers. Ideally, such a measurement apparatus should not change the shape or size of the eyedrop bottle; otherwise, the years of human factors research that have gone into designing such devices for optimal human usage would be nullified.

We have developed an electronic adherence monitoring system capable of addressing these unmet needs that offers several innovations over existing technologies. First, the system affixes wireless flexible electronic systems underneath the label of any eyedrop bottle currently on the market, thus lowering barriers to widespread adoption. The bottle electronics contain force sensors and

gyroscopes to detect when a drop is being administered (in the correct orientation), along with circuits, antennas, and coils for wireless telemetry. Second, the electronics-equipped bottle records the date and time of drop delivery and wirelessly transmits a digital signature of adherence data via Bluetooth Low Energy (BLE) to a smart phone or tablet, where it can be archived and/or sent to the cloud. Third, it has the capability to provide dosing reminders to the patient, alert physicians of poor patient compliant behavior, and even alert pharmacies to refill prescriptions. Here, we report the performance of this system under a wide range of testing conditions to demonstrate its accuracy, reliability, and feasibility for clinical deployment.

MATERIALS AND METHODS

Fully Integrated Rigid-Flexible Electronic System

This system builds upon recently demonstrated multi-functional uses of thin and flexible electronics for medical monitoring[41,42], can be fabricated to be imperceptible to the user. This prototype does not significantly alter the shape or size

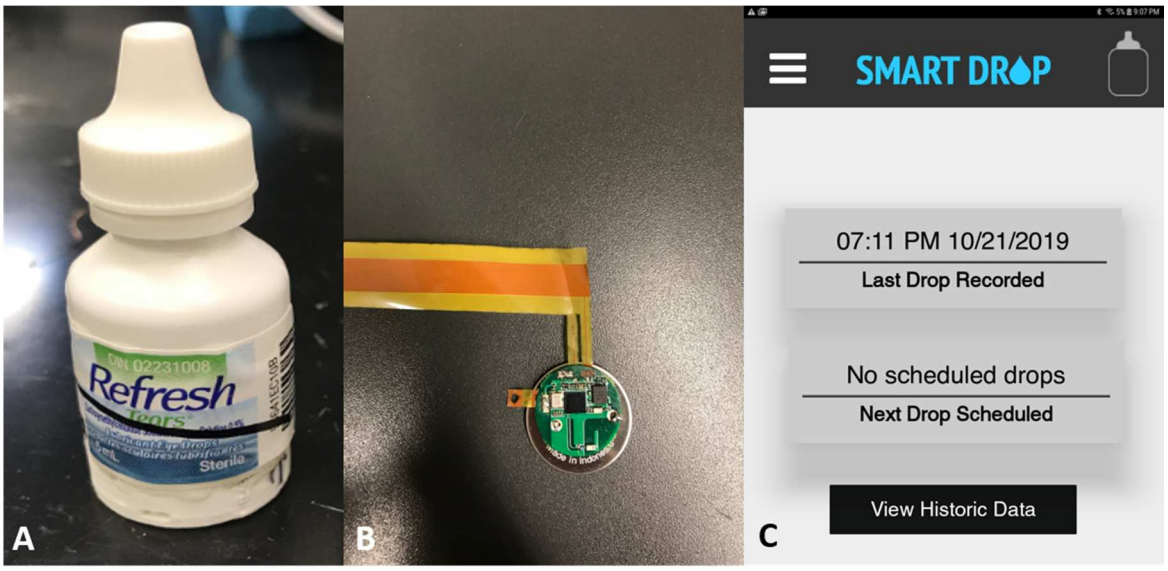

Figure 1: A: Rigid-flexible electronics attached to a normal eyedrop bottle. B: Closeup of a rigid-flexible integrated circuit and antenna for sensing, processing and Bluetooth transmission. C: A smart phone application which can track eyedrop adherence from the instrumented bottle via Bluetooth and be programmed for reminders.

of the bottle. As shown in Figure 1, a flexible sensor is placed under the adhesive label of the eyedrop bottle. This flexible sensor is embodied in a rigid but thin circuit placed beneath the bottle.

Our prototype of smart eyedrop system consists of a standard eyedrop bottle outfitted with flexible electronics to detect when the bottle is squeezed. A gyroscope allows the smart eyedrop bottle detects the squeezing of the bottle only when it is upside down, decreasing the false positives as it is discussed below. A Bluetooth chip from Cypress Semiconductor is used to enable a Bluetooth connection between the smart eyedrop bottle and the smart phone application. A coin cell battery, also beneath the eyedrop bottle, powers the system and power

consumption performance will be discussed in the below section. The data about squeezing is transmitted via Bluetooth low energy to a mobile device, such as a tablet or a cellphone. The information from the mobile device is transmitted to a database that in principle can allow doctors to have access to patient information about eye drops administration.

Smart Eyedrop Bottle Behavior

The smart eyedrop bottle is designed to reduce false positives and save energy for identifying attempts at drop administration by activating the microprocessor and wireless system only when the bottle is in an upside-down orientation and when sufficient finger force is applied to the bottle. This provides situations when the bottle is bumped around in a purse or bag.

Upon activation of the microprocessor, the smart drop bottle will send registered drop information to the smart phone application. After there are no drop administration actions for 30 seconds, the microprocessor enters a hibernate mode in order to save energy.

Performance Testing

A range of tests were performed on the eyedrop bottle sensor prototypes in the laboratory environment. These tests were aimed at validating the accuracy of the sensor and additionally evaluating readiness for clinical deployment.

Battery Consumption Test: A key objective of the design of the sensor prototype was to ensure adequate battery life for clinical testing. While some glaucoma medications are dosed once daily, several classes of glaucoma medications are dosed twice or three times daily. In addition, patients with glaucoma are often undergoing simultaneous treatment for both eyes. Therefore, to simulate maximal usage, we decided to test the prototype sensor with 6 delivery events daily. We recorded the battery life among 6 different bottles to ascertain the average battery life of the prototype. Battery life was defined as the number of days between the first day of delivery events and the last day when a delivery event was successfully registered and transmitted. The final voltage of each bottle's battery was also recorded.

Distance Tests: To evaluate the maximum distance at which wireless transmission of a medication delivery event between the sensor on the bottle and the application could be achieved, testing was performed with varying distances between the sensor prototype and the tablet where the user interface application was installed. This simulates real-world conditions where patients may not always be administering their eye drops immediately adjacent to a smart phone or tablet containing the application. Two variations of distance testing were performed: 1) straight distance test and 2) through the door/wall test. The straight distance test was used to illustrate the maximum distance for successful communication between the bottles and the application. To perform this test, a tablet with the application installed was placed on a table. Then, each bottle was squeezed every

5 feet as it was moved away from the tablet until it disconnected from the application. The distance at which the bottle became disconnected from the application was measured and recorded for two bottles with five repetitions each in order to see if the result from each bottle is consistent. The second variation of the test, the “through the door/wall test”, was performed similarly but with a door and wall positioned between the tablet application and the bottle sensor. This further simulated the home environment, where patients may be using glaucoma medications in a separate room than where their tablet or smart phone may be located. The second variation of the distance test was performed on the same bottles as the first variation, in order to directly evaluate the effect of intervening physical structures on the connectivity of the sensor.

False Positive and False Negative Tests: To ensure that the sensor would record only true medication delivery events rather than arbitrary movements, we performed the following sequence of tasks: we placed the bottle in a packed bag, turned the bag upside down and manually shook it for 5 seconds, walked around and then dropped the bag on the ground. The tablet application was then analyzed to evaluate for any registration of medication delivery events during this sequence when the bottle was not intentionally squeezed (i.e. to evaluate for any false positives). These false positive tests were performed on two bottles for ten times each to evaluate the consistency of the bottles.

Two iterations of false negative testing were done to demonstrate that the application would not fail to register medication delivery events. First, each bottle used in the movement sequence above was intentionally squeezed, and the application was analyzed to evaluate for successful registration. This also demonstrated whether any of the bottles were damaged during the false positive test. In the course of working with the bottles, we also incidentally noticed that if squeezes the bottle is squeezed multiple times in quick succession, the application may not register all the squeezes. Therefore, we developed another iteration of a false negative test by squeezing the bottles two times separated by 0.5, 1, 2, and 3 seconds to observe how the sensor would react. These false negative tests were performed on two bottles for five repetitions each.

Temperature Test: Testing of connectivity between the sensor and the tablet application was also performed in various extremes of temperature. The objective was to evaluate whether the sensor could still function if placed in low temperature settings such as the refrigerator (which is a common source of medication storage for glaucoma patients, who sometimes use the cold sensation to help gauge whether an eyedrop has reached their eye successfully. Two bottles were tested for five repetitions each for the low temperature condition. Bottles were placed in a *3*℃ refrigerator for 2, 4, 6, 8, and 14 hours, with the 14-hour setting simulating overnight storage conditions. After each period of cold exposure, we removed the bottle and immediately squeezed once to evaluate the connectivity to the tablet.

For each test, descriptive statistics were generated using Microsoft Excel (Redmond, WA). Data from the tests were analyzed and visualized using R.[43]

RESULTS

Battery Consumption Test

Our current design has a BLE and microprocessor system-on-a-chip which consumes most of the energy during transmission to a smartphone. Each BLE transmission incurs a maximum of 0.25s. Figure 2 illustrates the battery consumption result from one bottle squeeze. Firmware optimization for which microprocessor activation does not ensue until the gyroscope and force sensor cross thresholds has strategically allowed us to optimize the small coin cell battery life to withstand over 1000 bottle squeezes, thus vastly exceeding the 1 month of 6 times daily or 186 bottle squeezes use constraint.

In a simulation of maximal clinical usage of glaucoma medications dosed 3 times daily for both eyes (for a total of 6 times daily), the tested bottles (n=6) had a mean (standard deviation, SD) battery life of 21.3 (1.3) days, ranging from 19 to 23 days (Figure 3). The mean (SD) battery voltage at the point at which delivery events were no longer successfully registered was 0.38 (0.37) V (range: 0.05 to 1.09 V).

Distance Tests

Among tested bottles that were progressively moved farther from the tablet application, successful medication delivery events were recorded up to a mean (SD) distance of 96 (8.3) feet (range: 75-100 feet). All (100%) bottles were successfully connected at 75 feet, and 80% of bottles were successfully connected even at 100 feet (Figure 4).

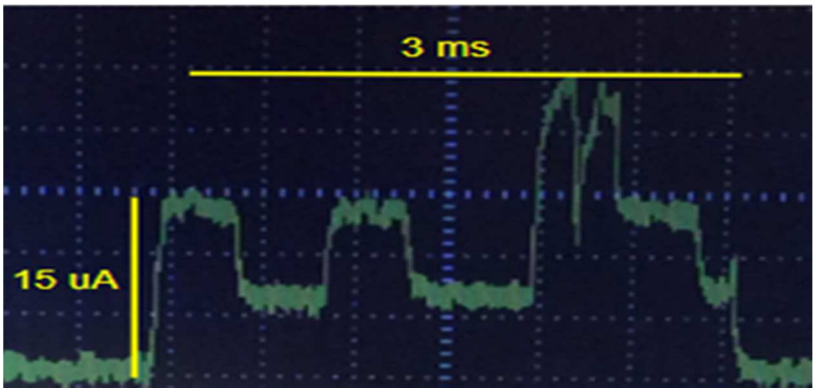

Figure 2: Each bottle squeeze consumes 12 A for 3 ms. Intact bottles can achieve >1000 pushes and BLE transmissions before battery voltage falls below 1.8-V.

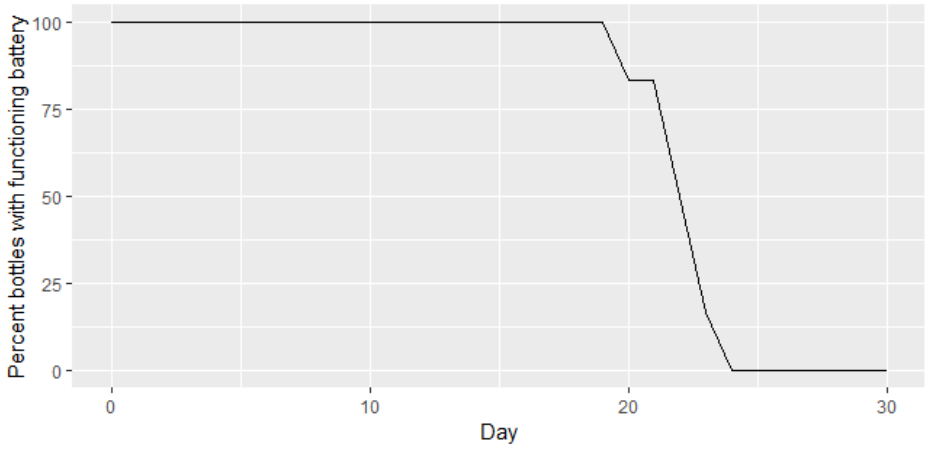

Figure 3: Each bottle was squeezed six times per day. The average duration of time the bottles last is 21.3 days.

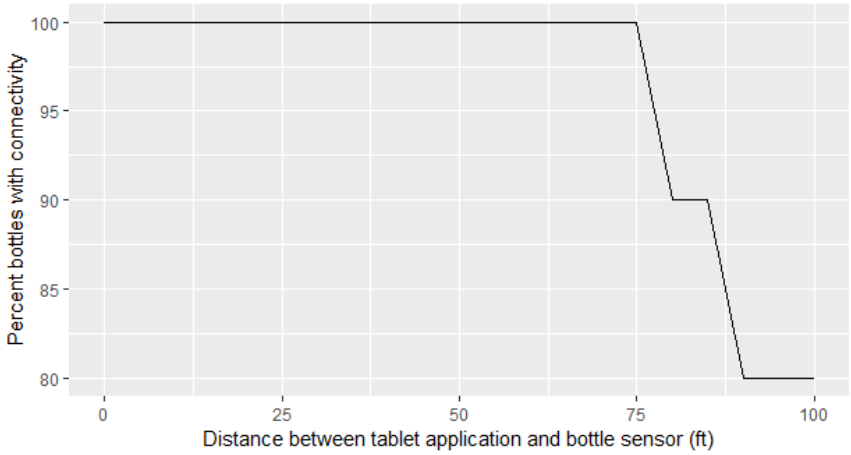

Figure 4: The bottle connection rates before 75 ft are 100%. The straight distance test was performed up to 100 ft.

When a door or wall was interposed between the tablet application and the bottles, the mean (SD) distance of successful medication delivery event registration was 36 (4.7) feet (range 30-40 feet). In this circumstance, 100% of the bottles were successfully connected within 30 feet, and then connectivity rates declined as bottles were moved to progressively farther distances.

False Positive and False Negative Tests

Despite rigorous movement involved in the sequence of testing done for evaluation for false positives (see Methods Section for details), the tablet application did not register any medication delivery events in the absence of intentional squeezing to deliver a medication dose, representing a false positive rate of 0% after 20 runs. In each run of the test, the connectivity of the sensor was

verified, ensuring that the false positive rate was truly 0% and not just a result of absent or faulty connectivity between the sensor and the tablet application.

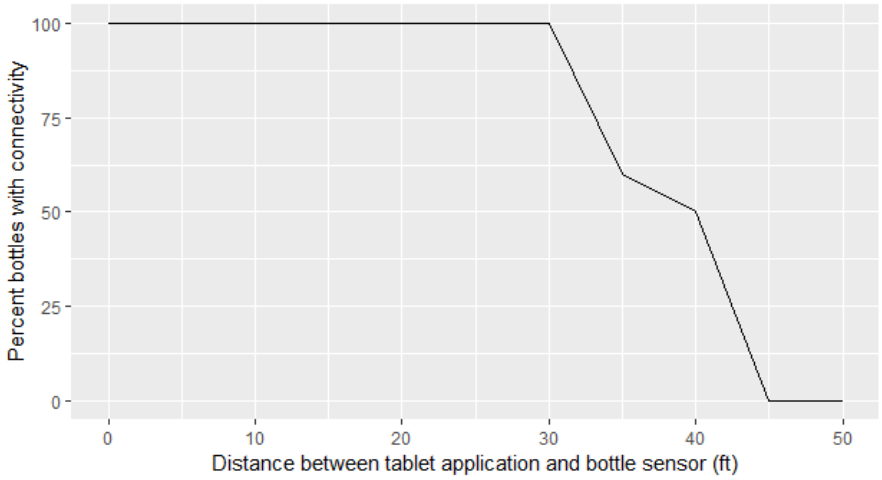

Figure 5: Through the door distance test. 100% connection rate up to 30 ft away from the tablet. The connection rate drastically falls starting from 30 ft.

Immediately after the false positive test, the one squeeze false negative test was conducted. The result shows that there were no false negatives in the tablet application when the bottles were squeezed only once. However, if the bottles were squeezed two times in quick succession, the tablet application did not always register the second squeeze, representing false negatives. The false negative rate was 50% if the two squeezes were separated by 0.5 second and decreased to 10% once the two squeezes were separated by 1 second (Figure 6). The false negative rate decreased to 0% once the time between squeezes was 2 seconds or longer.

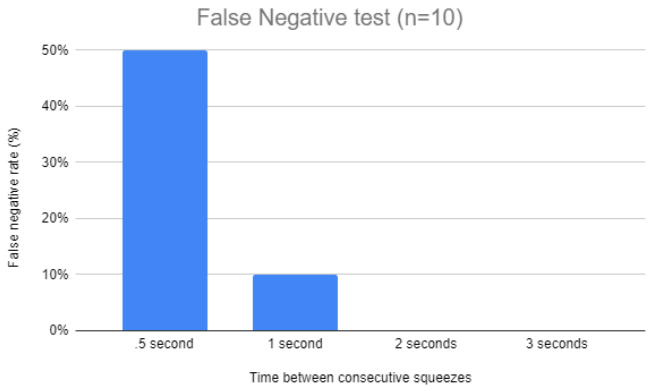

Figure 6: False negative test with two consecutive squeezes. For 2 and 3 seconds between squeezes, the false negative rate is at 0 %.

Temperature Tests

The sensor bottles were tested at low temperature settings (*3*℃). From the result, every bottle was able to successfully register medication delivery events in the tablet application even after 14 consecutive hours.

DISCUSSION & CONCLUSION

We have developed a fully functioning eyedrop bottle prototype that can successfully transmit a signal wirelessly to a smart device and document when a drop is administered in the appropriate orientation. This represents a novel innovation to monitor glaucoma medication adherence, which remains a substantial public health challenge.

Here, we present the results of laboratory-based testing, which demonstrate the feasibility of this prototype for real-world deployment. First, the battery life averaged approximately 21 days, allowing three weeks of adherence data collection, which in most cases would capture a representative slice of patient behavior. Rarely in ambulatory clinical practice are health data obtained daily (or multiple times daily) for consecutive weeks. Supplying three weeks' worth of data represents an excellent starting point. In the future, we will work toward extending battery life or developing recharging capabilities such that the sensor can continue recording adherence data until the patient runs out of medication in the bottle. Another consideration is that the battery life testing was performed under the scenario of maximum dosage delivery (6 times daily). Several classes of glaucoma medications, including prostaglandin analogues, beta blockers, and carbonic anhydrase inhibitors, are dosed just once or twice daily and would therefore entail less frequent squeezes. Therefore, in clinical practice the battery life would likely be longer for the many patients who are using a given medication less than 6 times daily.

Connectivity between the sensor on the bottle and the tablet application storing the adherence data was maintained at distances of almost 100 feet, but the connectivity decreased to an average of 36 feet if there was an intervening door or wall between the bottle and the tablet. In initial deployment, it may be sensible to advise patients to administer their eyedrops within the same physical room as the device (smartphone or tablet) running the application, as ~30 feet would

encompass the dimensions of most indoor rooms in private homes. However, future iterations may allow for longer-range data transmission, such as using another Bluetooth chipwith optimized antennas (e.g. Nordic semiconductor) which patients could use their drops in any room and would not need to be physically near their device in order for adherence data to register.

Several other features support this prototype's readiness for the clinic. The false positive rate of the sensor was 0%, thus mitigating any concerns that dosages would be improperly recorded from eyedrop bottles being carried in patients' purses or backpacks. The system only registered a dose as given if the bottle was in the correct orientation and squeezed with the appropriate force. Similarly, the false negative rate was 0% for single squeezes. Although there were some false negatives for squeezes in quick succession (separated by 1 second or less), this would not represent a major issue, since in the context of typical patient use, multiple successive squeezes often constitute a single "dose" anyway.

Furthermore, the sensor demonstrated successful connectivity in low-temperature settings, illustrating that adherence data would be successfully collected even if the patients store their eyedrops in the refrigerator. In short, these results suggest that the sensor will be able to perform not only in the laboratory, but also in real-world environments. This technology offers several key advantages over current practice. First, most clinicians monitor adherence by interviewing patients and acquiring self-reported data. Unfortunately, several research studies

have shown that patients' self-reported adherence is often overestimated. Another method of monitoring adherence is examining claims data or medication dispensing data. This can be difficult if the patient has multiple forms of insurance and/or uses multiple pharmacies, both of which are not uncommon scenarios. In addition, claims and dispensing data do not have the level of dose-to-dose granularity. Finally, previously reported electronic dosing trackers for eye drops have all required separate hardware and often bulky designs that limit widespread adoption. Using an unobtrusive device that is integrated with the eyedrop bottle itself to gather data on individual dose adherence provides a source of objective and granular data to help guide glaucoma management. Future studies to better understand how patients will use and interact with this technology and how clinicians will integrate these new data streams into their workflows will be critical.

Altogether, we provide a unique and promising tool for monitoring and fostering glaucoma patient adherence, with the goal of enhancing provider-patient communication and patient engagement to improve outcomes, ultimately reducing the burden of irreversible blindness of advanced glaucoma.

Chapter 1, in part is currently being prepared for submission for publication. Aguilar-Rivera, Marcelo; Erudaitius, Dieanira T.; Tantiongloc, Justin; Kang, Dae; Wu, Vincent; Baxter, Sally; Weinreb, Robert N.; Coleman, Todd P. Vincent Wu will be the co-author of this material.

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