Digitally enabled AI-interpreted salivary based ovulation prediction: a feasibility study

Elizabeth Peebles, William Finley, Thao-Mi Nguyen, Samuel Barrett, Hemanth Kandula, Carrie Sarcione, Kaitlyn E. James, Hadi Shafiee, Shruthi Mahalingaiah

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Table of Contents

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Abstract

Background: Females with irregular or unpredictable cycles, including those with polycystic ovary syndrome (PCOS), have limited options for validated at-home ovulation prediction. The majority of over-the-counter ovulation prediction kits use urinary luteinizing hormone (LH) indicators that were optimized for those with regular menstrual cycles exhibiting a predictable mid-cycle LH surge. Artificial intelligence (AI) holds potential to address this health deficit via a smartphone-based salivary ferning ovulation test. Research on populations with irregular menstruation and PCOS can be challenging due to the duration and frequency of menstrual cycles.

Objective: The objective of this study was to determine the feasibility for participants with diverse menstrual cycle lengths to complete study tasks designed to train and develop an AI model for salivary-based ovulation prediction.

Methods: Participants were recruited for two menstrual cycles where retention, engagement, and adherence were evaluated. Participation entailed remotely collecting and uploading daily data (saliva, LH values), attending lab visits, and returning biological saliva samples.

Results: Of the 133 females recruited from February to October 2023 via targeted patient messages and a public research website, 69 were eligible (age 19 to 35 years old at enrollment, currently menstruating, able to read and comprehend English, weigh more than 110 pounds, have an active primary care or gynecological provider, and able to commute to the Mass General Hospital main campus within 10 days of their ovulatory event). Of those who received a Study Kit, 57% of participants (n=17) began data collection, 31% of participants (n=9) provided data for one menstrual cycle, and 24% of participants (n=7) completed the study.

Conclusions: To optimize future scaled participant completion, the study design would include a more targeted recruitment message to address the high ineligibility status, to streamline study procedures to ease participant burden, and to incorporate health education to equip participants with ovulatory health information to ameliorate the potential stress impacts of observing anovulation. After optimization, when scaled, this study design will provide an AI model with sufficient data to develop a smartphone-based ovulation predictor specifically tested on females with irregular or unpredictable cycles, including those with PCOS. Well informed study design is the foundation to AI advancement and femtech growth, particularity for ovulatory and fertility digital health.

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Digitally enabled AI-interpreted salivary based ovulation prediction: a feasibility study

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Keywords: ovulation prediction; salivary ferning; polycystic ovary syndrome (PCOS); irregular menstrual cycles; digital health; reproductive health technology

Introduction

Femtech, the technology sector focused on enhancing women's health, is gaining momentum, particularly with the rise of convenient, at-home, personalized health tracking solutions.[1] Ovulation tracking, through the means of smartphone applications and at-home tests, empowers menstruators with valuable ovulatory status and fertility information, allowing them to make informed family planning or pregnancy protection decisions. Additionally, ovulation acts as a vital sign for other health conditions (i.e., hormonal, reproductive health) occurring in the body.[2] Most at-home ovulation tests utilize urinary luteinizing hormone (LH) indicators and were optimized for those with predictable menstrual cycles due to the expected mid-cycle LH surge. However, menstruators with irregular or unpredictable cycles, including those with polycystic ovary syndrome (PCOS), are often unable to predict ovulation using LH based tests due to tonically elevated or fluctuating LH levels with resulting false positive results.[3]

PCOS, a heterogenous endocrine disorder affecting about 5-10% of women (up to 21% depending on the criteria and studied population), is characterized by abnormal hormone profiles, disordered ovulation, and irregular menstrual cycles. It is a leading contributor to ovulatory infertility.[4–7] Without a reliable, at-home test for ovulation prediction, menstruators with irregular or unpredictable cycles—such as those that are experiencing temporary irregularity (e.g., transition off birth control or adjusting to longer cycles) or those with PCOS—face a deficit in options and can experience challenges in understanding their fertility and making informed health decisions.[8]

An accurate at-home ovulation test that does not utilize LH levels to determine ovulatory status would provide those with irregular or unpredictable cycles, including those with PCOS, an opportunity for reliable ovulation prediction. Prior to an LH surge, serum estrogen levels in the body rise and can be detected in multiple biofluids such as cervical mucus and saliva.[9] In the saliva, changes in estradiol levels correspond with increased concentrations of salivary electrolytes, particularly sodium chloride (NaCl) and certain proteins. The interactions between NaCl and proteins generate consistent fern-like structures due to NaCl crystallization.[10–12] The concentration of estrogen, NaCl, and proteins have been observed in a 4 day window leading up to ovulation, corresponding with the 3-5 day fertility window prior to ovulation.[9,10,13–15]

Artificial intelligence (AI) has the potential to objectively, accurately, and rapidly analyze saliva ferning patterns from images captured using an inexpensive smartphone-based optical sensor, helping to bridge the ovulatory prediction gap for individuals with irregular or unpredictable cycles,

including those with PCOS. Among the various ovulation tests on the market that do not rely on LH levels—such as ultrasonography, salivary beta-glucuronidase activity evaluation, serum progesterone, rectal or oral basal body temperature [BBT], and cervical mucus characterization—salivary ferning analysis offers an at-home, low-cost, and simple method.[9,16] BBT is a competitive alternative but, unlike salivary ferning, can be influenced by a multitude of factors including alcohol consumption, emotional or physical stress, sleep disturbance, change of room temperature, change of waking time, and change of climate.[9] Recent research in salivary ferning technology performed by this study team has revealed that using both artificial and human saliva samples of individuals with regular cycles (n=6), an AI-enabled smartphone device displayed a >99% accuracy in effectively predicting ovulation.[16] The tested saliva did not include irregular or unpredictable cyclers or those with PCOS, leaving this area of research in ovulation development unexplored.

This study was conducted to evaluate the feasibility of menstruators with irregular or unpredictable cycles, including those with PCOS, to remotely collect saliva samples and LH values throughout the duration of 2 menstrual cycles. This data ultimately assesses the achievability of participants providing sufficient data to train and develop an AI model for salivary-based ovulation prediction.

Methods

Eligibility

To be eligible for the Precision Ovulation Prediction for Patients with PCOS (PEONy) study, a participant must have been of age 19 to 35 years old at enrollment, currently menstruating, able to read and comprehend English, weigh more than 110 pounds, have an active primary care or gynecological provider, and be able to commute to the Mass General Hospital (MGH) main campus within 10 days of their ovulatory event. Participants were excluded if they had current use of hormonal therapy, a history of surgical menopause (no ovaries or no uterus), history of or currently undergoing chemotherapy or radiation, a thyroid or prolactin disorder, or were currently breastfeeding and/or postpartum. Participants who stopped hormonal therapy were eligible upon having one menstrual cycle after cessation (n=1).

Ethics Approval

The Mass General Brigham Institutional Review Board (IRB) approval this study (#2022P001812).

Overall Design

Once a participant was recruited, considered eligible, and consented, they were sent a baseline survey. Upon completing the survey, participants were sent a Study Kit containing materials to collect and upload daily dried saliva photos and urinary LH values for the duration of two menstrual cycles. After indication of ovulation or after 38 days of data collection, participants were brought in for lab tests to confirm ovulation. The dried saliva samples were returned to the study team for potential AI model development. A summary of the study tasks from recruitment to study conclusion can be found in Figure 1.

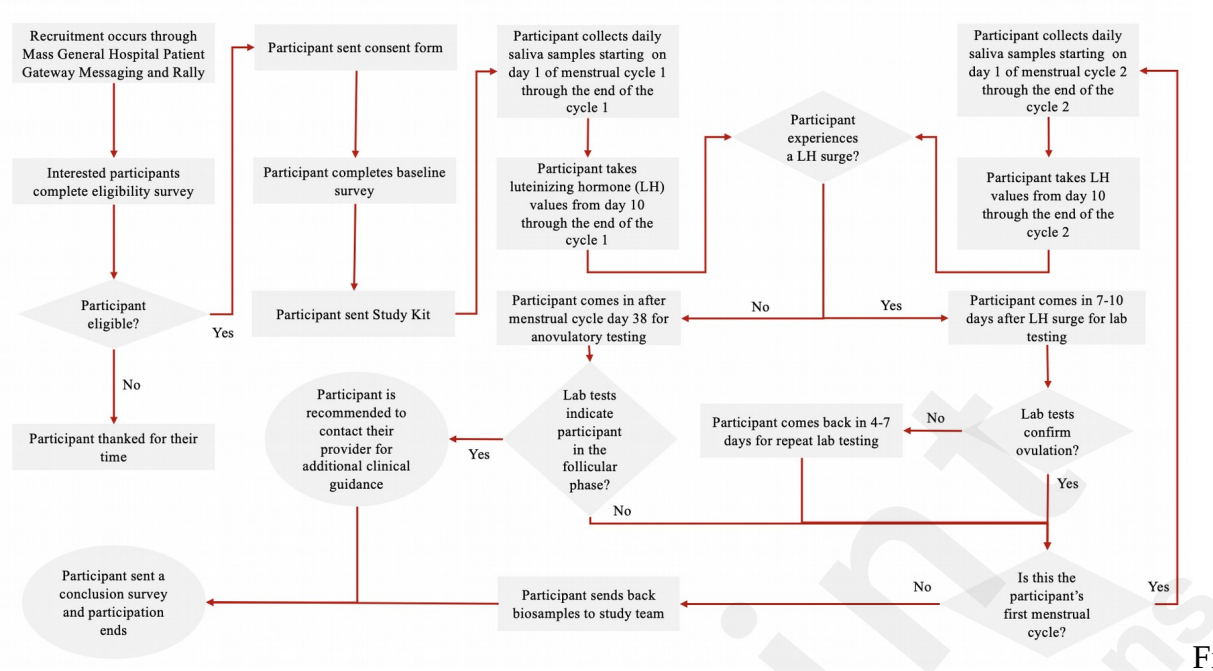

Figure 1. Study summary flowchart of participant study tasks from enrollment to study completion.

Recruitment

Participants were recruited into the study from February to October 2023 through 2 methods: MGH Patient Gateway and MGH Rally, a public website utilized for research recruitment. Using the MGH Patient Gateway secure communication, to over-sample individuals with irregular cycles, 7,130 targeted messages were sent to a group that fell within the target population (International Classification of Diseases [ICD] codes of irregular menstruation or PCOS). The message contained the study's purpose and description, eligibility criteria, participation expectations (time commitment, tasks, travel requirements), compensation, and a link to the study's Rally post (Multimedia Appendix). The Rally post provided the same information as the Patient Gateway message (Multimedia Appendix). Interested participants could contact that study email, provided in the Patient Gateway message, or submit their contact information on Rally to trigger study team outreach.

Informed Consent and Survey Descriptions

Consent forms and participant surveys were distributed via email utilizing the MGH REDCap system. After expressing interest, the individual was sent an eligibility survey, and if found eligible, the participant received an e-consent form. After the consent process, participants received a unique link via email to a baseline survey which included demographic, reproductive health history, substance-use history, and menstrual cycle history questions. At the end of participation or at the end of the study, whichever came first, all eligible participants were sent a conclusion survey. This survey evaluated reasons individuals chose to participate, obstacles to completing study tasks, study technology, participant demand, and it offered an opportunity to share additional thoughts.

Incentive

Participants were compensated $50 for each menstrual cycle provided (2 maximum) and $75 for completing the conclusion survey, sent to all eligible participants.

Participation

After completing the baseline surveys, participants were sent a Study Kit which contained a Motorola Moto G Pure phone, an optical hardware device, 100 saliva collection chips, 2 empty chip

holders for collected samples, a thin tip Sharpie, 4 Modern Fertility ovulation prediction kits (80 LH test strips), 4 Modern Fertility pregnancy tests kits (16 pregnancy tests), 2 urine collection cups, 2 lab parking vouchers, a FedEx return shipping label, an instruction manual (Multimedia Appendix), and a study calendar (Multimedia Appendix). The optical hardware device was internally built and made to be attached to the provided phone to assist in capturing an illuminated photograph of the saliva chips (Figure 2). Each phone contained a pre-downloaded PEONy app, internally designed, which provided instructions and reminders on the relevant study actions.

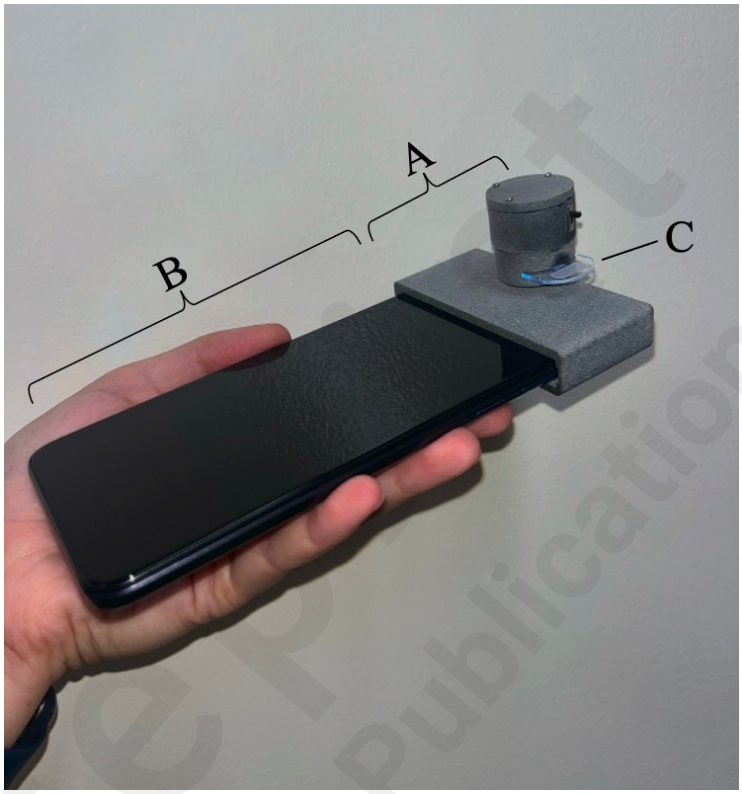

Figure 2. Internally built optical hardware device (A) provided to participants in the Study Kit that affixes to the study phone (B) to assist in capturing illuminated photographs of the dried saliva chip (C).

Starting on the first menstrual bleed day of a participant's cycle, participants were to collect daily saliva samples first thing in the morning, before brushing teeth or consuming food, to exclude discrepancies in salivary electrolyte concentration. To collect the sample, the participant was to place a clean finger under their tongue (bilingual region) then press their finger onto the provided chip. The chips were self-labeled with the menstrual cycle number (C1 or C2) and menstrual cycle day (e.g., D10) using the provided Sharpie. Once the saliva dried, approximately 10 minutes, they were to place the chip in the provided optical hardware device, affix the device to align with the front camera of the provided phone, and use the PEONy app to image and upload a photo of the dried saliva. The study team could view the photos once uploaded. On cycle day 10, in addition to collecting and uploading saliva samples, the participants were asked to collect LH values using the provided Modern Fertility ovulation prediction kits and report the value on the PEONy app. After a participant's reported LH value was greater than 25 IU/L, the participant was scheduled for a lab visit at the MGH main campus within 10 days. This LH trigger value was later redefined to a LH surge (when LH values rise to a peak and decreased again) which was tracked by the study staff as some patients never surged to 25 IU/L.

A serum progesterone level was obtained to confirm ovulation. Participants continued to record and

submit daily saliva samples and LH values until the study team received their lab tests results. If ovulation was confirmed, data collection for 1 cycle was concluded; participants were asked to provide 2 cycles worth of data. If ovulation was not confirmed, the participant continued data collection and came in 4 to 7 days later for another serum progesterone blood test.

If a participant's LH values did not surge after 38 days, they were instructed to come into the hospital for anovulatory evaluation including serum pregnancy (bHCG), estrogen (17B estradiol), and progesterone lab tests. If the lab results indicated that the participant was in the follicular phase, the study team recommended that the participant contact their provider and schedule an appointment for additional clinical guidance.

Participation was considered complete at the return of labeled chips for analysis and use in potential AI model training.

Study Team Communication

To encourage participation and study retention, ongoing communication was implemented via 2 streams: PEONy app notifications and direct, individual study team communication via email and phone calls. The PEONy app provided reminders at a cadence programmed to study participation tasks (Multimedia Appendix). The study staff initially communicated upon Study Kit delivery and after an ovulatory event. As the study progressed and some participants remained inactive over an extended period, communication efforts increased, requiring hiring additional study staff. In the event a participant did not completing study tasks as scheduled, additional study staff outreach occurred (phone call and/or email) to encourage reengagement in study activities.

Results

Recruitment

From the 7,130 MGH gateway recruitment letters sent out, 79 individuals contacted the study staff via email. An additional 54 individuals expressed study interest through the MGH Rally platform. Slightly over half of individuals (52%) who completed the eligible screener were found to be eligible for participation. Criteria limiting eligibility included use of hormonal birth control (n=35), thyroid or prolactin disorder (n=9), not having an active primary care or gynecological provider (n=7), age (n=6), postpartum (n=6), not currently menstruating (n=4), and below 110 pounds (n=3). Of those found to be eligible, 84% completed the consent form, 74% started the baseline survey, and 64% completed the baseline survey. A participant flow diagram can be found in Figure 3.

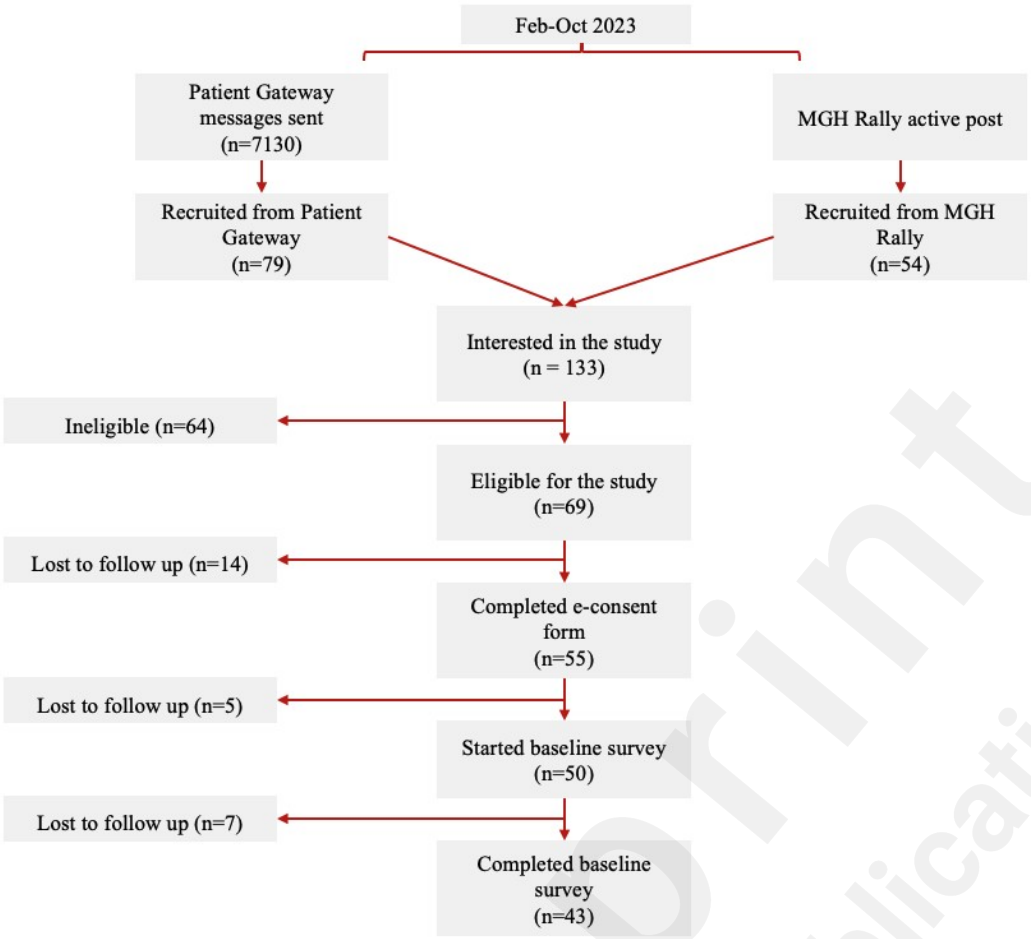

Figure 3. Participant flow chart displaying study recruitment and beginning study tasks. Abbreviations: MGH, Mass General Hospital

Data Contribution

From February to October 2023, 29 participants received a Study Kit. The median wait time to receive a Study Kit after enrolling was 11 days (Interquartile range [IQR] 6, 71 days) with a 1 day minimum and a 156 day maximum. Eleven participants (38%) waited over 2 months for a Study Kit after enrolling. A participant retained the Study Kit for a median of 112 days (IQR 34, 151 days) with a minimum of 12 days and a maximum of 418 days, excluding those who never returned the Study Kit (n=6). Eight Study Kits were lost in transit, and 6 Study Kits were never returned due to participants being lost to follow up. Ultimately, 79% of participants who received a Study Kit returned it (n=23), regardless of data contribution. Participant data contribution is summarized in Figure 4. Overall, 7 participants completed the study. The average duration of data contribution for cycle 1 and cycle 2 were 19 and 26 days, respectively. Those that withdrew after starting data collection (n=4) averaged 17 days of data contribution.

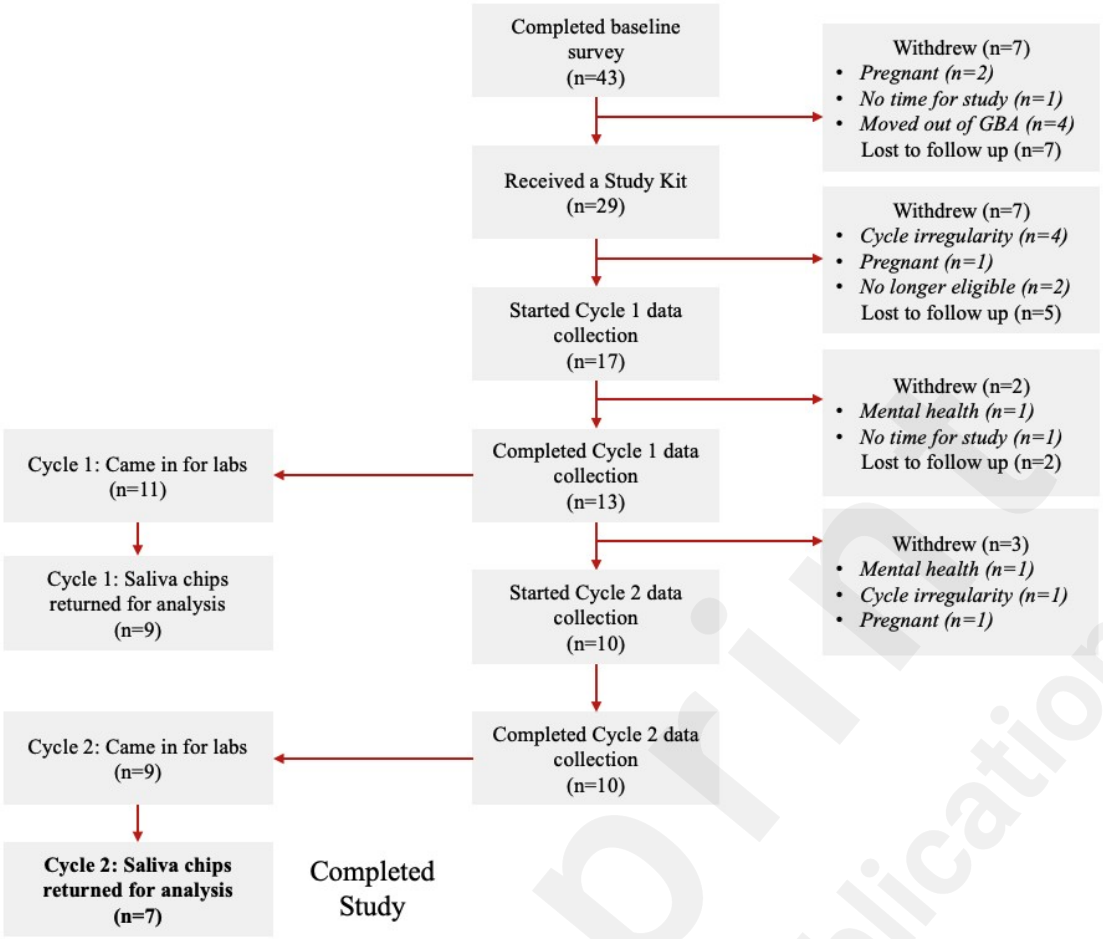

Figure 4. Participant flow chart displaying study contribution and withdrawal/lost to follow up for those that received a Study Kit. Abbreviations: GBA, Greater Boston area

Demographics

Demographic data was available for those that were eligible, consented, and completed the baseline survey (n=43). Demographics were further stratified for those that began data collection (n=17) and those that completed the study (n=7), as noted in Table 1.

Table 1. Demographics and health characteristics of those eligible, consented, and who completed the baseline survey (n=43), further stratified for those that began data collection (n=17) and those that completed the study (n=7).

Characteristic	Eligible and Completed Baseline Surveys (n=43)	Provided Some Data (n= 17)	Completed Study (n=7)
Age at baseline, Mean ± SD	28.8±4.8	28.4±4.9	29.6±6.4
Race/Ethnicity, *N* (%)			
White	24 (55.8)	8 (47.1)	3 (42.9)
Black/African	3 (7)	1 (5.9)	0 (0)

American			
East Asian	0 (0)	0 (0)	0 (0)
Southeast Asian	0 (0)	0 (0)	0 (0)
South Asian	2 (4.7)	0 (0)	0 (0)
Middle Eastern	1 (2.3)	1 (5.9)	1 (14.3)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
American Indian	0 (0)	0 (0)	0 (0)
Hispanic	8 (18.6)	5 (29.4)	2 (28.6)
Other	1 (2.3)	1 (5.9)	0 (0)
Multiple races	4 (9.3)	1 (5.9)	1 (14.3)
Gender Identity			
Female	42 (97.7)	16 (94.1)	7 (100)
Nonbinary/third-gender	1 (2.3)	1 (5.9)	0 (0)
Body mass index (BMI, kg/ m^2) at baseline, Mean ± SD	28.9±7.8	29.2±7.2	27.9±6.7
Occupational Status, *N* (%)			
Paid employment	33 (76.7)	13 (76.5)	5 (71.4)
Unemployed	4 (9.3)	2 (11.8)	2 (28.6)
Not employed outside of home	2 (4.7)	0 (0)	0 (0)
Student	3 (7.0)	2 (11.8)	0 (0)
Retired	0 (0)	0 (0)	0 (0)
Not working due to disability	1 (2.3)	0 (0)	0 (0)
Highest grade or level of schooling completed at time of enrollment, *N* (%)			
Less than 8^{th} grade	0 (0)	0 (0)	0 (0)
8^{th}-11^{th} grade	0 (0)	0 (0)	0 (0)
12^{th} grade or completed high school	1 (2.3)	0 (0)	0 (0)
Post high school training other	2 (4.7)	2 (11.8)	0 (0)

than college			
Some college	8 (18.6)	4 (23.5)	1 (14.3)
College graduate	17 (39.5)	6 (35.3)	2 (28.6)
Postgraduate (ex. master's, professional, doctorate)	15 (34.9)	5 (29.4)	4 (57.1)
Smoked at least 100 cigarettes in your lifetime, *N* (%)	4 (9.3)	1 (5.9)	0 (0)
Ever smoked weed or marijuana in lifetime, *N* (%)	26 (60.5)	7 (41.2)	3 (42.9)
Self-reported overall health, *N* (%)			
Excellent	7 (16.3)	4 (23.5)	1 (14.3)
Very good	18 (41.9)	7 (41.2)	4 (57.1)
Good	16 (37.2)	6 (35.3)	2 (28.6)
Fair	2 (4.7)	0 (0)	0 (0)
Poor	0 (0.0)	0 (0)	0 (0)
Self-reported health compared to other people of same age			
Better than most	12 (27.9)	3 (17.6)	2 (28.6)
About the same as most	26 (60.5)	13 (76.5)	4 (57.1)
Worse than most	5 (11.6)	1 (5.9)	1 (14.3)
Cycle Pattern			
Self-Reported Regular (21 -35 days)	23 (53.5)	11 (64.7)	6 (85.7)
Self-reported Irregularity (21 days, >35 days)	15 (34.9)	4 (23.5)	1 (14.3)
I don't know	5 (11.6)	2 (11.8)	0(0
Self-reported PCOS Diagnosis Status % POST study			

Yes	29 (67.4)	16 (94.1)	7 (100)
No	14 (32.6)	1 (5.9)	0 (0)
Age at PCOS diagnosis, Mean ± SD (years)	20.4±5.3	18.5±3.8	17.0±2.5

Abbreviations: SD, standard deviation; PCOS, polycystic ovary syndrome

Of the 43 participants who were eligible, consented, and completed the baseline survey, the majority were White (56%), employed (77%), highly educated (74 % college or more), and had an average BMI of 28.9 kg/m2. The majority of participants (61%) also reported that their health was about the same as other people their age. About two thirds of participants (68%) reported a PCOS diagnosis, and just over half of the participants (54%) reported irregular cycles. The group that completed the study has similar self-reported demographics and health data, but the sample size was too small to make significant comparisons. Everyone who completed the study had PCOS and 29% experienced irregular cycles (<21 days, >35 days) at the time of enrollment (Table 1). More detailed demographic and health information on the 7 participants that completed the study can be found in the Multimedia Appendix.

Study Team Communication

Increased communication efforts occurred six months into the study. Additional communication allowed the study team to quickly identify study kits lost in transit, facilitate participation, and reduce the time to withdrawal of those no longer interested in the study. As a result, participant possession of a Study Kits reduced from on average 179 days to 93 days. In attempts to recollect Study Kits, a total of 328 individual outreaches were sent across 28 participants, totaling about 12 outreaches per participant.

Withdrawn or Lost to Follow Up

Among participants who completed informed consent and completed the baseline survey (n=43), 36 participants did not complete the remainder of the study, defined as not accomplishing the following for two menstrual cycles: remotely collecting and uploading daily data, attending lab visits, and returning biological saliva samples. One participant never attended lab visits due to study miscommunication, and two participants did not return saliva samples (protocol miscommunication [n=1], lost in transit [n=1]). Nineteen participants withdrew; reasons for withdrawal included menstrual cycles being too irregular for the study timeline (n=5), becoming pregnant (n=4), moving outside the Greater Boston area (GBA; n=4), no time to dedicate to the study (n=2), ineligibility (n=2), and stress related to observing anovulation (n=2). The remaining 40 participants were lost to follow up, 7 of which received Study Kits and 2 of which started data collection (Figure 3, Figure 4).

Conclusion Survey

A total of 14 participants completed the conclusion survey, with 10 providing some or all data (90% completing cycle 1) and 4 contributing no data. Those who did not contribute data withdrew due to their cycles being too irregular to begin participation (n=3) or because they moved outside of the GBA (n=1). Of those who took the survey, 7 had irregular cycles. Four of them reported that their irregular cycles made it more difficult to complete the study, while 2 participants reported that it discouraged them from participating altogether. When asked about the in-person component, 79% of respondents (n=11) indicated they would be more likely to complete the study if the lab testing was located closer to home. Of the 13 participants who received a Study Kit and instructions, everyone understood the saliva collection protocol. Among the 10 that contributed some data, 80% reported that the number of tasks was manageable, while 60% found the daily demand to be challenging. One

respondent mentioned that it was hard to bring the materials when traveling, a common issue reported by participants resulting in delay of initiating data collection. For the urine collection, 36% of participants (n=5) reported that it was inconvenient, with some expressing concerns about issues such as unsanitariness and the time commitment. The remaining questions on the conclusion survey focused on study communication, the PEONy app, and the technology used for collecting and uploading data. Regarding study communication, 38% of respondents (n=5) requested more frequent reminders with no participants reporting that the app notifications were very effective. Multiple participants reported inaccurate programmed time on the phone, making reminders and submissions more difficult. One respondent suggested that notifications should be sent to their personal devices instead of the provided Study Kit phone with another participant noting the study would be easier to complete using their personal phone overall. The PEONy app design was reported to be easy to navigate by 82% of participants (n=9), and no one reported it being difficult or very difficult to use; however, 70% (n=7) did not use any app assistance features. Half of those that collected some data reported technical issues regarding app crashing (n=2) or inaccurate programmed time on the phone (n=3). There were also some app technical issues for those that did not ovulate and those that did not get periods. Lastly, some respondents wrote that the optical hardware device was flimsy, one reporting that by the end they were using a personal phone flashlight to improvise.

Discussion

Principal Results

This study was conducted to determine the feasibility for participants with majority irregular or unpredictable cycles, including those with PCOS, to complete study tasks designed to train and develop an AI model for salivary-based ovulation. Of the 133 females with diverse menstrual cycle lengths recruited from February to October 2023 via targeted patient messages and a public research website, 69 were eligible for the study. Out of those who received a Study Kit (n=29), 57% began data collection, 31% provided one menstrual cycle worth of data, and 24% completed the study.

Comparison with Prior Work

Previous research studies have successfully recruited and retained participants with regular cycles utilizing study designs with similar[17–19] or greater[20–22] participant burden (i.e., longer time contribution, more daily tasks, more in-person visits) compared to our study. However, menstrual cycle research within populations with irregular or unpredictable menstruation, including those with PCOS, is highly nuanced. The desired study population makes up a small percentage of the total population (25.6%) and is further complicated by the duration and frequency of menstrual cycles and ovulation patterns.[23] Irregular or long menstrual cycles can delay the start date or length of expected daily data contribution given participants with irregular cycles or PCOS can contribute ~20 days more per cycle than those with regular cycles. For example, a previous ovulation study that also collected participant heartrate and BBT recruited fewer irregular cycling participants compared to regular cycling participants, and those with irregular cycles contributed less cycles per person in part due to >20% of irregular cycling participants unable to determine ovulation days.[21] Additionally, ovulation testing is a sensitive subject due to implications related to health and current or future family planning. Throughout the study, multiple participants withdrew due to stress concerns related to observing anovulation. The study team must keep this in mind when communicating with participants, particularly those in this population who may ovulate infrequently or be anovulatory. Additionally, providing participants with menstrual and ovulation health educational materials upon enrollment could help ameliorate the potential stress related to observed anovulation, especially given low fertility awareness seen in a cross-sectional study of reproductive women across the

United States.[24] This study and future studies on this population have to account for these nuances, especially in the setting of remote data collection with no in-person study staff support, to create the opportunity to advance women's health through at-home, affordable, AI-enabled digital health assays. This smartphone based salivary ovulation prediction method would provide a reliable opportunity for those with irregular or unpredictable cycles around 35-45 days in length. Those with acute cycle irregularity, such as extreme oligomenorrhea where ovulation events are highly infrequent (4 or less times a year), would need to consult a provider for proper ovulatory care.[25]

Strengths and Limitations

This study had many strengths, including successful participant recruitment, retention, engagement, and adherence in collecting menstrual cycle data that could train an AI-model for salivary ovulation-tracker development. Recruitment efforts engaged 63 eligible participants, more than the study's target sample size of 50, and MGH Patient Gateway and the MGH Rally post recruitment methods offered an alternative to direct recruitment through clinics, such as infertility clinics, which facilitated the recruitment of a population outside of the infertility treatment setting.[26] Recruited participants were still medically interfaced (required medical provider and/or contacted through hospital affiliated email addresses) which may limit generalizability. Retention levels were high (41%) for those that started data collection relative to the recruited cohort (10%) given the daily data contribution demand. Additionally, deviations reported in data collection, study actions, and technology submission affected a small percentage of participants (29%). Consistent with previous research, organized and persistent communication, facilitated by hiring additional research staff, contributed to higher retention and completion rates.[27] This suggests that funding for menstrual cycle and AI data collection studies would require adequate budgeting for staffing to ensure contact and follow up.

Though there were many strengths, there were also study challenges, particularly participant ineligibility, limited study material, time and travel burden, and technological issues. A large proportion of participants (48%) were ineligible at screening with current hormone use being the most common ineligibility criterium. Irregular cyclers or those with PCOS commonly manage cycle length and regularity via hormones which would alter the body's natural LH and estradiol surges and cause ovarian supression.[28] The high ineligibility due to hormone use was not surprising, especially given Peters et el. experience with similarly high levels of ineligibility at screening even for participants with regular cycles.[17] However, a more targeted recruitment method that addresses this ineligibility criterium should be implemented in future studies utilizing the target population of irregular cyclers. Limited and lost-in-transit study materials resulted in delays in participants receiving Study Kits, with 38% of participants waiting over two months to receive one. Participants were also subject to rapid reproductive and geographic status changes. The ability to collect data immediately upon enrolling and simultaneously across participants necessitates sufficient supplies. Furthermore, utilizing outpatient lab services closer to participants home address could prove instrumental in increasing recruitment and retention. This adjustment in design could also help reduce participant burden and encourage those that delayed starting or withdrew in traditionally busy seasons (e.g., holidays), a trend seen in other recruitment studies.[26] The conclusion survey also highlighted technological issues (app crashes, time discrepancies) that affected adherence to the study protocol. The feedback gathered from the conclusion survey will inform necessary technology fixes before this study design is implemented at a larger scale. Lastly, participants reported internet disturbances (e.g., power outages, loss of Wi-Fi) that hindered data submission, highlighting the risks associated with technology-based studies.

Conclusions

Robust AI models typically require large amounts of data for training, and an AI model designed for ovulation prediction would need data to learn from and to test its parameters effectively. Therefore, in this study, a participant's cycle 1 data can be used for AI training followed by the participant's cycle 2 data for testing accuracy. A total of 7 participants with PCOS, some of which experience irregular or unpredictable cycles, were able to complete daily, demanding tasks without in-person study team oversight, attend lab visits, and return biological samples. To optimize participant completion, the study design would target recruitment to address frequent ineligibility, to ensure sufficient study materials, to reduce travel burdens, to enhance study team support and communication, and to incorporate health education to equip participants with ovulatory health information to ameliorate the potential stress impacts of observing anovulation. This feasibility study revealed limitations, which after optimization, when scaled, will provide an AI model with sufficient data to develop a smartphone-based ovulation tracker specifically tested on females with irregular or unpredictable cycles, including those with PCOS. The study's insights can be generalized to broader women's health and femtech research, especially as the medical sphere shifts into more remote spaces and can be used to advance femtech in AI-centered areas.

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Conflicts of Interest

None declared.

Abbreviations

LH: luteinizing hormone
PCOS: polycystic ovary syndrome
NaCl: sodium chloride
AI: artificial intelligence
BBT: basal body temperature
MGH: Mass General Hospital
IRB: institutional review board
ICD: International Classification of Diseases
SD: standard deviation
GBA: Greater Boston area

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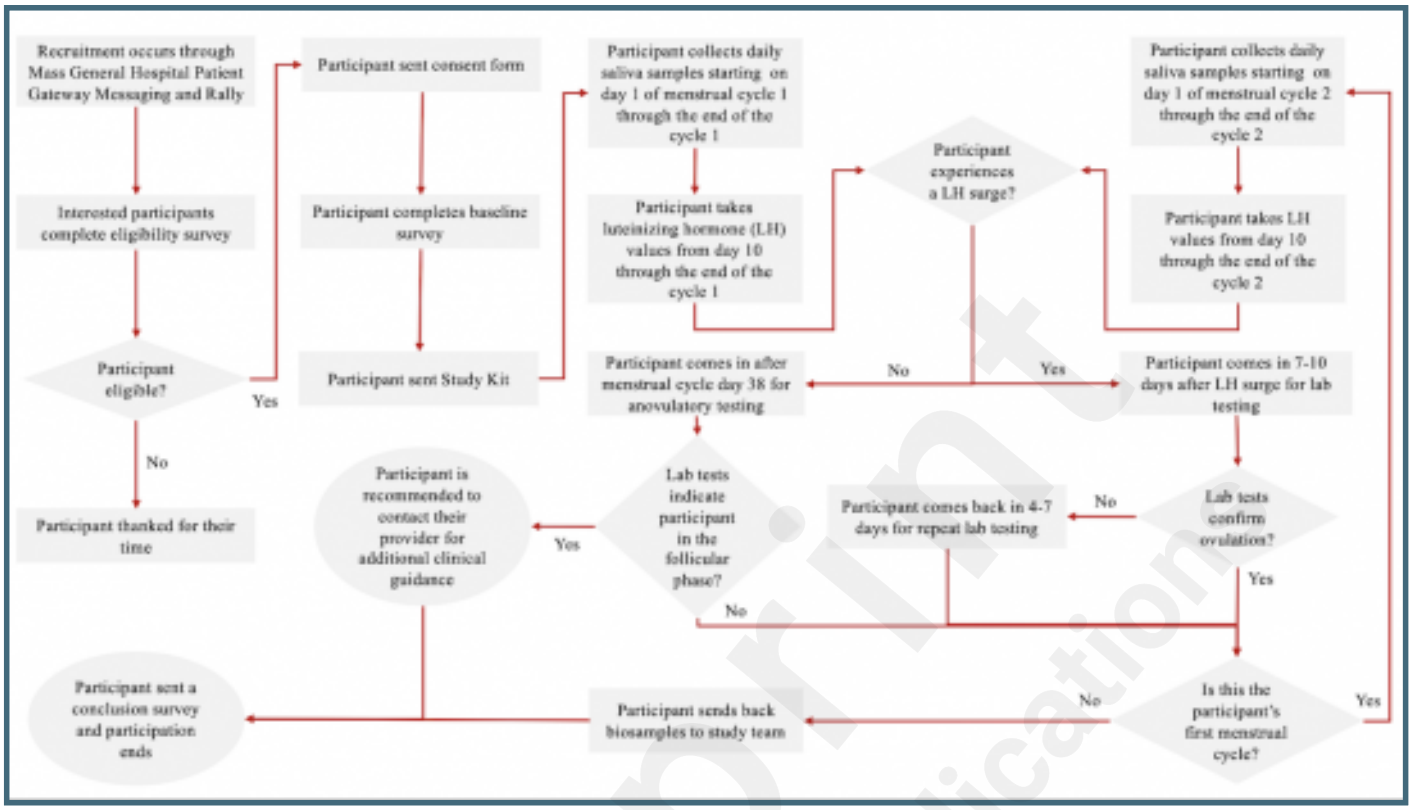
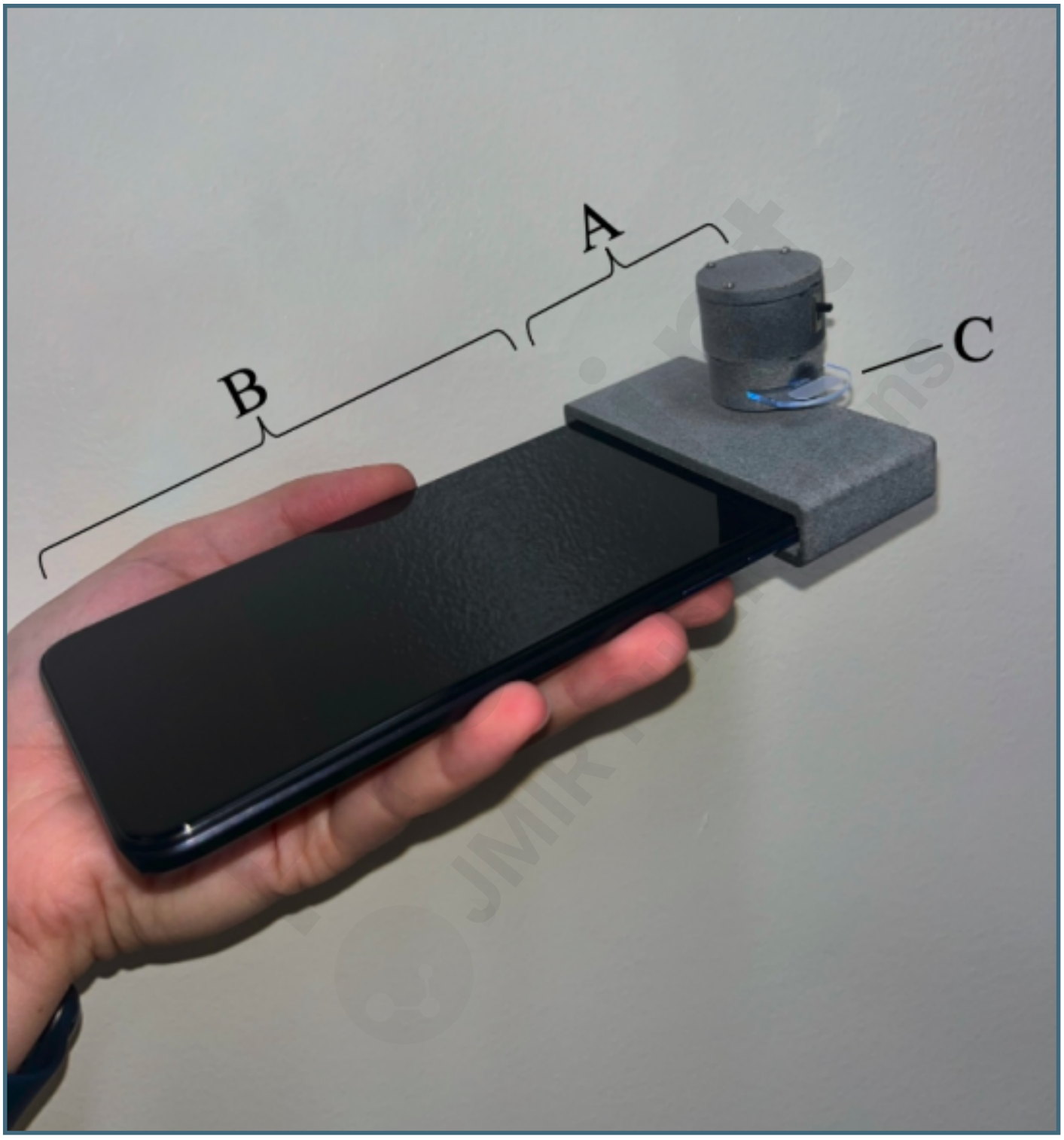
Supplementary Files

Figures

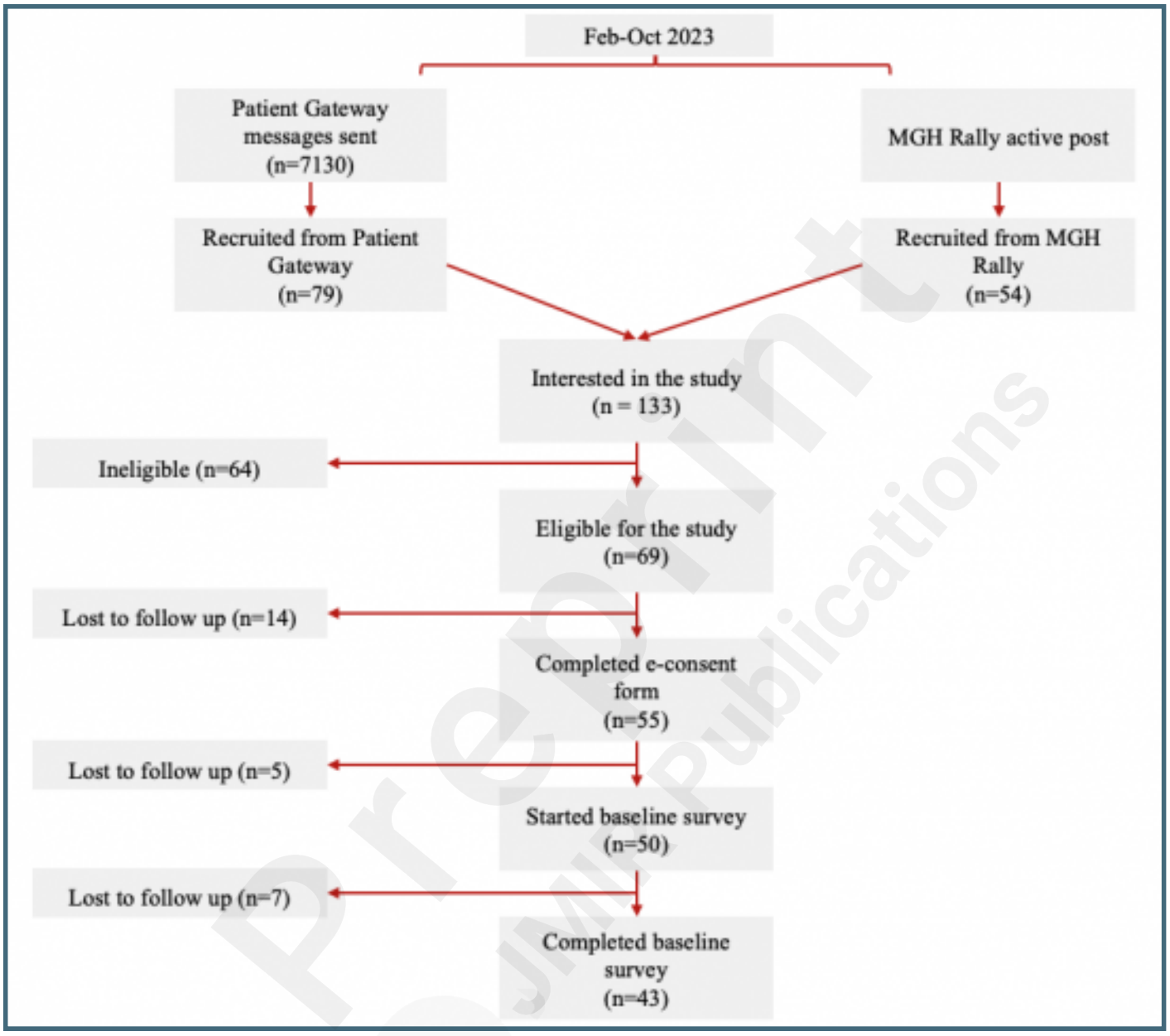
Study summary flowchart of participant study tasks from enrollment to study completion.



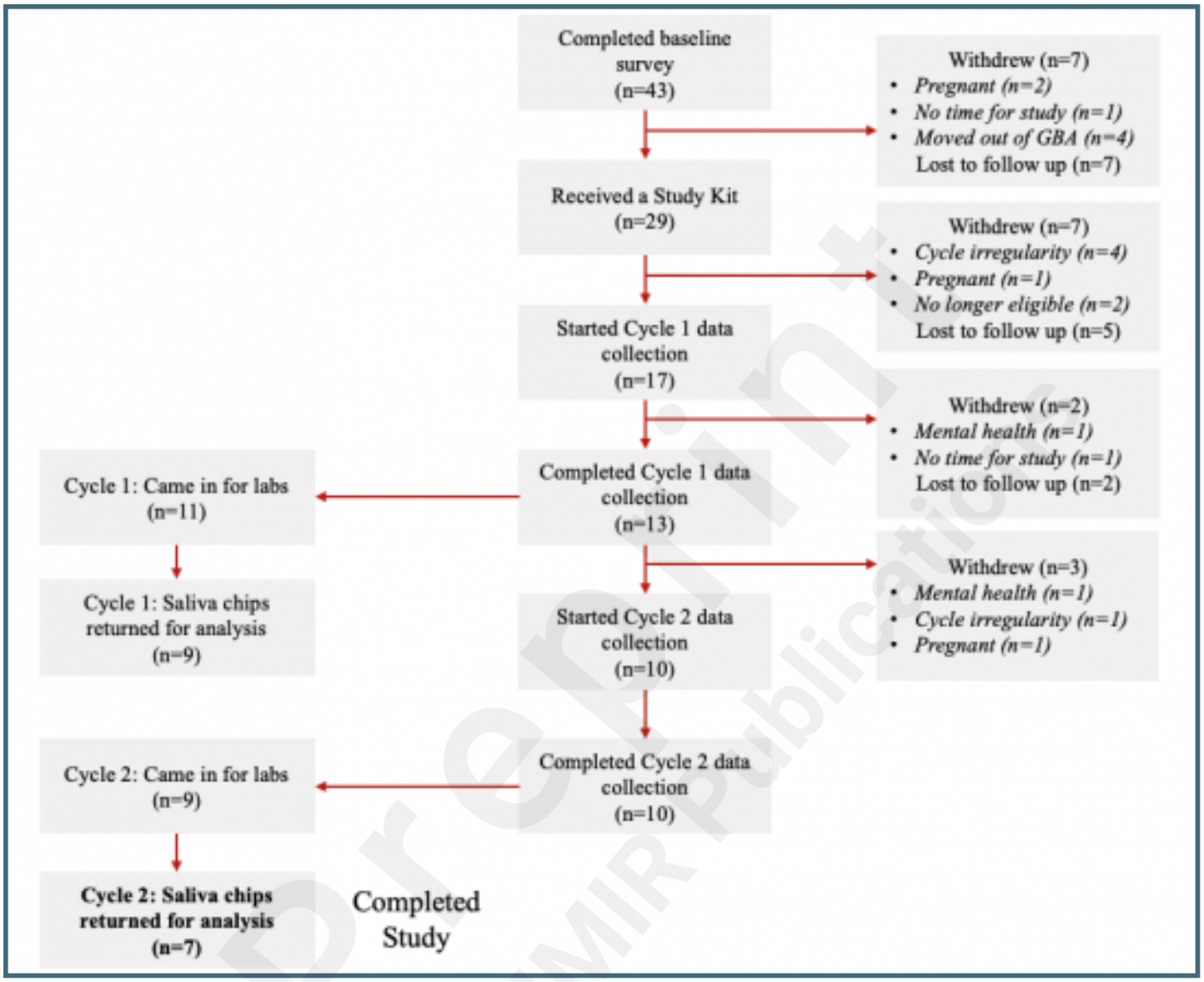
Internally built optical hardware device (A) provided to participants in the Study Kit that affixes to the study phone (B) to assist in capturing illuminated photographs of the dried saliva chip (C).



Participant flow chart displaying study recruitment and beginning study tasks. Abbreviations: MGH, Mass General Hospital.



Participant flow chart displaying study contribution and withdrawal/lost to follow up for those that received a Study Kit. Abbreviations: GBA, Greater Boston area.



Multimedia Appendixes

Recruitment post on the Mass General Hospital Rally website to promote the study. This was one of two methods used for participant recruitment.
URL: http://asset.jmir.pub/assets/25956159842d8b02c4dffb1cda7e7d6c.pdf

Recruitment letter sent to targeted patients via the Mass General Hospital Patient Gateway system. This was one of two methods used for participant recruitment.
URL: http://asset.jmir.pub/assets/c521391fca55154bb71da16fdaaa5c67.pdf

Study instruction manual provided to eligible participants who received a Study Kit to explain the study tasks.
URL: http://asset.jmir.pub/assets/a8dbf016450771386012d96b8b8a254a.pdf

Study calendar provided to eligible participants who received a Study Kit to explain the cadence of their study tasks.
URL: http://asset.jmir.pub/assets/09aa28e374611f311f77f0d166f56de4.pdf

Demographic breakdown of participants that completed the study (n=7).
URL: http://asset.jmir.pub/assets/16720dd82104ad800616798b87e55287.docx