Prior Authorization Review Panel
MCO Policy Submission

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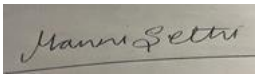
Plan: Keystone First Community HealthChoices	**Submission Date**: 9/1/2024
Policy Number: ccp.1545	**Effective Date:** 9/2024 **Revision Date:** August 1, 2024
Policy Name: Prescription digital therapeutics for contraception	

Type of Submission – Check all that apply:

- ☒ **New Policy**
- ☐ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Manni Sethi, MD, MBA, CHCQM	

Keystone First
Community HealthChoices

Prescription digital therapeutics for contraception

Clinical Policy ID: CCP.1545

Recent review date: 8/2024

Next review date: 12/2025

Policy contains: Clue; contraception; Natural Cycles; pregnancy prevention; prescription digital therapeutic.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

The following prescription digital therapeutics are clinically proven and, therefore, may be medically necessary as a method of contraception, when provided in accordance with plan- or state-specific requirements, and when specific criteria for use are met:

- Natural Cycles™ (version 3.0) (Natural Cycles Nordic AB, % Heyer Regulatory Solutions LLC, Amherst, Massachusetts) for female members aged 18 years or older (Berglund, 2017; Pearson, 2021a, 2021b).
- Clue Birth Control© (Biowink GmbH, San Francisco, California) for female members ages 18 to 45 years old with predictable 20 to 40 day cycles (i.e., that vary by less than 10 days) and, if applicable, members who have had at least three cycles (four periods) after stopping hormonal birth control or following the most recent pregnancy (Jennings, 2019).

Limitations

There are no absolute contraindications to using prescription digital therapeutics for contraception, but there are conditions for which fertility-awareness methods should be used with caution or delayed until the condition has been corrected. These conditions include: irregular menstrual cycles, breastfeeding, or post abortion; reproductive tract infections and diseases; use of drugs that affect cycle regularity, hormones, or fertility signs; and acute or chronic diseases that elevate body temperature (Curtis, 2016).

Alternative covered services

- Intrauterine devices.
- Progestin-only contraceptives (oral, injection, or implant).
- Combined hormonal contraceptives (oral, patch, or vaginal contraceptive ring).
- Barrier methods (diaphragm, cervical cap, sponge, male condom, female condom, spermicides).
- Female and male sterilization.
- Contraceptive counseling.

Background

Several options exist for contraception. In the female, reversible methods include intrauterine devices, hormonal methods, barrier methods, lactational amenorrhea, and fertility-awareness methods (Centers for Disease Control and Prevention, 2024).

Fertility-awareness methods, also referred to as "natural methods," are based on the ability to identify and avoid the fertile period of the menstrual cycle, favoring intercourse on the unfertile days of the month. Fertility-awareness methods are symptom-based (cervical mucus, basal body temperature, and symptothermal) or calendar-based (e.g., Standard Days) and may be used in combination with abstinence or barrier methods during the fertile time. They appeal to women who cannot use or do not want to use hormonal or invasive methods. However, fertility-awareness methods are associated with higher failure rates, and effectiveness will depend on menstrual regularity and correct and consistent use throughout the menstrual cycle (American College of Obstetricians and Gynecologists, 2022; Centers for Disease Control and Prevention, 2023).

A prescription digital therapeutic is a category within digital health technologies that is evidence-based, U.S. Food and Drug Administration-authorized or -cleared software used to treat or manage medical conditions. They may be used as a stand-alone or adjunct intervention and are available only by prescription by a licensed clinician (Shafai, 2023).

Two prescription digital therapeutics have been cleared for use in the United States as Class II software applications for women wishing to use a fertility-awareness method of contraception. Both predict fertile and non-fertile days and provide patient-specific recommendations related to contraception through proprietary algorithms, but they differ in use populations, user input, and technical characteristics:

- Natural Cycles is a mobile-based and stand-alone software application intended for women 18 years and older. There are no other conditions for approval, but women who have been on hormonal birth control within 60 days may have a higher risk of becoming pregnant compared to women who have not been on hormonal birth control within the previous 12 months. The application may not be appropriate for women with underlying medical conditions in whom a pregnancy would be associated with a significant risk to the mother or the fetus. The end user enters daily basal body temperature; menstruation cycle information (i.e., start date, number of days); and optional ovulation or pregnancy test results. Temperature can be measured using an Apple® Watch, a Bluetooth® enabled thermometer, or an Ōura ring (U.S. Food and Drug Administration, 2018, 2023).
- Clue Birth Control is a mobile-based software application intended for women ages 18 to 45 years old with predictable 20 to 40 day cycles (that vary by less than 10 days), who have had at least three cycles (four periods) after stopping hormonal birth control or since the end of a pregnancy. The user enters period start date information to provide predictions of "high risk days" and "low risk days" for becoming pregnant (U.S. Food and Drug Administration, 2021).

The Pearl Index and the life table analysis are methods commonly used to measure contraception efficacy, but there is a lack of agreement on which method to use. The Pearl Index calculates efficacy in terms of how well a method works when used correctly and consistently and the directions for use are followed (perfect use) and how well it works when sometimes used incorrectly or inconsistently (typical use). In clinical trials, it calculates the number of contraceptive failures per 100 woman-years. A lower Pearl Index suggests higher efficacy. However, it assumes a constant failure rate over time, which does not account for user experience and fertility that change over time, or for participant discontinuation during the entire study duration. As a result, the Pearl Index cannot be used to compare studies of differing lengths (Mauck, 2023).

Often, non-hormonal methods are studied for regulatory approval in trials that are much shorter than one year. While a Pearl Index can be calculated, it does not reflect a true one-year pregnancy outcome, because the product was not evaluated for that length of time, making comparisons of contraception effectiveness imprecise. Life table analysis is a method of survival analysis that attempts to overcome these limitations. The results are expressed as the likelihood of becoming pregnant within a specific time period, typically a 12- or 13-cycle time period, which allows valid comparisons among different studies extending over different time periods (Mauck, 2023).

Findings

Guidelines

According to the National Institute for Health and Care Excellence (2021), Natural Cycles is most likely to be used by people who prefer to use a non-hormonal method, and when other methods of contraception are unsuitable or contraindicated. Natural Cycles is feasible to use and may provide a more accurate prediction of fertility for the user, but it has not been compared directly to any other contraception method. Life table analyses from five observational studies found Natural Cycles had a typical use pregnancy rate of approximately 7%, which compared favorably to rates for calendar-based methods (24%) or condom use (8%). Three of the four experts who reviewed the available evidence highlighted the need for further research before adopting Natural Cycles in the National Health System.

The American College of Obstetricians and Gynecologists (2022) states that fewer than one in five women out of 100 women will become pregnant during the first year when fertility-awareness methods are used correctly and consistently throughout the menstrual cycle. Pregnancy rates rise to 12 to 24 women out of 100 with typical use, defined as sometimes incorrect or inconsistent use. The College states smart phone applications and web sites are available to help record information about the menstrual cycle and calculate fertile periods, but it does not specifically endorse or address any software application for contraception.

The Centers for Disease Control and Prevention guidance on medical contraception states fertility-awareness methods do not exacerbate underlying medical conditions but, given their higher failure rates, may require additional training or caution to ensure proper use. These methods do not protect against sexually transmitted diseases, and some conditions may make pregnancy an unacceptable risk. Conditions for which fertility-awareness methods should be used with caution or delayed until the condition has been corrected include: irregular menstrual cycles, breastfeeding, or post abortion; reproductive tract infections and diseases; use of drugs that affect cycle regularity, hormones, or fertility signs; and acute or chronic diseases that elevate body temperature (Curtis, 2016).

Evidence reviews

The evidence presented below suggests prescription digital therapeutics are effective fertility-awareness methods for contraception, provide immediate access to critical fertility information, and encourage correct, consistent use. Variations in study populations and methods used in clinical trials to determine pregnancy failure

rates hinders accurate comparisons of these software applications to other fertility-awareness methods or even to each other. Using the data from Peragallo (2018) below, Natural Cycles appears to compare favorably to the basal body temperature method, and Clue Birth Control seems to compare favorably to calendar-based methods:

Table 1. Comparison of fertility-awareness methods based on life table pregnancy probabilities or Pearl Index, per 100 woman-years

	First-year typical use	First-year perfect use
Standard Days	11.2 to 14.1	4.8
Basal Body Temperature	9.0 to 9.8	0.4

Source: Peragallo (2018).

The evidence of efficacy of the Natural Cycles application consists of large convenience samples from Sweden (Berglund, 2017, n = 22,785; Bull, 2019, n = 16,331), the United Kingdom (Pearson, 2021b, n = 12,247), and the United States (Pearson, 2021a, n = 5,879), all sponsored by the manufacturer. Users who reported a pre-existing medical condition or other factors that could have a potential effect on the length and or variability of their cycles (i.e., polycystic ovary syndrome, endometriosis, hypothyroidism, recent/current pregnancy, current hormonal treatment, or symptoms of menopause) were generally excluded from the analyses. Key demographics of current users were consistent across all three cohorts. The majority of users were of a mean age of 30, of normal body weight, university educated, in stable relationships, and without children. Most used oral contraceptives or condoms as their primary contraceptive prior to using Natural Cycles.

Natural Cycles has a perfect-use Pearl Index of 1.0 to 2.0, a typical-use Pearl Index of 6.1 to 6.9, and a 13-cycle pregnancy rate of 7.1% to 8.3%. User behavior, such as the ability of the user to measure basal body temperature on a regular basis and the ability to abstain from sex or use condoms on fertile days, strongly influenced application effectiveness (Berglund, 2017; Pearson, 2021a, 2021b). Previous users of intrauterine devices experienced a greatly increased risk of unintended pregnancy on Natural Cycles (Bull, 2019). Approximately 40% to 50% of participants were still using the application at the end of the studies. The main reason for discontinuation was described as “unknown,” but 5% discontinued use due to confirmed pregnancy (Berglund, 2017; Pearson, 2021a, 2021b).

The efficacy of Clue Birth Control was based on the results of the prospective Dynamic Optimal Timing clinical efficacy trial (ClinicalTrials.gov ID NCT02833922), which assessed the same proprietary algorithm as the one used in the Clue software. The study followed 718 U.S. women aged 18 to 39 over a full year (13 cycles), providing a total of 6,616 cycles. Participants had not used hormonal contraception in the previous three cycles, had consistent cycles between 20 and 40 days long with less than 10 days’ variation, and had had at least three menstrual periods following the most recent pregnancy, if applicable. There were 25 unintended pregnancies, including one that occurred during perfect use. Clue had a perfect use Pearl Index of 0.8, a 13-cycle perfect-use failure rate of 1.0% (95% confidence interval 0.9% to 2.9%), and a 13-cycle typical-use failure rate of 5.0% (3.4% to 6.6%). There were no statistical differences between the demographic variables and pregnancy status. In all, 12.8% of participants were lost to follow-up (Jennings, 2019).

Direct comparisons to other fertility-awareness methods or fertility applications designed for contraception are limited. In a cohort of 42,579 users, investigators compared the accuracy of Natural Cycles, the Standard Days Method, and the Rhythm Method for predicting the fertile window, relative to the reference standard of a positive luteinizing hormone test followed by a basal body temperature rise within one to two days. Over a 12-month cycle (16,386 total cycles), the fraction of wrong fertile days was 0.12% allocated by Natural Cycles using basal body temperature only, 0.07% by Natural Cycles using luteinizing hormone and basal body temperature measurement, and 0.93% by the Standard Days Method. Over cycles seven through 12 (9,742 total cycles), the

Rhythm Method algorithm allocated a wider fertile window but with a higher fraction of wrong fertile days (0.26%). No contraceptive failure rates were reported for comparison (Kleinschmidt, 2019).

A review of seven studies analyzed the accuracy of five fertility-tracking applications used for contraception or conception: Natural Cycles, Ava Fertility, Clearblue Connected, Ovia Fertility, and Dynamic Optimal Timing. All predicted fertility status throughout a woman's menstrual cycle using various proprietary algorithms, biometric data, and self-reported menstrual cycle data, but each varied with respect to intent (conception or contraception), platforms, required data input, and external device requirements. Details of the proprietary algorithms and the population data used to derive the algorithms were not available, making their generalizability to other populations and comparative accuracy difficult to determine (Saugar, 2023).

References

On June 6, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “menstrual cycle” (MeSH), “natural family planning methods” (MeSH), “mobile applications” (MeSH), “Natural Cycles,” “prescription digital therapeutics,” and “contraception.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

8/2024: initial review date and clinical policy effective date: 9/2024