

2019

Identifying women at risk for polycystic ovary syndrome using a mobile health application

<https://hdl.handle.net/2144/36694>

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**IDENTIFYING WOMEN AT RISK FOR POLYCYSTIC OVARY SYNDROME
USING A MOBILE HEALTH APPLICATION**

by

ERIKA MARIE RODRIGUEZ

B.S., New York University, 2017

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2019

Approved by

First Reader

Shruthi Mahalingaiah, M.D., M.S.
Assistant Professor of Reproductive Endocrinology and Infertility

Second Reader

Vickery Trinkaus-Randall, Ph.D.
Professor of Biochemistry

ACKNOWLEDGMENTS

I would first like to thank my family and friends for their unwavering support. The kindness and patience you have all shown has made this journey much more bearable.

A special thank you to my fellow research assistant, Pascaline Karanja, for her support throughout the year. She has been instrumental in so much of the work that has been accomplished in the Mahalingaiah lab. Without her tremendous help, I would not have had the incredible research experience I did.

I would also like to thank the team at Clue® for their help in compiling data from their users and allowing us to implement this tool with their application. Working with a tech team dedicated to the improvement of women's health was an eye-opening experience.

Additionally, I would like to thank Dr. Vickery Trinkaus-Randall for reading my thesis and providing feedback. Her help as an advisor while pursuing my Master's degree has been extremely valuable.

Lastly, I would like to thank Dr. Shruthi Mahalingaiah for her guidance and dedication not only with her students, but also with her patients, family, and fellow physicians. She has been the driving force behind my growing fascination in the field of women's health. I am especially grateful to have this physician-scientist as my mentor. Her never-ending encouragement, sincerity, and passion for learning are unrivaled.

IDENTIFYING WOMEN AT RISK FOR POLYCYSTIC OVARY SYNDROME USING A MOBILE HEALTH APPLICATION

ERIKA MARIE RODRIGUEZ

ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is an endocrine disrupting disorder affecting at least 10 percent of reproductive-aged women. In many cases, women develop comorbidities such as diabetes, cardiovascular disease, and other metabolic disorders. In North America and Europe, it takes several years and multiple doctors for women to receive a diagnosis of PCOS. This results in lost time for risk-reducing interventions. Menstrual tracking applications are one potential tool to alert women of their risk for PCOS and prompt them to seek further evaluation from a medical professional.

Objective: The objective was to develop the Irregular Cycles Feature (ICF) on the mobile phone application Clue®, which generates a probability of a user's risk for PCOS. The secondary aim was to assess the accuracy of the tool by testing the feature on virtual test subjects.

Methods: A literature review was conducted to generate a list of signs and symptoms of PCOS. Probabilities were assigned to each variable and built into a Bayesian Network. The Irregular Cycles Feature, an adaptive questionnaire, was then developed in order to detect high-risk PCOS patients. The ICF detected at risk Clue® users through self-reported menstrual cycles and answers to medical history questions. Upon completion of the questionnaire, a Result Screen is displayed to the user. The Screen is a summary of the individual's probability of having PCOS. For each eligible user, a Doctor's Report is

also generated. This is a screen containing information regarding menstrual irregularities and a brief medical history to be used by a medical professional in order to make a final diagnosis. Both the Result Screen and Doctor's Report disclose information about PCOS and detailed explanations for consulting a medical provider. A brief statistical validation was then performed to compare the output of the network to predictions made by a physician-scientist using a correlation coefficient, a p-value, and a Pearson's coefficient.

Results: The Irregular Cycles Feature successfully predicts probability of PCOS based on eight test cases. The correlation between the network's calculation and the assessment made by a board-certified reproductive endocrinology/infertility physician-scientist was 0.82, with a p-value of less than 0.05. The Pearson's coefficient was calculated to be 0.69. These values indicate that the ICF made statistically significant predictions when compared to the physician-scientist.

Conclusions: The ICF provides consumer-friendly ways to improve interactions between medical providers and patients. The tool can be adapted to capture other causes of menstrual irregularities and can serve as an important mechanism for drawing attention to potentially hazardous health problems. Further validation studies will be conducted to confirm the utility of the ICF with Clue® users, particularly amongst those who receive an official diagnosis from a medical professional.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS.....	iv
ABSTRACT	v
TABLE OF CONTENTS	vii
LIST OF TABLES	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS	xi
INTRODUCTION.....	1
THE EVOLUTION OF THE DOCTOR-PATIENT RELATIONSHIP	1
TECHNOLOGY IMPROVING ACCESS TO HEALTHCARE.....	2
DEFINING THE MENSTRUAL CYCLE.....	4
MENSTRUAL CYCLE IRREGULARITIES.....	5
POLYCYSTIC OVARY SYNDROME.....	6
ROLE OF MOBILE PHONE APPS TO TRACK MENSTRUAL CYCLES	11
SPECIFIC AIMS.....	14
METHODS.....	15

DEFINING MENSTRUAL IRREGULARITIES TO DETERMINE ELIGIBILITY FOR THE IRREGULAR CYCLES FEATURE	16
DEVELOPING THE IRREGULAR CYCLES FEATURE.....	18
VALIDATING THE IRREGULAR CYCLES FEATURE	28
RESULTS.....	31
DISCUSSION	40
CONCLUSION	43
LIST OF JOURNAL ABBREVIATIONS.....	44
REFERENCES.....	45
CURRICULUM VITAE	50

LIST OF TABLES

Table	Title	Page
1	Menstrual Cycle Parameters	4
2	PALM-COEIN Classification System	6
3	PCOS Prevalence According to Rotterdam Criteria	10
4	Physician Assessments and ICF Assessments of Test Cases	30
5	Physician Assessments and Assigned Probabilities for Test Cases	31
6	Sample Test Cases for the Irregular Cycles Feature Validation	34
7	Summary of 9 Test Cases Used for Statistical Calculations	37
8	Summary of Statistical Calculations for 9 Test Cases	37
9	Summary of Statistical Calculations for 8 Test Cases	38
10	Summary of Statistical Calculations for 8 Test Cases 2 nd Iteration of ICF	39

LIST OF FIGURES

Figure	Title	Page
1	Overlap of Signs and Symptoms of Diseases Presenting like PCOS	8
2	Handwritten Menstrual Tracking Chart	12
3	Clue® Home Screen and Calendar View	13
4	Irregular Cycles Feature Prompt Flow	15
5	Eligibility Flow Diagram	17
6	Bayesian Network Used to Determine Probability of PCOS	19
7	Image of the ICF Clue® User Prompt	21
8	Abbreviated Hair Growth Questionnaire Flow Diagram	22
9	Positive Result Screen	24
10	The Doctor's Report for Suspected PCOS Diagnosis from Clue®	26
11	The Doctor's Report for Other Menstrual Irregularities from Clue®	27
12	Sliding Scale Percent Probability Ranges	32
13	Linear Regression with Pearson's Coefficient for 8 Test Cases	38

LIST OF ABBREVIATIONS

ACOG.....	American College of Obstetricians and Gynecologists
App.....	Mobile Phone Application
APPLICATIONS	
Application comprehensiveness, Price, Paid Subscription, Literature used, In-App Purchases, Connectivity, Advertisements, Text search field, Interdevice compatibility, Other components, Navigation ease, Subjective presentation	
FIGO.....	The International Federation of Gynecology and Obstetrics
ICF.....	Irregular Cycles Feature
PCOS.....	Polycystic Ovary Syndrome

INTRODUCTION

THE EVOLUTION OF THE DOCTOR-PATIENT RELATIONSHIP

Medicine has fluctuated between many phases; it has evolved from treating malaise, performing surgeries, administering medications to patients after identification of microbes, to treating individuals with chronic conditions (Porter, 2004). In conjunction with this evolution of medicine, the relationship between doctors and patients has undergone significant transformation.

Historically, healthcare providers have treated patients in a paternalistic manner. More specifically, doctors felt they could make decisions regarding a patient's care independently from the patient (McKinstry, 1992). One theory describing this authoritative relationship argues that up until the twenty-first century, the healthcare system could primarily be described by one of two models: the activity passivity and guidance cooperation models (Szasz *et al.*, 1955). Both models posit that a patient is comparable to a child seeking care from a doctor regardless of the age of the individual. The patient is expected to ask no questions and to comply with whatever the doctor recommends (Szasz *et al.*, 1955). These roles emerged because patients were expected to know less than doctors. This in turn caused the doctors to feel as though they needed to put restrictions on how much information they divulged to the patient. In the 18th century, as hospitals opened up for all patients, and not just aristocrats, doctors were trained more rigorously, and the knowledge gap between providers and their patients expanded further; consequently, the doctor-patient relationship became even more distant (Kaba and Sooriakumaran, 2007). Greater differences in pay between physicians and patients led to

further isolation of the patient as social, political, and economic views began to diverge (Kaba and Sooriakumaran, 2007). This disparity was and is still exasperated by cultural and gender differences between doctors and their patients (Muaygil, 2018).

In Western societies, the patient-centered care model gained popularity in an effort to move away from the paternalistic nature of medicine. Patients slowly became more autonomous, and the practice of medicine became more of a partnership rather than a relationship in which the doctor dominates. An interesting example of this change can be seen in Croatia as it transitions from a communist state to a capitalist state. While communist, this country had limited patient autonomy, but now doctors are being retrained to be more aware of including patients in their treatment plans (Murgic *et al.*, 2015). A major component in this new training is obtaining consent from patients and explaining how decisions regarding care are made. This allows individuals to play a more active role in their treatment. Now, doctors are expected to consider the patient as a whole and understand more than just symptoms. Conversations extend beyond just physical ailments, and doctors are held to a higher standard for coming up with a treatment plan while working in conjunction with the patient (Mead and Bower, 2000). The demand for this patient-centered model of medicine thrives as technology improves, and patients take a greater role in their care.

TECHNOLOGY IMPROVING ACCESS TO HEALTHCARE

In the modern era, the demand for technological advances flourishes. About 77% of adults in the United States say they own a smartphone (Perrin, 2017). Furthermore, there are an increasing number of low-income Americans using their smartphones to access the

Internet (Perrin, 2017). As a result, the healthcare industry has responded to the increased patient demand. A little over half of smartphone owners have reported using health-related mobile phone applications (apps)(Krebs and Duncan, 2015). This is particularly important as appointment times in the United States average about 15 minutes (Irving *et al.*, 2017). Thus, there lies a greater emphasis in the ability to communicate changes in health in a faster and more streamlined manner. Therefore, having personal data easily accessible provides vital diagnostic information to doctors in the short amount of time they have with patients.

Women in particular report greater smartphone usage and higher rates of downloading health apps (Derbyshire and Dancey, 2013). This movement into telemedicine is particularly important because women tend to be at higher risk for doctor's downplaying their health concerns (Noe Pagán, 2018). In a prospective study done in emergency departments, it was found that women were less likely to receive analgesic treatments despite similar pain scores to men. Additionally, women were much more likely to have longer wait times before analgesic treatment, even when controlling for age, race, and pain score (Chen *et al.*, 2008). This can have serious implications for diagnosis, especially for disorders that are harder to identify.

Furthermore, the disparity between genders becomes even more apparent when analyzing data surrounding heart disease. Data has shown that women are more likely to present with non-chest pain related symptoms, which tends to delay clinical diagnosis of heart attack leading to further complications (Litchman *et al.*, 2018). This has serious implications when considering both the short-term and long-term problems associated

with heart attacks. As women access technology, their autonomy in healthcare can be significantly improved. The benefits of this type of technology are not only limited to pain management and cardiovascular health, but also show promise in menstruation and ovulation.

DEFINING THE MENSTRUAL CYCLE

In 2011, terms to describe the menstrual cycle were redefined to standardize the way physicians discuss normal and abnormal bleeding (Fraser *et al.*, 2011). The International Federation of Gynecology and Obstetrics (FIGO 2011) Menstrual Disorders Working Group recommended several new terms and definitions in order to systematize terminology and consequently treatment plans. The group used literature reviews and existing data to develop new definitions, which are summarized in Table 1. The normal limit for frequency of menses was defined as 24-38 days (Fraser *et al.*, 2011). The normal range for variation cycle to cycle was determined to be \pm 2-20 days, and the normal duration of flow as 4.5-8.0 days (Fraser *et al.*, 2011). While not everyone fits into these parameters, the redefined normal menstruation criteria allow physicians to discuss any irregularities that may be of concern with their patients.

Table 1. Menstrual Cycle Parameters: Adapted from Fraser et al 2011.

Clinical Parameter	Normal Range
Frequency of menses	24-38 days
Regularity of menses: variation over 12 months	\pm 2-20 days
Duration of flow	4.5-8.0 days

MENSTRUAL CYCLE IRREGULARITIES

Prior to the work done by FIGO, terms adapted from Greek and Latin were used to describe menstrual irregularities including: menorrhagia, too heavy menstrual bleeding, and metrorrhagia, abnormal bleeding. These terms, and many similar others, were ill defined and created issues for research and clinical diagnoses. Furthermore, the terms were difficult to translate between languages and made it hard to explain to patients where the dysfunction they were experiencing stemmed from (Fraser *et al.*, 2011).

Through the creation of these new definitions by FIGO, better descriptions of abnormal bleeding were determined. Categories created included whether disruptive bleeding was due to ovulatory or anovulatory issues; in other words, whether ovulation occurs, or whether it does not (What Are Menstrual Irregularities, 2017).

Additionally, the FIGO PALM-COEIN classification system for abnormal uterine bleeding was developed. These categorizations were created for women presenting to clinics with abnormal uterine bleeding as an additional means of alleviating challenges in diagnosis. Four of the criteria are visually assessed. These include polyps, adenomyosis, leiomyomas, and malignancy and hyperplasia; subsets of leiomyomas include submucosal myomas or other varieties that do not impact the endometrial cavity (Munro *et al.*, 2011). The other four categories are unrelated to structural issues. These include: coagulopathy, ovulatory dysfunction, endometrial, and iatrogenic anomalies (Munro *et al.*, 2011). These categories are summarized in Table 2.

Table 2. PALM-COEIN Classification System: Adapted from Munro *et al.*, 2011

Polyp		Coagulopathy
Adenomyosis		Ovulatory dysfunction
Leiomyoma	Submucosal	Endometrial
	Other	Iatrogenic
Malignancy & Hyperplasia		Not yet classified

Lastly, the new sets of terminology allow for better patient-centered care. The Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists agreed to take a more holistic approach and defined abnormal uterine bleeding to include the physical, emotional, and social aspects the bleeding has on the woman (Whitaker and Critchley, 2016). This is particularly meaningful as 14-25% of the population experiences some sort of abnormal bleeding (Whitaker and Critchley, 2016).

POLYCYSTIC OVARY SYNDROME

Criteria. Polycystic Ovary Syndrome (PCOS) is a disorder that is classified by ovarian dysfunction and clinical manifestations. In 2003, the Rotterdam group revised the diagnostic criteria of PCOS to include 2 out of 3 of the following signs and symptoms: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries upon ultrasound (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group). It is also largely diagnosed by exclusion of other disorders

that may present with similar signs and symptoms such as: congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group).

The etiology of PCOS is unknown, but is expected to be due to a hormonal imbalance (Gibson-Helm *et al.*, 2016). Because of the uncertainty surrounding what causes PCOS, the criteria for assessing women has been highly controversial (Lizneva *et al.*, 2016). As more is learned about the disorder, groups adapt the defining criteria. For instance, The Androgen Excess and PCOS Society includes definitions similar to those proposed by the Rotterdam criteria, but add the stipulation that other androgen excess diseases be excluded (Azziz *et al.*, 2009). Furthermore, Monash University also proposed new guidelines, which include lifestyle and emotional wellbeing as not only part of the clinical assessment, but also as an important approach to treating aspects of PCOS (Monash University, 2018).

Overlapping disorders. Several disorders have features similar to PCOS. These include Cushing's syndrome, Hypothyroidism, and Hyperprolactinemia. Cushing's syndrome is the result of excess treatment of an individual with glucocorticoids and generally presents with signs and symptoms such as dermatologic issues, gonadal problems, neuropsychiatric symptoms, musculoskeletal disorders, and metabolic complications (Sharma *et al.*, 2015). The major symptoms overlapping with PCOS include weight gain, hirsutism or alopecia, hypertension, and glucose intolerance (Sharma *et al.*, 2015 and Lizneva *et al.*, 2016). Hypothyroidism typically presents when there are deficiencies in iodine intake. However, in areas where iodine is more widely

available, the prevalence is typically due to an autoimmune disease (Vanderpump, 2011). Additionally, there tends to be a higher incidence of the disease amongst women, with typical clinical presentation featuring goiters, fatigue, weight gain, and menorrhagia (El-Shafie, 2003). Lastly, Hyperprolactinemia affects less than 1% of the general population, however amongst women with reproductive disorders, the prevalence jumps to 17%, especially amongst those with PCOS (Pałubska *et al.*, 2017 and Majumdar and Mangal, 2013). Women with this disorder typically present with oligomenorrhea, amenorrhea, galactorrhea, and infertility (Majumdar and Mangal, 2013). Figure 1 illustrates the potential areas of overlap between all four of these diseases.

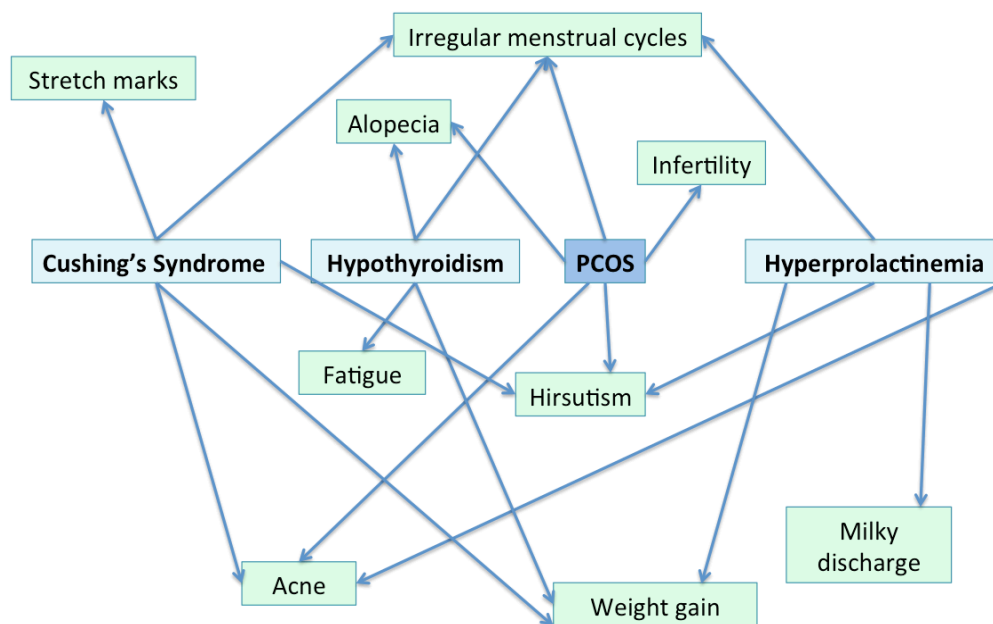


Figure 1. Overlap of Signs and Symptoms of Diseases Presenting like PCOS. Data from Sharma *et al.*, 2015, Cushing syndrome 2018, Hypothyroidism, 2018, Polycystic Ovary Syndrome (PCOS), 2017, and Prolactinemia, 2018

Prevalence. PCOS is suspected to affect roughly 9% to 18% of reproductive-aged women (Gibson-Helm *et al.*, 2016). Table 3 summarizes several studies that estimate the prevalence of PCOS using the Rotterdam diagnostic criteria. Despite the high prevalence, it is likely that many women still remain undiagnosed. Complications in inclusion criteria stem from using various definitions, which skews the expected prevalence of the disease (Lizneva *et al.*, 2016). Additionally, studies currently lack racial and ethnic diversity, and because of these limitations, it is even more difficult to correctly diagnose a patient and estimate the prevalence of PCOS (Bozdag *et al.*, 2016).

Table 3. PCOS prevalence according to Rotterdam Criteria: Adapted from Bozdag *et al.*, 2016.

Author(s) and Year	Prevalence (%)	95% CI
Europe: <ul style="list-style-type: none"> • Lauritsen, 2014 • Yildiz, 2012 • Eilertsen, 2012 • Michelmores, 1999 	<ul style="list-style-type: none"> • 17% • 20% • 21% • 8% 	<ul style="list-style-type: none"> • 13-20 • 16-24 • 17-27 • 5-12
Prevalence: 16% (11-22)		
Australia <ul style="list-style-type: none"> • March, 2012 	<ul style="list-style-type: none"> • 12% 	<ul style="list-style-type: none"> • 10-14
Prevalence: 12 % (10-14)		
Asia <ul style="list-style-type: none"> • Rashidi, 2014 • Zhuang, 2014 • Li, 2013 • Tehrani, 2011 • Mehrabian, 2011 • Ma, 2010 • Chen, 2008 • Kumarapeli, 2008 	<ul style="list-style-type: none"> • 14% • 11% • 6% • 15% • 15% • 6% • 2% • 6% 	<ul style="list-style-type: none"> • 11-17 • 10-13 • 5-6 • 12-17 • 13-18 • 5-7 • 1-3 • 5-7
Prevalence 9% (6-12)		
America <ul style="list-style-type: none"> • Gabrielli, 2012 • Moran, 2010 	<ul style="list-style-type: none"> • 8% • 7% 	<ul style="list-style-type: none"> • 7-10 • 3-11
Prevalence: 8% (7-10)		
Overall Prevalence 10% (8-13)		

Long-Term Health Effects. A PCOS diagnosis is associated with increased reproductive, metabolic, cardiovascular, and psychological co-morbidities. More specifically, women

with PCOS are at an increased risk for metabolic syndrome, insulin resistance, and cardiovascular disease (Lim *et al.*, 2018, Polak *et al.*, 2017, and Blagojevic *et al.*, 2017). Additionally, PCOS has serious implications for fertility as 40% of women with the syndrome experience difficulties conceiving a child (Teede *et al.*, 2010). Additionally, women with long or highly irregular cycles have an increased risk of developing diabetes, even if they are not obese (Soloman *et al.*, 2001). A recent study conducted in the United States estimates that abnormal uterine bleeding costs a woman over \$2000 per year (Frick *et al.*, 2009). In 2005, the economic burden of evaluating and providing care to women of reproductive age, specifically with PCOS, was \$4.36 billion USD, which is the equivalent of \$5.65 billion USD in 2018 (Azziz *et al.*, 2005). This estimate includes doctors' appointments, hirsutism treatments, and infertility treatments. Researchers suggest this was probably a conservative estimate as it limited the cost to reproductive years despite cardiovascular disease and other metabolic disorders persisting beyond these years (Azziz *et al.*, 2005).

ROLE OF MOBILE PHONE APPS TO TRACK MENSTRUAL CYCLES

With better access to mobile phones, more apps can be developed for the specific purpose of improving a woman's ability to care for her menstrual health. Because menstrual data can be a potential indicator of serious health problems, relying on obsolete menstrual diaries and calendars to record ovulatory and menstrual health can lead to more inaccurately reported signs and symptoms (Figure 2) (Johannes *et al.*, 2000).

Thus, improvements to available apps are extremely necessary. A group of researchers created the APPLICATIONS scoring system to objectively and subjectively

determine which mobile phone apps are the most helpful to obstetricians/gynecologists (Farag *et al.*, 2014). Additional studies using the same scoring system were conducted to rate accuracy and applicability of various apps to pregnant women (Chyjek *et al.*, 2015). Even though it has only been used in pregnancy related apps thus far, the APPLICATIONS scoring system can also be adapted to menstrual and ovulatory health. Furthermore, studying and assessing the role of these targeted apps can help women with menstrual irregularities track changes more accurately (Boyle *et al.*, 2018). Data collected can be analyzed and later disseminated highlighting why a variety of issues arise during the menstrual cycle. App companies can then make information accessible to their consumers and have a potentially major impact on overall gynecological health.

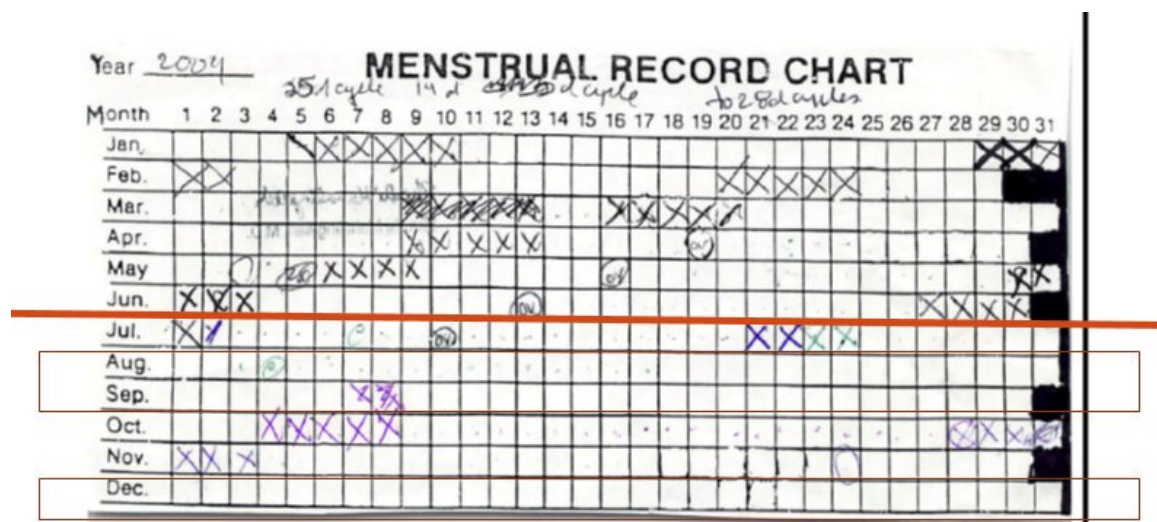


Figure 2. Handwritten Menstrual Tracking Chart: This figure shows a handwritten menstrual tracking chart used by a medical resident highlighting irregular periods during August, September, and December.

Clue®. Clue® is a mobile phone application created by the company Biowink GmbH. The purpose of the application is to serve as a menstrual tracking app and provide users with important information about their health as it relates to menstruation and ovulation. The app may be downloaded free of charge on iOS or Android app stores as a way for users to input information about their menstrual cycles. Data the app collects includes, but is not limited to, day one of the menstrual cycle, duration of flow, and birth control use. Beyond menstrual data, the app collects information such as age, height, and weight to generate a user profile specific to each individual. This phone app is unique in that it not only provides health information to women using the app, but also cites scientific literature to support statements regarding the menstrual cycle. It is listed in the top 20 menstrual tracking applications as rated by a modified APPLICATIONS scoring system (Moglia *et al.*, 2016). Figure 3 illustrates the home screen and calendar view of the menstrual tracking app.

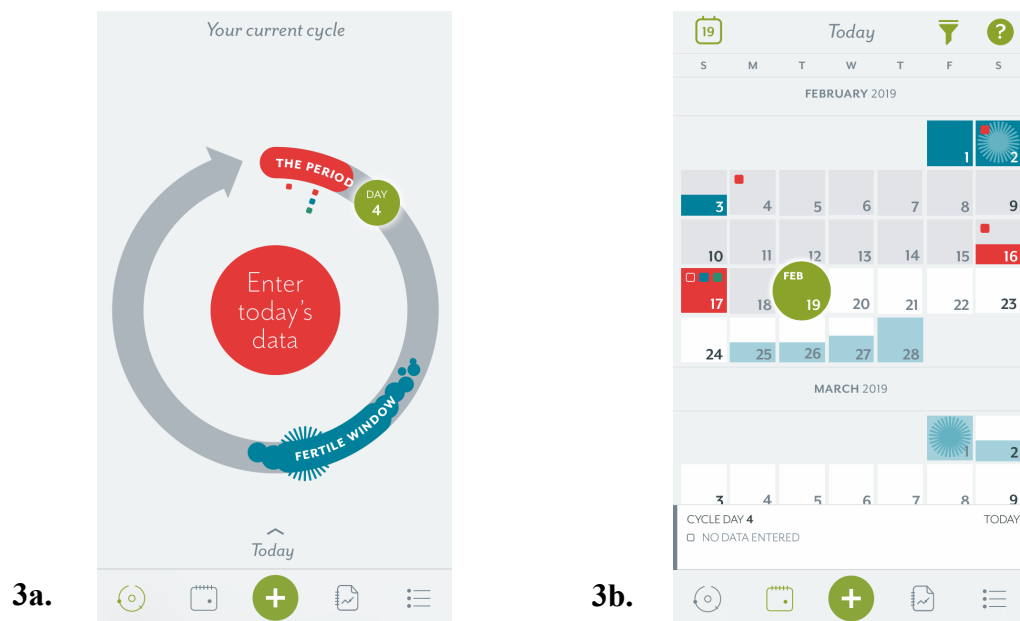


Figure 3a. Clue® Home Screen and 3b. Calendar view

Specific Aims

In order to raise awareness about PCOS and encourage women at high risk to seek out evaluation by a medical professional, this study will:

1. Define menstrual irregularity as used by the Irregular Cycles Feature
 - 1a. Determine which users are eligible to participate in the Irregular Cycles Feature
2. Develop the Irregular Cycles Feature to predict probability of PCOS for Clue® users and communicate the results
 - 2a. Create a Bayesian Network to generate a joint probability using risk factors of PCOS
 - 2b. Construct a Screener to determine eligibility amongst individuals with self-reporting irregular cycles
 - 2c. Design the appropriate questionnaire flow for users prompted with the Irregular Cycles Feature
 - 2d. Compose Results Screens to help users identify potential irregularities with their menstrual cycle and formulate a Doctor's Report for presentation to a medical professional
3. Determine how accurately the Irregular Cycles Feature predicts PCOS in test cases
 - 3a. Assess the validity of the Irregular Cycles Feature by calculating a correlation coefficient, p-value, and Pearson's coefficient through comparison with the physician-scientist assigned probability

METHODS

The ***Irregular Cycles Feature*** (ICF) is an algorithmic mobile phone application system designed to calculate risk of PCOS for women logging irregular cycles in the Clue® app. The ICF consists of a screener, questionnaire, the results from the questionnaire, termed the ‘Results Screen’, and a summary for medical professionals, termed the ‘Doctor’s Report’. Figure 4 illustrates the flow of the ICF for Clue® users over the age of 16 who are not using hormonal birth control; those who do not meet the eligibility requirements are those who are under 16 years old or are taking hormonal birth control.

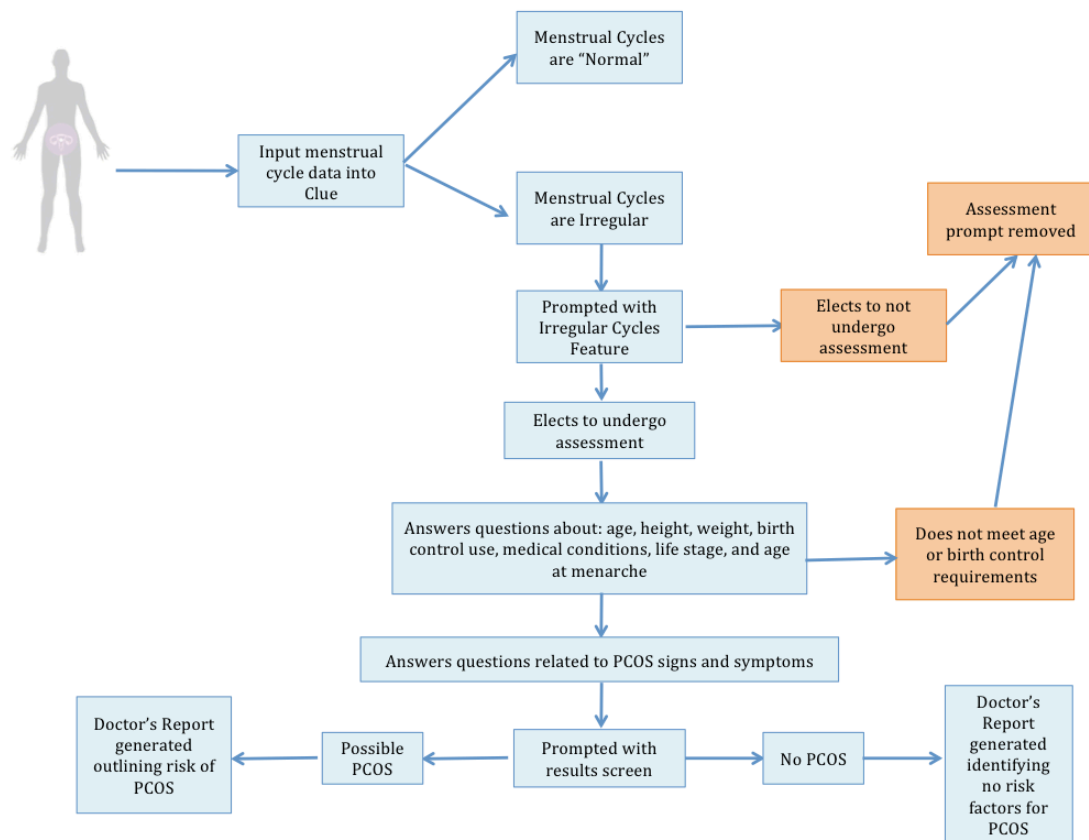


Figure 4. Irregular Cycles Feature Prompt Flow. Orange indicates removal of the ICF prompt.

To create the framework for the questionnaire, researchers and a physician-scientist compiled signs and symptoms associated with PCOS. A literature review was then conducted in order to determine the prevalence of each factor in PCOS. Each variable was then incorporated into a Bayesian Network. This predictive modeling tool combined the distributions found in the literature review to calculate cause and affect relationships. The network ultimately determined the risk of PCOS based on the signs and symptoms using joint probabilities.

A compilation of data collected from current Clue® users was then manipulated to create several sample patients with differing degrees of risk for PCOS. Each fabricated test case was put through the ICF in order to ensure the tool correctly generated a probability, prompted the individual with the appropriate Results Screen, and produced the correct Doctor's Report. To determine the validity of the calculated risk outputs by the ICF, a board-certified reproductive endocrinology/infertility physician-scientist calculated her own probabilities based on the same test patient scenarios. Lastly, a statistical analysis was completed to analyze the accuracy of the ICF for predicting the probability of PCOS as compared to the physician-scientist.

DEFINING MENSTRUAL IRREGULARITIES TO DETERMINE ELIGIBILITY FOR THE IRREGULAR CYCLES FEATURE

The definitions for normal cycles for the study were based on the FIGO suggested "Normal" limits parameters as listed in Table 1. The normal menstrual cycle length is typically 24-38 days with 4.5-8.0 days of bleeding (Fraser *et al.*, 2011).

After establishing the criteria for normal periods, the parameters for selecting Clue® users with irregular periods were generated. In order to be prompted with the feature, users must be logging irregular cycles for at least 6 months or have not logged a period in 90 days. Furthermore, they must have cycles longer than 38 days or a high cycle length variation that is higher than average for their age group. For individuals between the ages of 16 and 26 years old, the cycle length variation threshold is greater than nine days cycle to cycle. For users over 27, the variation between cycle lengths should be greater than 7 days. Figure 5 summarizes the individuals who are ultimately prompted with the ICF. If a user meets the eligibility requirement of menstrual cycle length irregularity, they are automatically prompted with the feature, and will be asked about age if they have not already included it in their user profile.

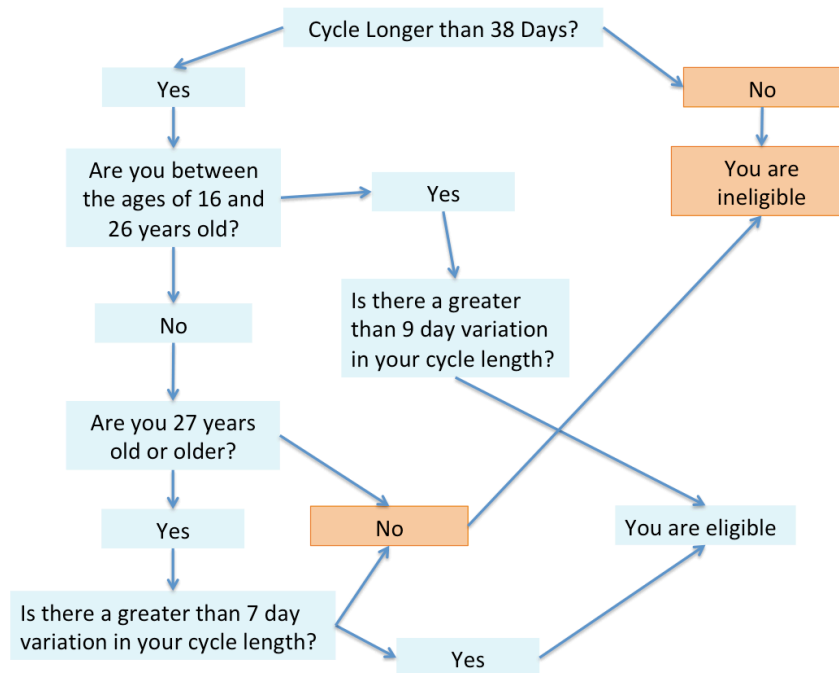


Figure 5. Eligibility Flow Diagram. Orange indicates ineligibility.

These criteria were defined in this manner because an individual with PCOS has a high likelihood of presenting with a menstrual cycle length outside the normal ranges defined by the FIGO recommendations for normal and abnormal bleeding (Fraser *et al.* 2011). Anywhere between 50% and 85% of women with PCOS will present with oligomenorrhea and anywhere from 20% to 40% of women with PCOS present with amenorrhea depending on the diagnostic criteria used (Hart *et al.*, 2004). Thus, these parameters will allow for individuals at risk for PCOS to be captured by the ICF.

DEVELOPING OF THE IRREGULAR CYCLES FEATURE

Building the Bayesian Network. A list of signs and symptoms for PCOS was generated based on the Rotterdam diagnostic criteria and differential diagnostics. Additionally, a list of possible confounding causes and comorbidities for the same symptoms was created (Figure 1). A literature review was then conducted for each item. The probabilities found in the literature review for each diagnostic criterion, including confounders, were used to build a Bayesian Network. This statistical modeling tool allows multiple, conditional states to be handled discretely in order to generate an overall probability of an outcome, in this case PCOS) (Weber and Simon, 2016). Figure 6 highlights all of the signs and symptoms that were used in the assessment with omitted probabilities. The light green boxes indicate the major diagnostic criteria suggested by the Rotterdam group. The purple and blue boxes indicate the questions asked by the ICF in order to obtain more detailed information from the user regarding the diagnostic criteria in order to perform probability calculations.

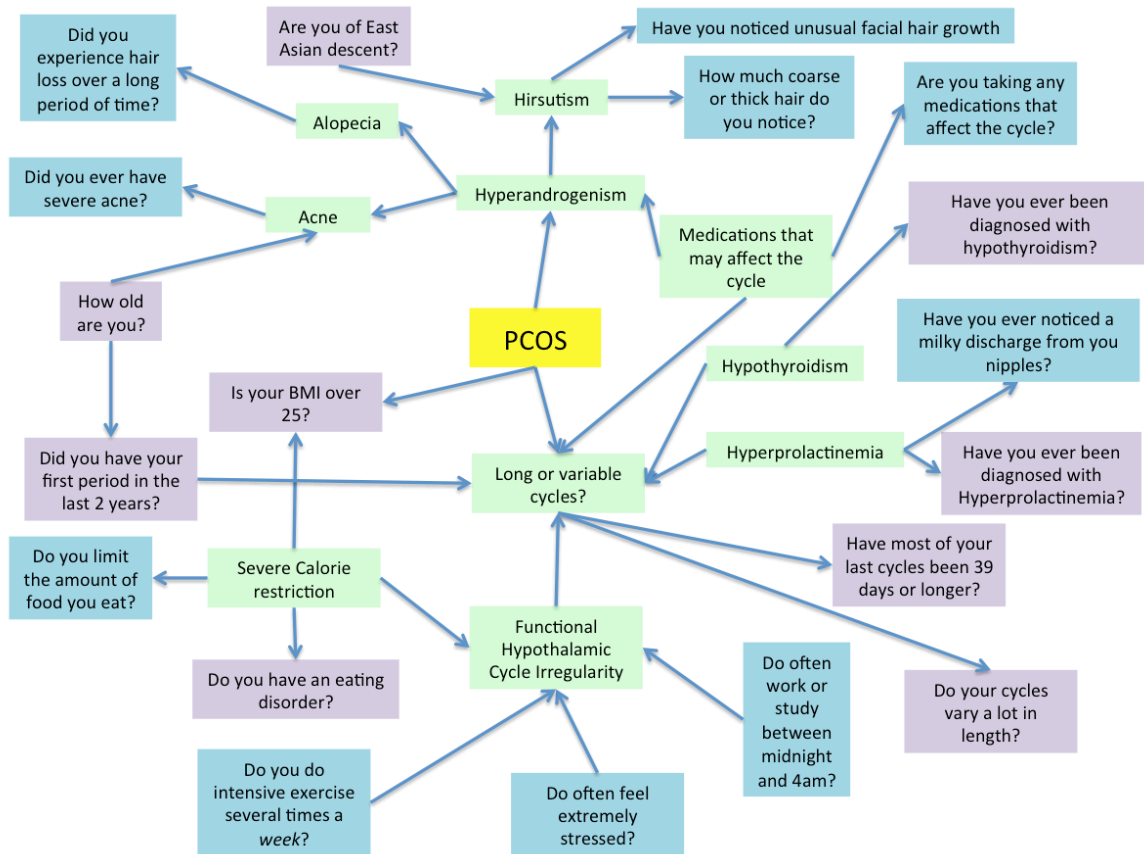


Figure 6. Bayesian Network Used to Determine Probability of PCOS.

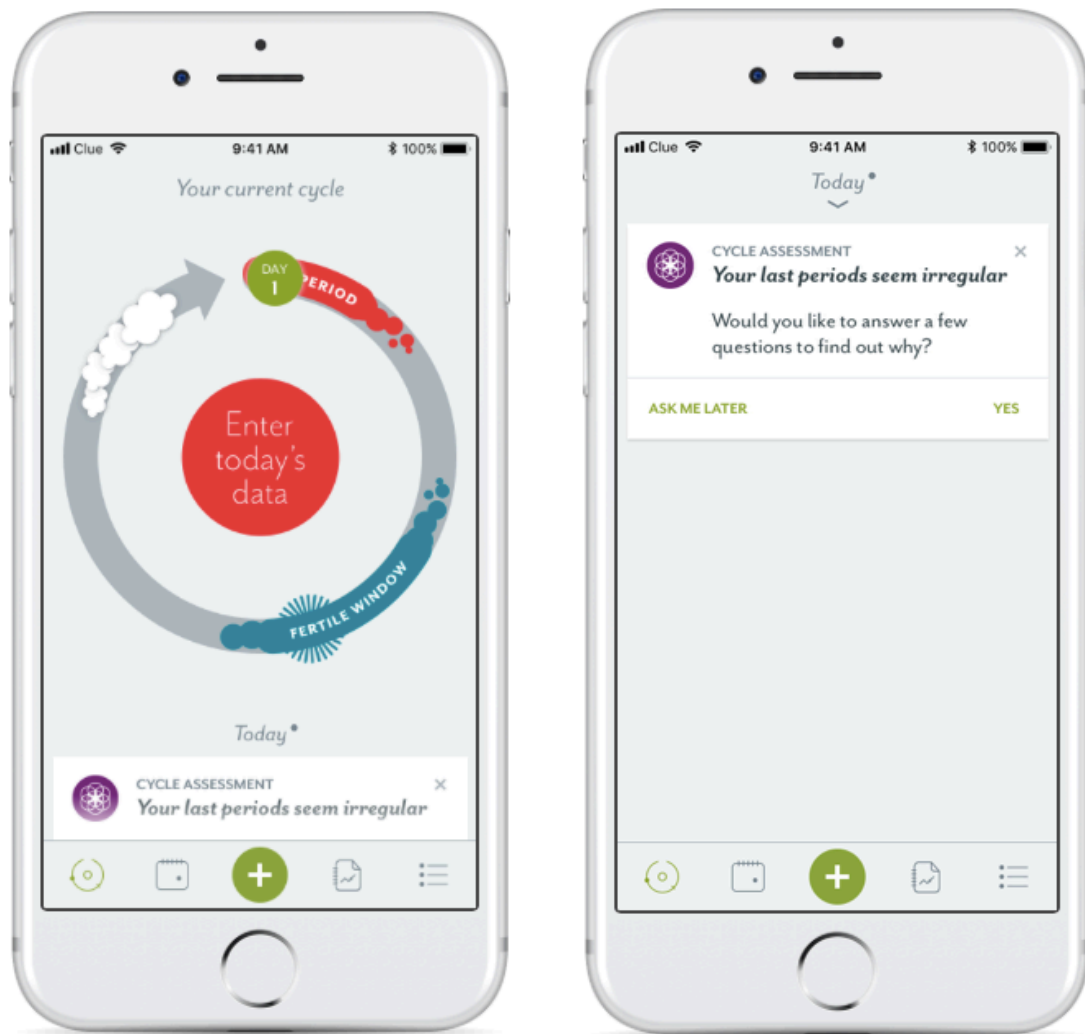
Green indicates features of PCOS. Purple indicates sample Screener questions. Blue indicates additional questions asked by the ICF.

Developing the Screener. Eight measures from the predetermined list of criteria are always used to evaluate an individual's eligibility to continue interaction with the feature. The variables for these eight questions were selected from the literature review, and were prioritized based on commonly reported symptoms Clue® collects from its user base. These eight variables include: height, weight, age, birth control use, medical conditions, life stage, age at menarche, and majority of cycles longer than 38 days. Those

who already record age, height, weight, and birth control in the Clue® app will only be asked the few additional questions. If the conditions for being prompted with the feature are not met, such as for age and birth control, the user is not prompted with more questions. This preliminary question set is termed the Screener.

It is important for the interface to assess the Screener variables because each can have an impact on cycle regularity. For instance, a woman that has had her first period within the past two years also has a high likelihood of having a menstrual cycle length outside the normal ranges (ACOG, 2015). In order to account for this potential confounder, and others that similarly affect cycle regularity, the ICF combines the individual's menstrual cycle data self-reported in the app, data about menarche, conditions affecting menstruation, and other pertinent medical history. Compiling this information, the network then calculates whether menstrual cycle irregularities are connected to PCOS or if they are due to a different medical condition. Special attention was paid to how these questions were formulated in order to ensure comprehension by a large, diverse population of users.

Questionnaire Flow. The interface provides a brief description of what the assessment entails, and informs users that a result will be generated based on answers to a series of brief questions (Figure 7). Participation in the survey is completely dependent on whether the individual elects to participate. Use of the Clue® app is not be altered if an individual decides not to participate.



a. Pop up window on Home screen

b. ICF User Prompt

Figure 7. Image of the ICF Clue® User Prompt.

After the Screener, a user is presented with additional questions in order to obtain a more complete picture of risk factors. These questions were adapted from the PCOS module in the Ovulation and Menstruation Health Study being conducted at Boston University. These variables include: how much thick hair is typical for the individual, medications being taken that affect the cycle, abnormal hair loss, acne, irregular sleep, stress, strenuous physical work, and eating habits. The ICF assessment portion was developed to be an adaptive questionnaire. Thus, not every question is asked to every individual, and only those questions deemed relevant are presented based on previous answers. For example, Figure 8 shows that if a user were to report that they are not concerned about excess hair growth, the tool will initiate a skip pattern such that they are not asked about how much thick hair is present on their face or body. In this manner, the model streamlines the amount of data and reduces the time it takes an individual to complete the questionnaire portion of the ICF.

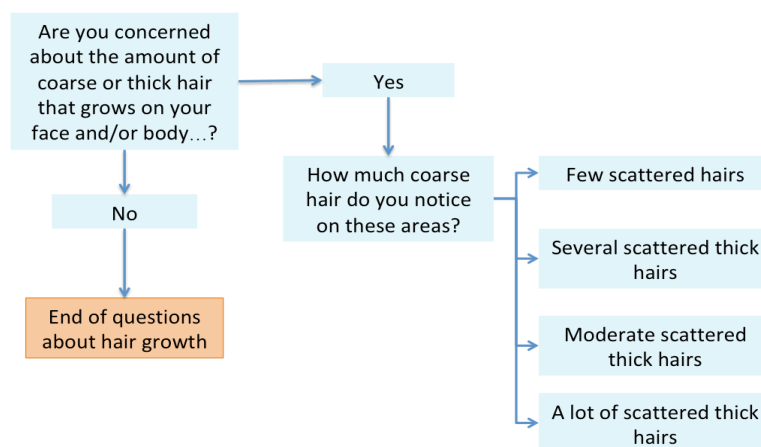


Figure 8. Abbreviated Hair Growth Questionnaire Flow Diagram. The orange indicates the end of the question set for hair growth. The blue indicates questions asked of the user.

The ‘Results Screen’. After a user completes the questionnaire, the ICF calculates a probability that she could be diagnosed with PCOS. Depending on the value, the Clue® user is prompted with one of three Results Screens. These were created in order to provide insightful feedback to users at the end of the questionnaire. The three possible outcome screens are: a Positive Result Screen, a Neutral Result Screen, and an Inconclusive Result Screen. In each scenario, the app highlights how the ICF analyzed cycle histories, the user’s health profile, and answers from the questionnaire to yield the probability. A call to seek medical attention is also included, as the intended use of the Result Screen is not for diagnosis.

For individuals that the network calculates as having a probability of PCOS that is greater than or equal to 3 in 10, a Positive Result Screen is displayed. While the results assure the user that immediate attention is not vital, the screen also indicates that long-term health may be affected. Additionally, the screen highlights the steps a medical profession may take to confirm a diagnosis for PCOS. For example, the screen describes that a doctor will likely perform a more detailed history regarding symptoms, a physical exam, and blood tests if necessary. An excerpt of the screen can be seen in Figure 9.

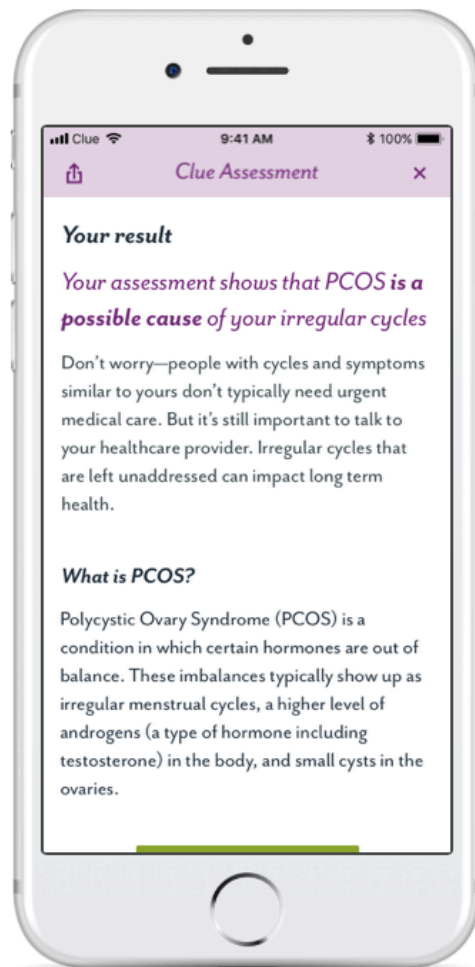


Figure 9. Clue® Positive Result Screen


For cases that have a probability of less than 3 in 10, an individual is presented with a Neutral Result Screen. The screen describes that a prediction cannot be made regarding what is causing the menstrual irregularities. Additionally, the user is prompted to seek a medical professional and additional possible diagnostic tests are listed. In an effort to dissipate more health knowledge to users, this screen also lists potential confounding diseases similar to PCOS that may cause menstrual irregularities. These include: stress, hypothyroidism, and Cushing's syndrome.

The Inconclusive Result Screen appears when an individual self-reports additional confounding variables. Those of particular interest when calculating PCOS probability are: hormonal birth control use, age, pregnancy, and breastfeeding. The potential endocrine disruption that occurs with hormones is beyond the calculation ability of the Bayesian Network. Thus, the Inconclusive Result Screen prompts an individual with physiological states or medications that contribute to menstrual irregularity to seek a medical professional for further assessment.

The Doctor's Report. The development of the Irregular Cycles Feature includes a Doctor's Report designed for presentation to a healthcare professional (Figures 10 and 11). The document is a summary that gives healthcare providers additional information regarding cycle irregularity and signs and symptoms detected by the ICF that are of concern. The report includes data that outlines the last six menstrual cycles of the individual, as well as average cycle length, average cycle variation, and average period length that can be assessed by the doctor. Specific symptoms, lifestyle habits, as well as age of menarche, BMI, and hormone-based medications are presented in one document. The document is unique to a user, and provides a condensed history that the doctor can use in making a final diagnosis. The Doctor's Report is generated whether the individual is expected to have PCOS or not. This ensures that the individual is able to provide important medical information to their provider regardless of the output so long as their cycles are irregular.

The questionnaire, the Results Screen, and the Doctor's Report were created in conjunction with one another in order to facilitate a user's understanding of their health, and consequently improve conversations between patients and doctors.

DOCTORS REPORT
 menstrual history and related symptoms



NAME Jane Doe
AGE 27 **BIRTH CONTROL** pill **EXPORTED** 08.02.2019

CYCLE HISTORY

Average cycle length: 29
 Cycle length is within normal range for your age group.

Average cycle variation: 4.4
 Cycle variation length is outside the normal range for your age group.

Average period length: 3
 Period length is within normal range for your age group.

LAST 6 CYCLES OVERVIEW
 Start date of last menstrual period:

Period Start	Period Length	Cycle Length
19.01.2019	2	26
18.01.2019	2	24
17.01.2019	3	28
16.01.2019	3	29
15.01.2019	2	26
14.01.2019	3	25

RELATED FACTORS:

SYMPTOMS		LIFESTYLE		OTHER	
Facial or body hair:	no	Limiting calories:	yes	BMI:	3.4567
Hair thinning on head:	yes	High stress:	yes	Age at menarche:	12
Severe acne:	yes	Intensive exercise:	no	Preexisting conditions:	yes
Nipple discharge:	no	Circadian rhythm disruption:	no	endometriosis, hypothyroidism	
Amount of facial or body hair:	several			Hormonal medication:	no

CLUE REPORT
 Based on cycle history and reported symptoms

 Note to healthcare providers: This result is based on calculations that combine menstrual history with assessment questions. Clue uses the FIGO recommendations of irregular cycle definitions¹. Calculations are based on up-to-date research, and were developed in collaboration with medical researchers and clinical experts.

Possible cause for irregular cycles:
 Polycystic ovary syndrome

Disclaimer
 Clue is not a diagnostic tool. Clue monitors your cycle using the latest research from our academic and clinical collaborators. Clue's guidelines do not replace the advice of a healthcare provider.

Sources
¹Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med.* 2011 Sep;29(5):383-90.

Interested to learn more about Clue or this report? Please contact us at support@helloclue.com.

Figure 10. The Doctor's Report for Suspected PCOS Diagnosis from Clue®

DOCTORS REPORT

menstrual history and related symptoms



NAME Sam Doe

AGE 27

BIRTH CONTROL pill

EXPORTED 08.02.2019

CYCLE HISTORY

Average cycle length: 35

Cycle length is within normal range for your age group.

Average cycle variation: 1.5

Cycle variation length is within normal range for your age group.

Average period length: 2

Period length is within normal range for your age group.

LAST 6 CYCLES OVERVIEW

Start date of last menstrual period:

Period Start	Period Length	Cycle Length
14.02.2019	3	25
30.01.2019	2	26
26.01.2019	3	29
17.01.2019	4	28
14.01.2019	3	24
13.01.2019	0	14

RELATED FACTORS:

SYMPTOMS

Facial or body hair: no

Hair thinning on head: yes

Severe acne: yes

Nipple discharge: no

Amount of facial or body hair: several

LIFESTYLE

Limiting calories: yes

High stress: yes

Intensive exercise: no

Circadian rhythm disruption: no

OTHER

BMI: 3.4567

Age at menarche: 12

Preexisting conditions: no

Hormonal medication: no

CLUE REPORT

Based on cycle history and reported symptoms

Possible cause for irregular cycles:

Unknown

Note to healthcare providers: This result is based on calculations that combine menstrual history with assessment questions. Clue uses the FIGO recommendations of irregular cycle definitions¹. Calculations are based on up-to-date research, and were developed in collaboration with medical researchers and clinical experts.

Disclaimer

Clue is not a diagnostic tool. Clue monitors your cycle using the latest research from our academic and clinical collaborators. Clue's guidelines do not replace the advice of a healthcare provider.

Sources

¹Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med.* 2011 Sep;29(5):383-90.

Interested to learn more about Clue or this report? Please contact us at support@helloclue.com.

Figure 11. The Doctor's Report for Other Menstrual Irregularities from Clue®

VALIDATING THE IRREGULAR CYCLES FEATURE

In order to validate the usability and accuracy of the Bayesian Network, the physician-scientist was asked to determine whether or not the probabilities found in the literature review were similar to assessments she would make in a clinical setting.

Creation of test cases. Beyond consulting the physician-scientist, as an additional validation step, the team created a set of fourteen test cases to compare the network's assessment to that of the board certified reproductive endocrinology/infertility physician-scientist. The test patients were created using aggregated data from Clue® users, but they are not based on actual individuals. Each of the test patients had unique answers to the validation criteria questions in order to test the ability of the network to produce an accurate PCOS probability. Varying levels of information were input in order to test the accuracy of the results generated, with particular interest in the ability of the ICF execute its functions despite a user not answering certain questions. Ultimately, eight out of fourteen different test cases were used to generate a numerical probability of PCOS.

Assigning probabilities. Each test case was presented to the physician-scientist for assessment. The specialist determined probabilities of PCOS based on clinical experience and rated a test patient as having low, moderate, high, or an indeterminable risk of PCOS. In order to determine a correlation between feature output and physician-scientist, the physician assessments were converted into numerical probabilities (Table 5). The comparison between the ICF and physician-scientist assessments is summarized in Table 4.

In order to assign a percent likelihood to the physician's categorical assessment, the team created a set of standards. These values were determined based on a modification of the Hillson 2005 proposed definitions for qualitative and quantitative definitions of probabilities (Hillson, 2005). For the cases the physician determined to be confounded by additional variables or felt that she could not make an accurate assessment, we assigned a probability of 10%, although the range encompassed values up to 25% to account for discrepancies pending the diagnostic criteria used, 10% was explicitly chosen for this study because it is reflective of the prevalence of PCOS in the general population based on the Rotterdam criteria. For test patients determined to have no to low risk of PCOS, the group assigned a value within the range of 0% to 9%. These criteria were used because the team wanted to ensure exclusion of PCOS prevalence in this category. For cases with moderate risk, the percentages were assigned within the range of 11% to 59%. For those deemed to be at high risk, the team assigned values within the range of 60-100% probability. A sliding scale summary of the assigned probabilities can be seen in Figure 12.

Statistical Analysis. After assigning probabilities via the ICF and the physician-scientist, a correlation coefficient, p-value, and Pearson's coefficient were calculated using Microsoft ® Excel. The p-value was calculated from the correlation coefficient in order to assess statistical significance of the correlation coefficient. This was done once using nine test cases. Because one test case significantly skewed the data, a second statistical analysis was conducted excluding the test patient in order to assess the validity of the ICF. Because an additional iteration of the tool was also completed to ascertain the

affect of hirsutism on PCOS patients, a third statistical analysis was conducted. The additional iteration consisted of modification of the existing Bayesian Network by lowering the probabilities for the hirsutism variables found in the original literature review. The modification was deemed necessary because current literature regarding the probability of hirsutism in PCOS patients appeared to suggest lower probabilities than what was initially determined in the original literature review.

Table 4. Physician Assessments and ICF Assessments of Test Cases. This table summarizes the original assessments of all test cases created for both the physician and the tool.

Patient Number	Physician Assessment	ICF Assessment
Patient 1	High	91%
Patient 2	High	93%
Patient 8	PCOS: 30% Hypothalamic pituitary: 70%	66%
Patient 12	Currently taking hormones: This is a special case- indication of irregular cycles means the feature should direct them to talk to their doctor	10%
Patient 14	Low PCOS	34%
Patient 17	Moderate to high PCOS	37%
Patient 5	Indeterminate	9%
Patient 7	High	14%
Patient 15	None	1%

Table 5. Physician Assessments and Assigned Probabilities for Test Cases. This table summarizes the probabilities assigned to the physician's qualitative assessments for all test cases.

Patient Number	Physician Assessment	Assigned Probability
Patient 1	High	80%
Patient 2	High	80%
Patient 8	PCOS: 30% Hypothalamic pituitary: 70%	30%
Patient 12	Currently taking hormones: This is a special case- indication of irregular cycles means the feature should direct them to talk to their doctor	10%
Patient 14	Low PCOS	5%
Patient 17	Moderate to high PCOS	70%
Patient 5	Indeterminate	10%
Patient 7	High	80%
Patient 15	None	0%

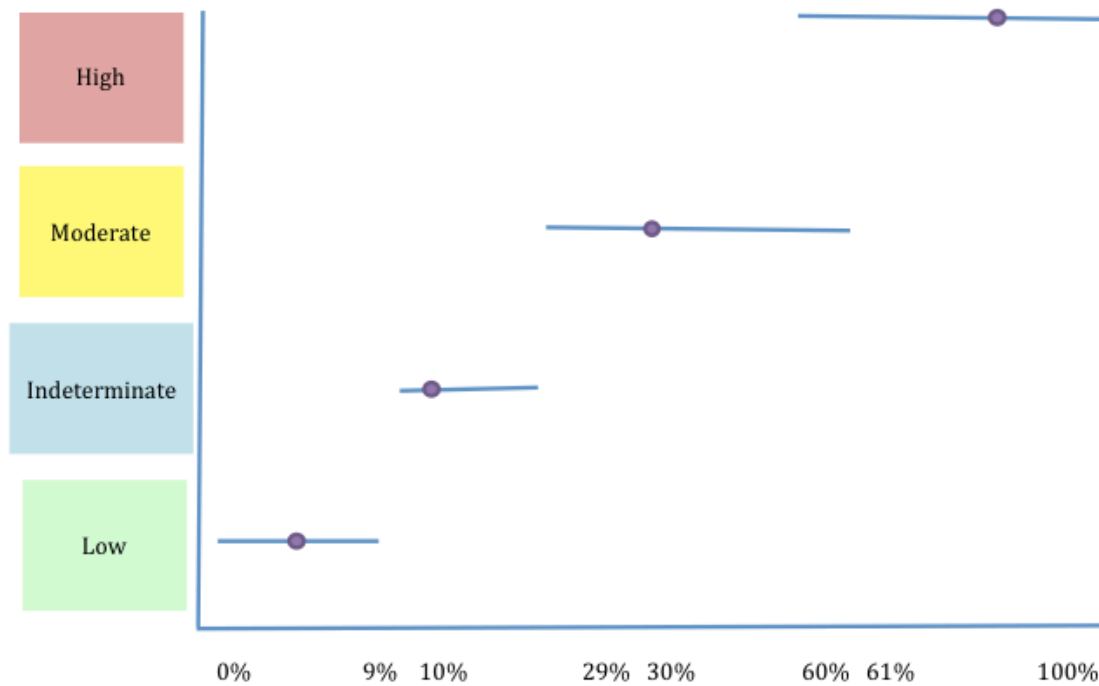


Figure 12. Sliding Scale Percent Probability Ranges: Adapted from Hillson, 2005.

The blue bar indicates the range of percentages that fall into the high, moderate, indeterminate, and low categories. The purple circle illustrates the percentage typically used in assignment of percent probability.

RESULTS

After completing the assignment of probabilities to test cases, a statistical analysis was conducted in order to determine how well the ICF predicted PCOS risk as compared to the physician-scientist. A few sample test case responses are shown in Table 6 in order to demonstrate the questions, answers, and predictions that were made by the tool compared to the physician-scientist.

Table 6. Sample Test Cases for the Irregular Cycles Feature Validation. This table shows questions and answers for select test patients and the probability generated by the ICF. Blue boxes indicate questions that are always asked of the user.

	Patient 1	Patient 8	Patient 12	Patient 15
Concerned about hair growth?	Yes	Yes	Yes	No
How much thick hair?	Lots of Hair	Several	Several	
Majority of cycles ≥ 38 days?	Yes	Yes	Yes	No
Taking meds that could affect the cycle?	No	No	Yes	
BMI over 25	No	No	No	
Cycle variation out of range?	Yes			No
Eating disorder?	No	Yes		
Hair loss?	No	No		
Acne?	No	No		
Menarche during last 2 years?	No			
Age Range?		19-40		
Of East Asian heritage?				
Diagnosed with Hypothyroidism?				
Irregular sleep?				
Stress?				
Strenuous physical work?				
Limiting food?				
Diagnosed with Hyperprolactinemia?				
PCOS Probability	91%	66%	10%	1%

Test Patient 1 is representative of an individual with many indicators of PCOS. This individual would be prompted with a Positive Result Screen. More specifically, the reports of excess hair growth and high cycle variability are significant clinical presentations of the disorder. Thus, the physician's assignment of high probability of PCOS matches the 91% probability generated by the network. This demonstrates that in certain cases of PCOS, such as those indicating hyperandrogenism, the tool is effective at successfully identifying an individual at high risk.

In Test Patient 8, the physician assigned a 30% probability of PCOS, and further suggested a diagnosis of hypothalamic pituitary dysfunction (Table 5). The ICF on the other hand generated a 66% probability. The network value is slightly higher than the physician's prediction because data regarding comorbidities such as hypothyroidism, were not answered for this test patient. This was done primarily to assess how the ICF would handle missing data. Despite the network's probability calculation being slightly higher than that of the physician, the assessment still proves useful for advising an individual to seek a healthcare provider for further testing because they are prompted with a Positive Result Screen. Adjustments to the probabilities within the Bayesian Network can also be made once based on this outcome.

For Test Patient 12, the model suggested a 10% probability. This reflects the incidence of PCOS in the general population, and a user would be prompted with an Inconclusive Result Screen. Slightly higher probabilities may be indicated depending on the diagnostic criteria used (Sirmans and Pate, 2013). The physician determined that the medications being taken by the individual indicated a special case. Because she was not

able to make a recommendation based on the given data, a probability that was also reflective of the general population was also assigned to the physician. This test case highlights the importance of the Screener questions and the ability of the tool to handle potential confounders. Because the ICF directs ineligible women to a Result Screen describing the confounding medications or other medical experiences they input, this tool functions similarly to the physician who requires more information before drawing conclusions for risk of PCOS.

For Test Patient 15, both the physician and the network predict a 0% to 1% chance of having PCOS. This patient did not report menstrual irregularities nor did they indicate areas of concern such as those associated with hyperandrogenism: acne, alopecia, or hirsutism. Similar individuals would be prompted with a Neutral Result Screen. This illustrates that the model can accurately eliminate individuals who are unlikely to have PCOS.

Statistical Analyses. Upon reviewing the test cases, a correlation coefficient, p-value, and Pearson's coefficient, were calculated in Microsoft ® Excel. With a p-value less than .05, the correlation coefficient was determined to be statistically significant for the eight test cases deemed usable by the study team. A summary of the statistics run can be seen in Tables 7-9.

Table 7. Summary of 9 Test Cases Used for Statistical Calculations

This table demonstrates all test cases created for the study and the probabilities assigned by the ICF and the physician-scientist.

	ICF	Physician-Scientist
Patient 1	91%	80%
Patient 2	93%	80%
Patient 8	66%	30%
Patient 12	10%	10%
Patient 14	34%	5%
Patient 17	37%	70%
Patient 5	9%	10%
Patient 15	1%	0%
Patient 7	14%	80%

Table 8. Summary of Statistical Calculations for 9 Test Cases

This table demonstrates the statistics for all test cases that were created by the team including patient 7 who was ultimately excluded because it was suspected to be an outlier based on the difference in statistical calculations.

Statistical Test	Value
Correlation	.62
P-value	0.08
Pearson's Coefficient (R^2)	.38

Table 9. Summary of Statistical Calculations for 8 Test Cases

This table demonstrates the statistics for test cases excluding patient 7 (the suspected outlier).

Statistical Test	Value
Correlation	0.82
P-value	0.01
Pearson's Coefficient (R^2)	0.69

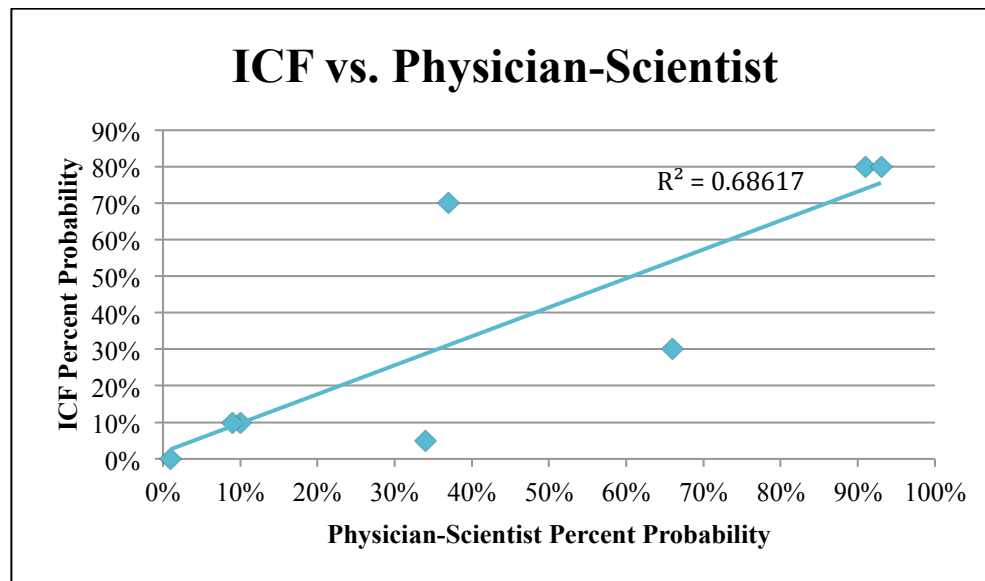


Figure 13. Linear Regression with Pearson's Coefficient for 8 Test Cases

This graph demonstrates the linear regression for 8 test cases, which excludes patient 7 (the suspected outlier).

Table 10. Summary of Statistical Calculations for 8 Test Cases 2nd Iteration of ICF.

This table demonstrates the statistics calculated with lowered probabilities of hirsutism in PCOS for all test cases excluding patient 7 (the suspected outlier).

Statistical Test	Value
Correlation	0.73
P-value	0.03
Pearson's Coefficient (R^2)	0.54

DISCUSSION

By completing a literature review, construction of a Bayesian Network, and validation using a board certified reproductive endocrinology/infertility physician-scientist's predictions, the Irregular Cycles Feature was created to draw attention to possible indicators of PCOS. The construction of this tool is critical for women taking charge of their health, as it will reduce the time for PCOS detection and facilitate conversations between patients and doctors through the use of the Result Screen and Doctor's Report. The goal of this study was to detect PCOS in a cohort of Clue® users by being as inclusive as possible. Wide parameters were set in order to capture the majority of women with irregular cycles for prompting with the feature.

PCOS is a condition diagnosed by menstrual irregularities, androgen excess, and polycystic ovaries upon ultrasound. It is associated with reproductive, metabolic, cardiovascular disease, and psychological co-morbidities (Lim *et al.*, 2018). It also has serious implications for fertility. PCOS is generally diagnosed through assessment of possible symptoms that may signal the disorder such as hirsutism, severe acne, alopecia, and chronic anovulation. Currently there are no well-defined in utero or early life risk factors for developing PCOS, and at reproductive age, the signs and symptoms may be confused with normal development (Welt and Carmina, 2013). It is thought that inappropriate eating behaviors that lead to obesity, which is also strongly associated with PCOS, makes weight a modifiable risk factor for PCOS, particularly in adolescents (Hajivandi *et al.*, 2018).

Because of the risk PCOS poses to reproductive health, developing a tool to help identify key features for the disease is crucial for helping women with this condition. By calculating the probability that an individual's signs and symptoms are indicative of PCOS, the Irregular Cycles Feature developed by the study team will allow app users to take consolidated information to their doctors. Because a summary is generated based on self-reported answers in the interactive survey, specialized care can be facilitated. Additionally, by providing the user with an outline of what the next steps are in terms of testing and visiting a doctor's office, the app helps drive patient autonomy. Furthermore, upon rollout to Clue® users, this novel tool could shorten the time to PCOS diagnosis.

The main limitation of this study is that it only used test cases and was not conducted in a human population. Additionally, the model cannot yet completely account for the affect of confounding factors on the menstrual cycle. Thus, it remains to be seen whether the Irregular Cycles Feature will be adaptable to the needs of human users.

Despite the limitations of the study, the Irregular Cycles Feature is one means by which users can take control of their gynecological health. By providing more information about PCOS and giving users feedback based on information they collected, the researchers believe that this feature will provide important information to those at high risk and potentially shorten the time for diagnosis.

A small sample of Clue® users has already begun testing the feature. With this small subset of individuals with irregular cycles, a further validation study can be conducted. The goal of the future validation would be to follow up with users who were prompted with the ICF at 3, 6, and 12-month intervals in order to assess the utility of the

tool. The follow up prompts would support continued communication with a doctor and determine whether or not a PCOS diagnosis was actually made. Additionally, this further validation will allow for improved sensitivity and specificity tests, which will capture more women with PCOS, more accurately, and may consequently shorten the time to diagnosis. Furthermore, future adaptations of this tool can be made to make assessments for other diseases that affect menstruation such as endometriosis or uterine fibroids.

CONCLUSION

In conclusion, the Irregular Cycles Feature, developed for Clue® users, was determined to generate a probability of PCOS comparable to that made by a board-certified reproductive endocrinology/infertility physician-scientist. It is important that this feature be used in conjunction with a doctor, as a user cannot rely on the tool as a diagnosis. Because menstrual cycles can be important indicators of overall health, it was especially important to create a tool that carefully studied irregularities. The development of this feature was vital as it also prompts users with potential confounding diagnoses to seek out a professional, something extremely novel in the realm of mobile health. Additionally, the potential to expand this tool to other diseases that cause menstrual irregularities further illustrates the importance of creating and validating this tool. In the future, the Irregular Cycles feature will likely be extremely valuable for doctors and patients alike.

LIST OF JOURNAL ABBREVIATIONS

AMA Arch of Intern Med	A.M.A. Archives of Internal Medicine
Clin Epidemiol	Clinical Epidemiology
Hum Reprod	Human Reproduction
J Family Community Med	Journal of Family & Community Medicine
J Hum Reprod Sci	Journal of Human Reproductive Sciences

REFERENCES

- American College of Obstetricians and Gynecologists: Committee on Adolescent Health Care. Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign (ACOG). <https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Menstruation-in-Girls-and-Adolescents-Using-the-Menstrual-Cycle-as-a-Vital-Sign?IsMobileSet=false>. Published December 2015. Accessed January 2019.
- Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and Sterility*. 2009;91(2):456-488. doi:[10.1016/j.fertnstert.2008.06.035](https://doi.org/10.1016/j.fertnstert.2008.06.035)
- Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health Care-Related Economic Burden of the Polycystic Ovary Syndrome during the Reproductive Life Span. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90(8):4650-4658. doi:[10.1210/jc.2005-0628](https://doi.org/10.1210/jc.2005-0628)
- Blagojevic IP, Eror T, Pelivanovic J, Jelic S, Kotur-Stevuljevic J, Ignjatovic S. Women with Polycystic Ovary Syndrome and Risk of Cardiovascular Disease. *Journal of Medical Biochemistry*. 2017;36(3):259-269. doi:[10.1515/jomb-2017-0020](https://doi.org/10.1515/jomb-2017-0020)
- Boyle J, Xu R, Gilbert E, et al. Ask PCOS: Identifying Need to Inform Evidence-Based App Development for Polycystic Ovary Syndrome. *Seminars in Reproductive Medicine*. 2018;36(01):059-065. doi:[10.1055/s-0038-1667187](https://doi.org/10.1055/s-0038-1667187)
- Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2016;**31**: 2841-2855.
- Chen EH, Shofer FS, Dean AJ, et al. Gender Disparity in Analgesic Treatment of Emergency Department Patients with Acute Abdominal Pain. *Academic Emergency Medicine*. 2008;15(5):414-418. doi:[10.1111/j.1553-2712.2008.00100.x](https://doi.org/10.1111/j.1553-2712.2008.00100.x)
- Chyjek K, Farag S, Chen KT. Rating Pregnancy Wheel Applications Using the APPLICATIONS Scoring System: *Obstetrics & Gynecology*. 2015;125(6):1478-1483. doi:[10.1097/AOG.0000000000000842](https://doi.org/10.1097/AOG.0000000000000842)
- Cushing syndrome - Symptoms and causes. Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/symptoms-causes/syc-20351310>. Published March 6, 2018. Accessed February 16, 2019.

- Derbyshire E, Dancey D. Smartphone Medical Applications for Women's Health: What Is the Evidence-Base and Feedback? *International Journal of Telemedicine and Applications*. 2013;2013:1-10. doi:[10.1155/2013/782074](https://doi.org/10.1155/2013/782074)
- El-Shafie KT. Clinical presentation of hypothyroidism. *J Family Community Med*. 2003;10(1):55-8.
- Farag S, Chyjek K, Chen KT. Identification of iPhone and iPad Applications for Obstetrics and Gynecology Providers: *Obstetrics & Gynecology*. 2014;124(5):941-945. doi:[10.1097/AOG.0000000000000510](https://doi.org/10.1097/AOG.0000000000000510)
- Fraser I, Critchley H, Broder M, Munro M. The FIGO Recommendations on Terminologies and Definitions for Normal and Abnormal Uterine Bleeding. *Seminars in Reproductive Medicine*. 2011;29(05):383-390. doi:[10.1055/s-0031-1287662](https://doi.org/10.1055/s-0031-1287662)
- Frick KD, Clark MA, Steinwachs DM, et al. Financial and Quality-of-Life Burden of Dysfunctional Uterine Bleeding Among Women Agreeing To Obtain Surgical Treatment. *Women's Health Issues*. 2009;19(1):70-78. doi:[10.1016/j.whi.2008.07.002](https://doi.org/10.1016/j.whi.2008.07.002)
- Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*. December 2016;jc.2016-2963. doi:10.1210/jc.2016-2963
- Hajivandi L, Noroozi M, Mostafavi F, Ekramzadeh M. A comprehensive interventional program for promoting eating behaviors in adolescent girls with polycystic ovarian syndrome (PCOS): protocol for a mixed methods study. *Reproductive Health*. 2018;15(1). doi:10.1186/s12978-018-0652-y
- Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2004;18(5):671-683. doi:[10.1016/j.bpobgyn.2004.05.001](https://doi.org/10.1016/j.bpobgyn.2004.05.001)
- Hillson D. Describing probability: The limitations of natural language. In: Edinburgh, UK: PMI Global Congress EMEA Proceedings; 2005:1-7. <http://www.risk-doctor.com/pdf-files/emeamay05.pdf>.
- Hypothyroidism - Symptoms and causes - Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/hypothyroidism/symptoms-causes/syc-20350284>. Published December 4, 2018. Accessed February 16, 2019.
- Irving G, Neves AL, Dambha-Miller H, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open*. 2017;7(10):e017902. doi:[10.1136/bmjopen-2017-017902](https://doi.org/10.1136/bmjopen-2017-017902)

- Johannes C, Woods J, Crawford S, Cochran H, Tran D, Schuth B. Electronic versus paper instruments for daily data collection. *Annals of Epidemiology*. 2000;10(7):457. doi:[10.1016/S1047-2797\(00\)00141-1](https://doi.org/10.1016/S1047-2797(00)00141-1)
- Kaba R, Sooriakumaran P. The evolution of the doctor-patient relationship. *International Journal of Surgery*. 2007;5(1):57-65. doi:[10.1016/j.ijssu.2006.01.005](https://doi.org/10.1016/j.ijssu.2006.01.005)
- Krebs P, Duncan DT. Health App Use Among US Mobile Phone Owners: A National Survey. *JMIR mHealth and uHealth*. 2015;3(4):e101. doi:10.2196/mhealth.4924
- Lim, S. S., Kakoly, N. S., Tan, J. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Obesity Reviews*. 2018; <https://doi.org/10.1111/obr.12762>.
- Lichtman JH, Leifheit EC, Safdar B, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137(8):781-790. doi:[10.1161/CIRCULATIONAHA.117.031650](https://doi.org/10.1161/CIRCULATIONAHA.117.031650)
- Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertility and Sterility*. 2016;106(1):6-15. doi:[10.1016/j.fertnstert.2016.05.003k](https://doi.org/10.1016/j.fertnstert.2016.05.003k)
- Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci*. 2013;6(3):168-75.
- Mckinstry B. Paternalism and the doctor-patient relationship in general practice. *British Journal of General Practice*. 1992;3.
- Mead N, Bower P. Patient-centredness: a conceptual framework and review of the empirical literature. *Social Science & Medicine*. 2000;51(7):1087-1110. doi:[10.1016/S0277-9536\(00\)00098-8](https://doi.org/10.1016/S0277-9536(00)00098-8)
- Moglia ML, Nguyen HV, Chyjek K, Chen KT, Castaño PM. Evaluation of Smartphone Menstrual Cycle Tracking Applications Using an Adapted APPLICATIONS Scoring System: *Obstetrics & Gynecology*. 2016;127(6):1153-1160. doi:[10.1097/AOG.0000000000001444](https://doi.org/10.1097/AOG.0000000000001444)
- Monash University, 2018, The International evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome (PCOS) 2018, Monash University, Australia, ISBN-13:978-0-646-98332-5. Available at: monash.edu/medicine/sphpm/mchri/pcos

- Muaygil RA. From Paternalistic to Patronizing: How Cultural Competence Can Be Ethically Problematic. *HEC Forum*. 2018;30(1):13-29. doi:[10.1007/s10730-017-9336-1](https://doi.org/10.1007/s10730-017-9336-1)
- Munro MG, Critchley HOD, Broder MS, Fraser IS, for the FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *International Journal of Gynecology & Obstetrics*. 2011;113(1):3-13. doi:[10.1016/j.ijgo.2010.11.011](https://doi.org/10.1016/j.ijgo.2010.11.011)
- Murgic L, Hébert PC, Sovic S, Pavlekovic G. Paternalism and autonomy: views of patients and providers in a transitional (post-communist) country. *BMC Medical Ethics*. 2015;16(1). doi:[10.1186/s12910-015-0059-z](https://doi.org/10.1186/s12910-015-0059-z)
- Noe Pagán, C. When Doctors Downplay Women's Health Concerns, The New York Times. <https://www.nytimes.com/2018/05/03/well/live/when-doctors-downplay-womens-health-concerns.html>. Published May 3, 2018. Accessed February 3, 2019.
- Pałubska S, Adamiak-Godlewska A, Winkler I, Romanek-Piva K, Rechberger T, Gogacz M. Hyperprolactinaemia – a problem in patients from the reproductive period to the menopause. *Menopause Review*. 2017;16(1):1-7. doi:[10.5114/pm.2017.67364](https://doi.org/10.5114/pm.2017.67364)
- Perrin A. 10 Facts About Smartphones as the iPhone Turns 10. *Pew Research Center*. <http://www.pewresearch.org/fact-tank/2017/06/28/10-facts-about-smartphones/>. Published June 28, 2017. Accessed December 30, 2018.
- Polak K, Czyzyk A, Simoncini T, Meczekalski B. New markers of insulin resistance in polycystic ovary syndrome. *Journal of Endocrinological Investigation*. 2017;40(1):1-8. doi:[10.1007/s40618-016-0523-8](https://doi.org/10.1007/s40618-016-0523-8)
- Polycystic ovary syndrome (PCOS) - Symptoms and causes. Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/syc-20353439>. Published August 29, 2017. Accessed February 16, 2019.
- Porter R. *Blood and Guts: A Short History of Medicine*. New York, NY: W.W. Norton & Company, Ltd.; 2004.
- Prolactinoma - Symptoms and causes. Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/prolactinoma/symptoms-causes/syc-20376958>. Published May 12, 2018. Accessed February 16, 2019.
- Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2004b). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility*. 81(1), 19–25.

- Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281-293. doi:[10.2147/CLEP.S44336](https://doi.org/10.2147/CLEP.S44336)
- Sirmans S, Pate K. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology*. December 2013;1. doi:10.2147/CLEP.S37559
- Solomon CG, Hu FB, Dunaif A, et al. Long or Highly Irregular Menstrual Cycles as a Marker for Risk of Type 2 Diabetes Mellitus. *DIABETES MELLITUS*.:6.
- Szasz TS. A Contribution to the Philosophy of medicine: The Basic Models of the Doctor-Patient Relationship. *AMA Arch of Intern Med*. 1956;97(5):585. doi:[10.1001/archinte.1956.00250230079008](https://doi.org/10.1001/archinte.1956.00250230079008)
- Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Medicine*. 2010;8:41. doi:10.1186/1741-7015-8-41
- Vanderpump MPJ. The epidemiology of thyroid disease. *British Medical Bulletin*. 2011;99(1):39-51. doi:[10.1093/bmb/ldr030](https://doi.org/10.1093/bmb/ldr030)
- Weber P, Simon C. *Benefits of Bayesian Network Models*. 1st ed. Hoboken, NJ: John Wiley & Sons, Incorporated; 2016.
- Welt CK, Carmina E. Lifecycle of Polycystic Ovary Syndrome (PCOS): From In Utero to Menopause. *The Journal of Clinical Endocrinology & Metabolism*. 2013;98(12):4629-4638. doi:[10.1210/jc.2013-2375](https://doi.org/10.1210/jc.2013-2375)
- What are menstrual irregularities? <http://www.nichd.nih.gov/>.
<http://www.nichd.nih.gov/health/topics/menstruation/conditioninfo/irregularities>. Accessed February 3, 2019.
- Whitaker L, Critchley HOD. Abnormal uterine bleeding. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2016;34:54-65. doi:[10.1016/j.bpobgyn.2015.11.012](https://doi.org/10.1016/j.bpobgyn.2015.11.012)

CURRICULUM VITAE

