PSI Webinar on Women's Health

Prof. Dr. Christoph Gerlinger

2024-05-15

Disclosures

// I'm a full-time employee of Bayer AG in Berlin, Germany

  // Bayer is a major drug manufacturer in women's health

// Occasionally, I work for the European Commission as paid expert evaluator of Horizon Europe research proposals

// I teach experimental gynecology at the Saarland State University as an unpaid professor

// I'm a registered lobbyist to the European Union on behalf of the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI). PSI is the UK member of EFSPI.

Clarification

// I will use the words „woman" and „man" in the biological sense, albeit

    // a trans-man with preserved uterus can menstruate and
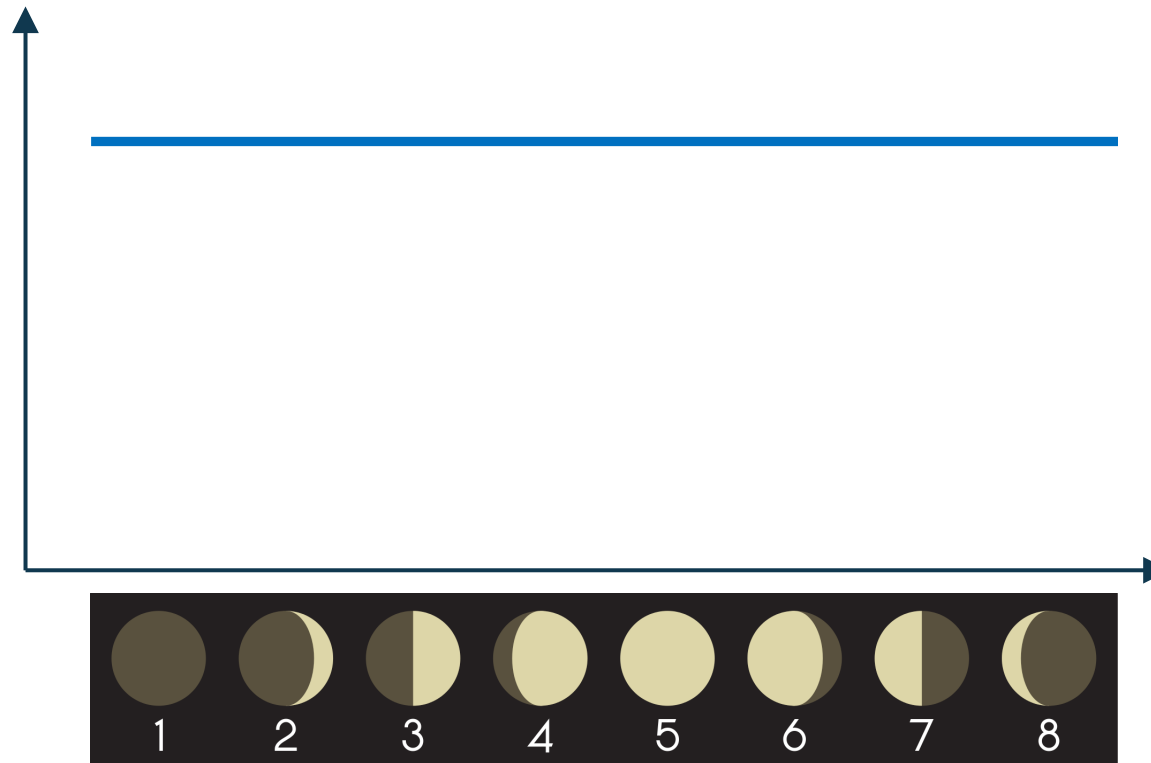
    // a trans-woman cannot.

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Agenda

// Menstrual cycle

    // Introduction for the layMEN

// Measurement of menstrual bleeding

    // Bleeding pattern

    // Measurement in ml
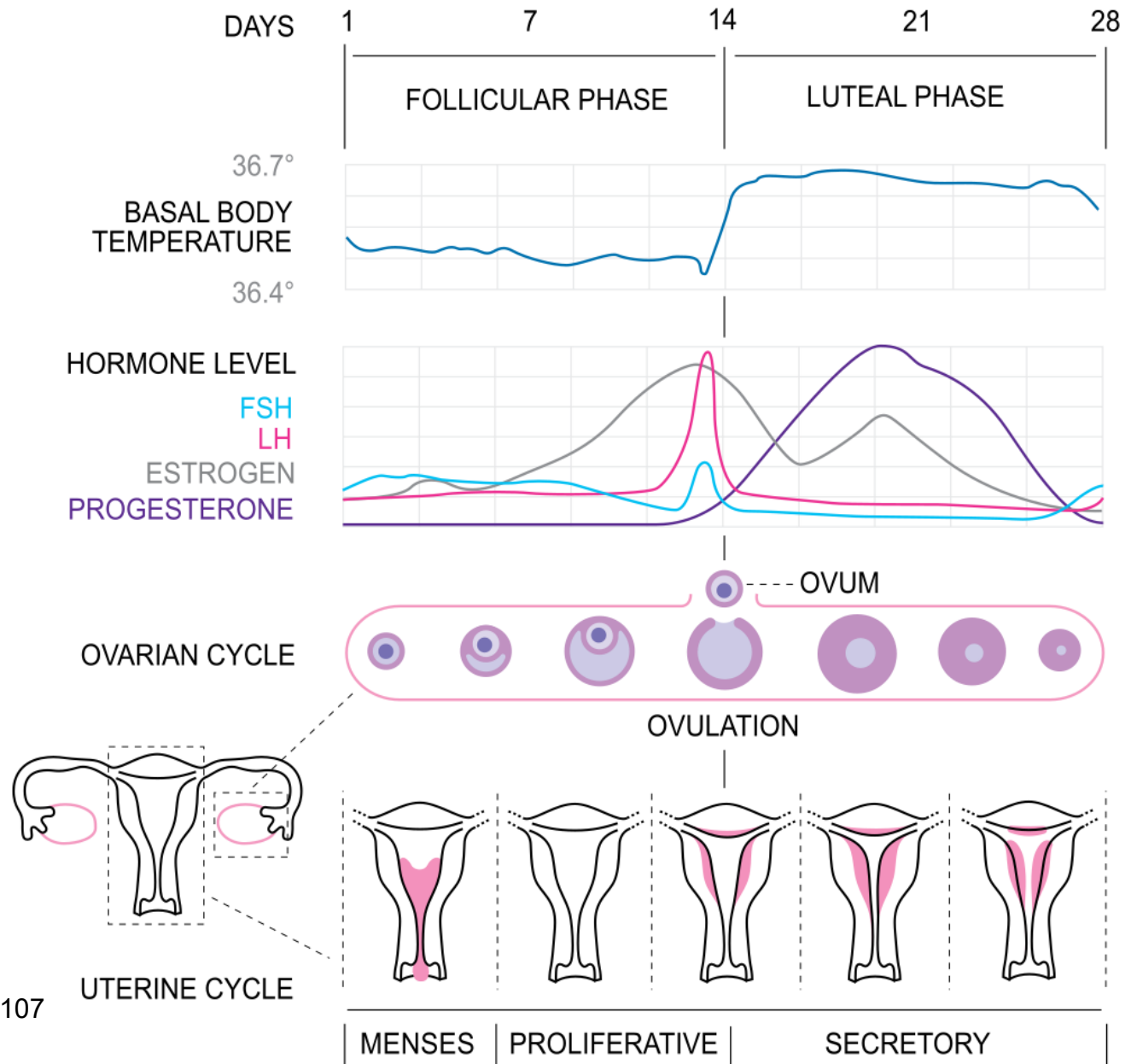
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The male „cycle"

Moon: By Pamplelune – Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4314744

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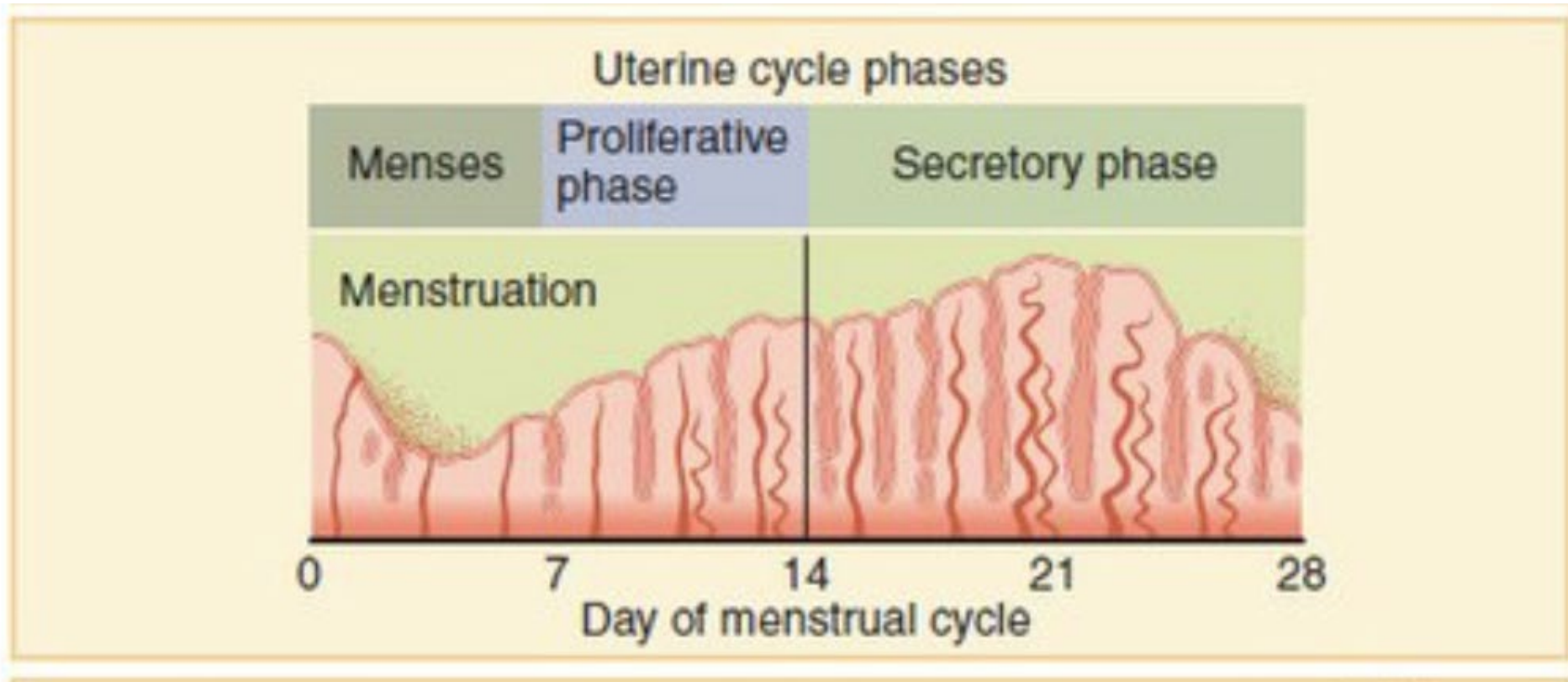# The female cycle

The menstrual cycle

Except from https://commons.wikimedia.org/wiki/File:Figure_28_02_07.jpg CC 3.0

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Menstrual health

// Fluctuating hormone levels may lead to

   // Pre-menstrual syndrome, e.g., acne, tender breasts, tiredness

   // Dysmenorrhea (menstrual cramps or period pain)

   // Fluctuations in

      // Epileptic seizure frequency

      // Endometriosis

      // Autoimmune diseases

   // Fluctuations in

      // Sportive performance

      // Cognitive performance

Other aspects of menstruation

// Menarche: first menstruation in a woman's life

// At age 10 to 14, with age going down over the years

// Menopause: last menstruation in a woman's life

// At age ~50, with no change over the years despite increasing life expectancy

// No relation to the lunar cycle

// 28 days is just the average cylce length of the average woman

// ~35 days is the average cycle length for chinmpanzees

// Menstruation occurs only in some primate, some bat, and one mouse species

Funny Ad: https://duckduckgo.com/?q=menarche&ia=web 2024-05-02

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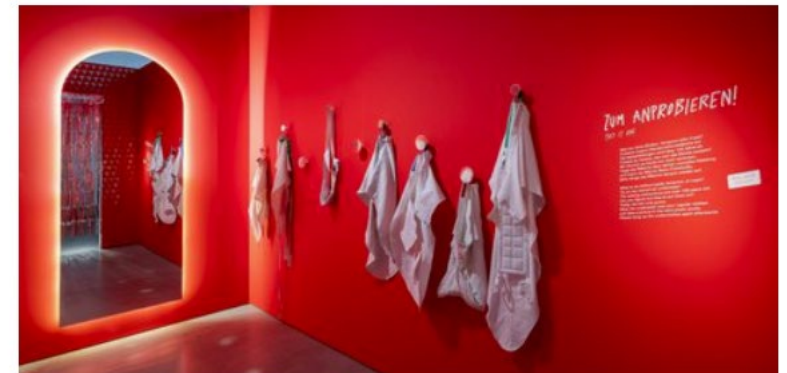
Social aspects of menstruation

Out of scope of this presentation,

See e.g.,

https://en.wikipedia.org/wiki/Culture_and_menstruation

https://www.smb.museum/en/museums-institutions/museum-europaeischer-kulturen/exhibitions/detail/flow-the-exhibition-on-menstruation/

Exhibition in Berlin until 06.10.2024

Museum Europäischer Kulturen
Flow: The Exhibition on Menstruation

Points to consider for statisticians

// Biological function may vary with the mensural cycle

// E.g., in PK studies women are often sycronized by starting treatment on the first day of mensturation

// E.g., for pain measurements 4-weekly windows are used rather than monthly windows

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Bleeding strength

// WHO definition:

  // Spotting: vaginal discharge not requiring sanitary protection (tampons, pads, etc)

  // Bleeding: vaginal discharge requiring sanitary protection

  // Note: definition is independent of actual use

// Bleeding/spotting episode

  // One or more consecutive days with bleeding/spotting bound on both ends by at least two bleedfree days

// Other definitions of bleeding strength sometimes used, e.g., no, spotting, light, moderate, severe bleeding

Bleeding pattern

// Natural cycles

    // More or less regular menses of 3-7 days every more or less 28 days

    // Main interest in prediction of next episode

// „pill" cycle

    // „cycle control" 21 days hormones + 7 days no drug designed to mimic natural cycles

    // Today also 24+4 and 26+2 regimens

// Long acting hormonal contraceptives

    // Bleeding pattern affected by constant release of low dose hormones from device plus endogenious hormones

    // Bleeding pattern much more variable, i.e., unpredictable

Prediction of bleeding pattern

// Many apps available

// Based on average cycle length

// Reliability of apps variable

// Typically, no medical device certification

// Some Apps also predict your fertile window

    // Use it if you wish to become pregnant, but
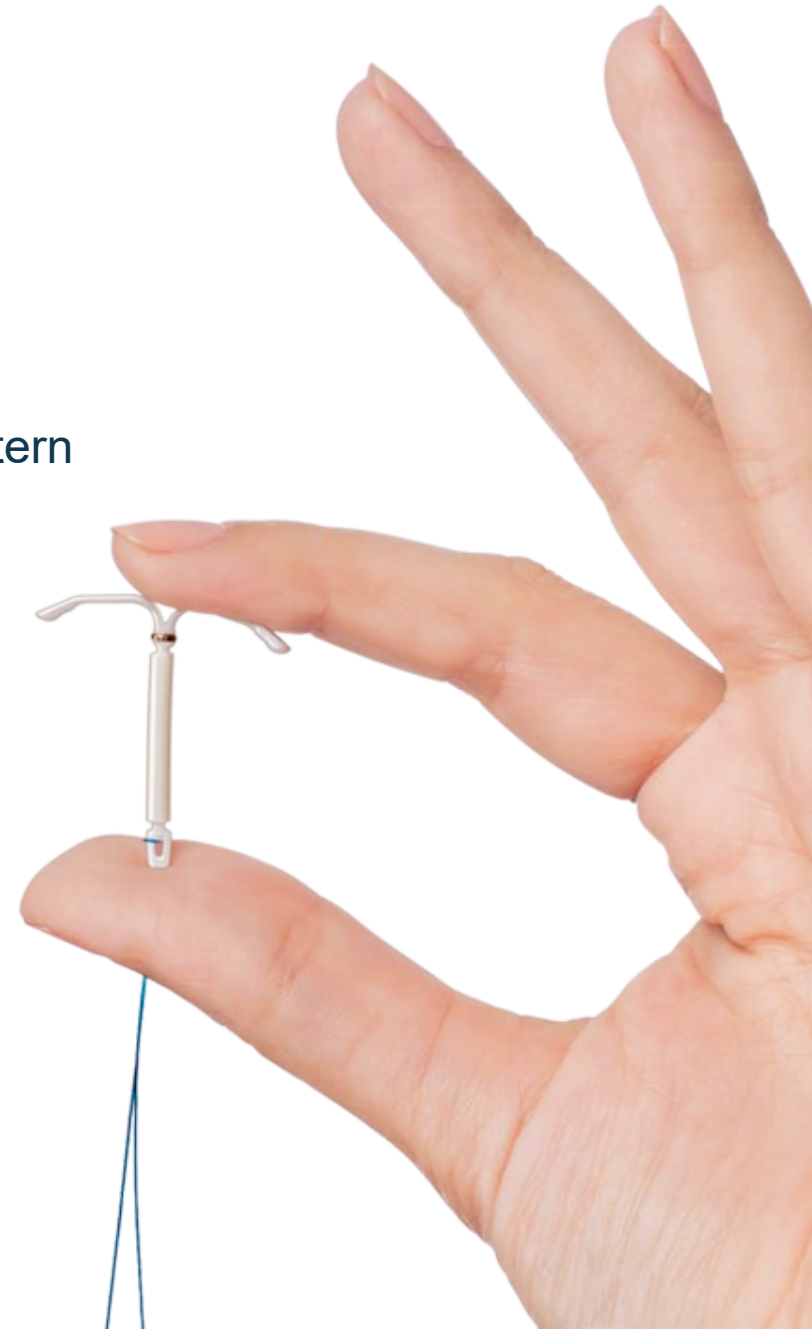
    // Never to reliably prevent pregnancy

Helloclue.com

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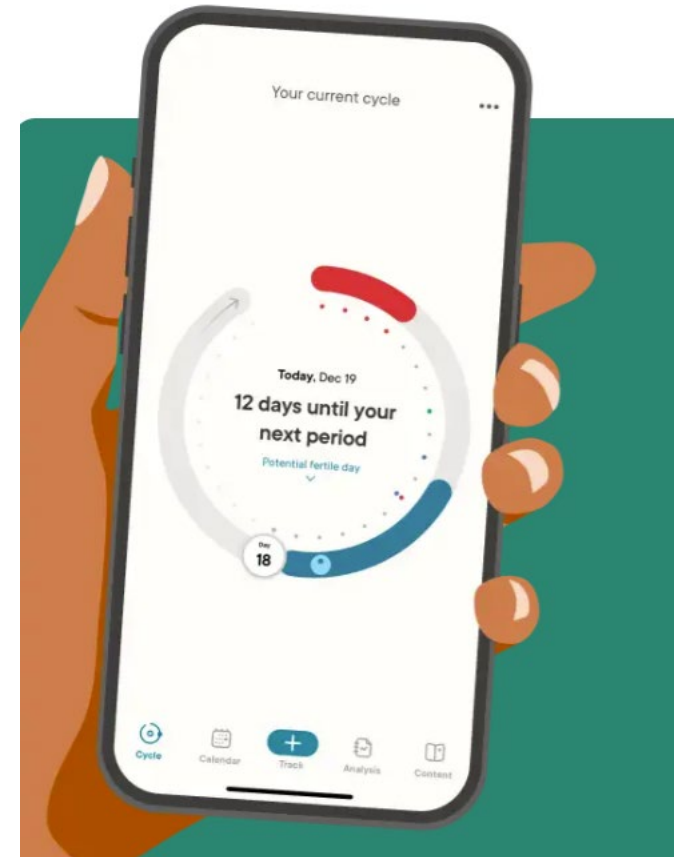
Bleeding pattern intra uterine device

// long-acting reversible contraceptive method

// hormonal influence interacts with menstrual bleeding cycle

// effect: potential alternation of previous familiar menstrual bleeding pattern

➤ unfamiliarity with "new" bleeding pattern

// after insertion: more menstrual bleeding
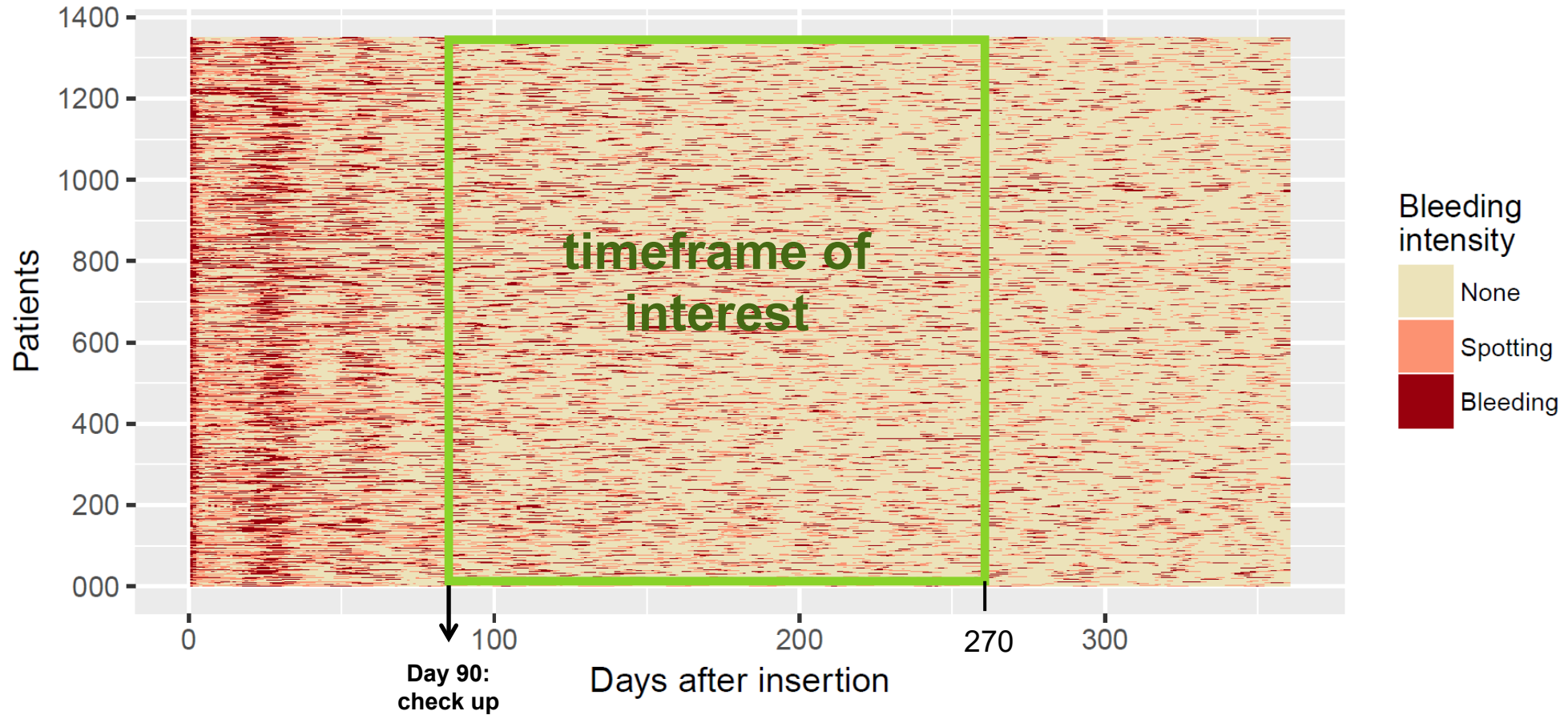
// after some time: less menstrual bleeding

// Prediction algorithm developed by Ann-Kathrin Frenz et al.

Prediction Time Frame and Information

Bleeding Diaries

timeframe of interest

Bleeding intensity
- None
- Spotting
- Bleeding

Patients

Days after insertion

Day 90: check up

270

// relevant prediction attributes: bleeding intensity & cycle regularity

Bleeding Intensity Clusters

Predominantly Amenorrhea (n=139)

Predominantly Spotting (n=478)

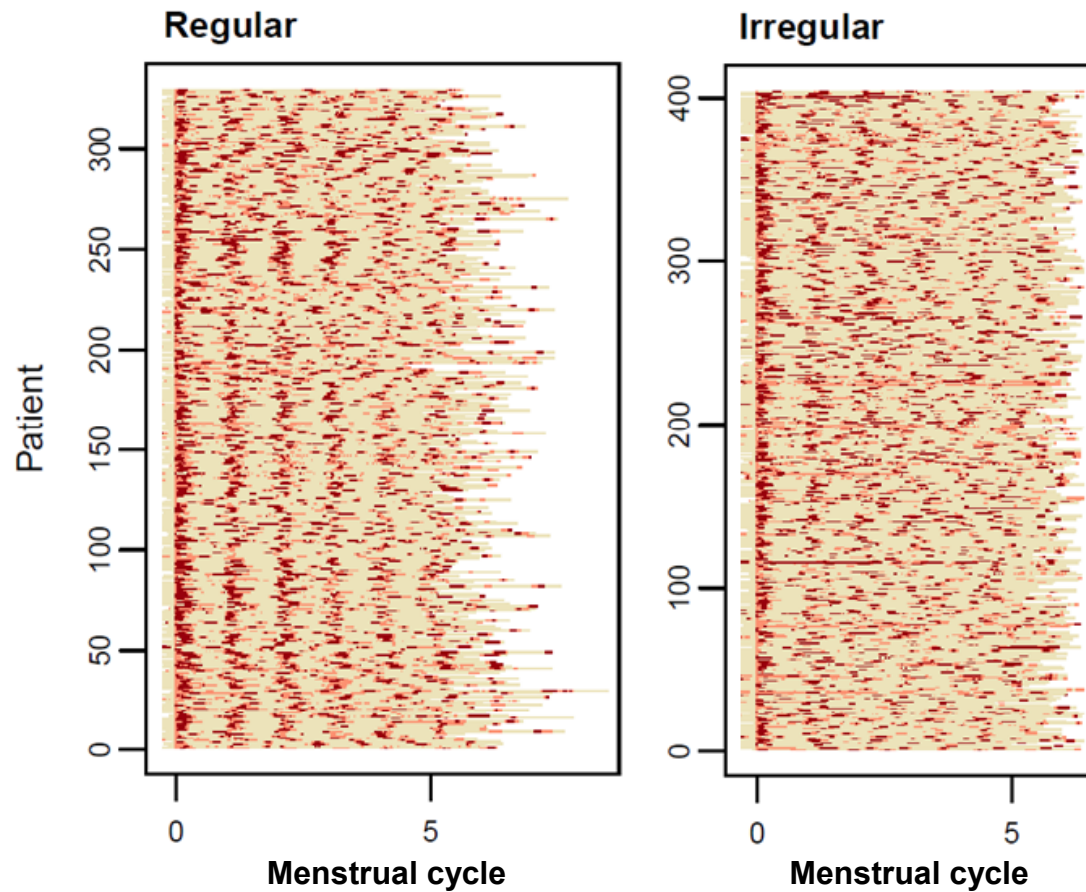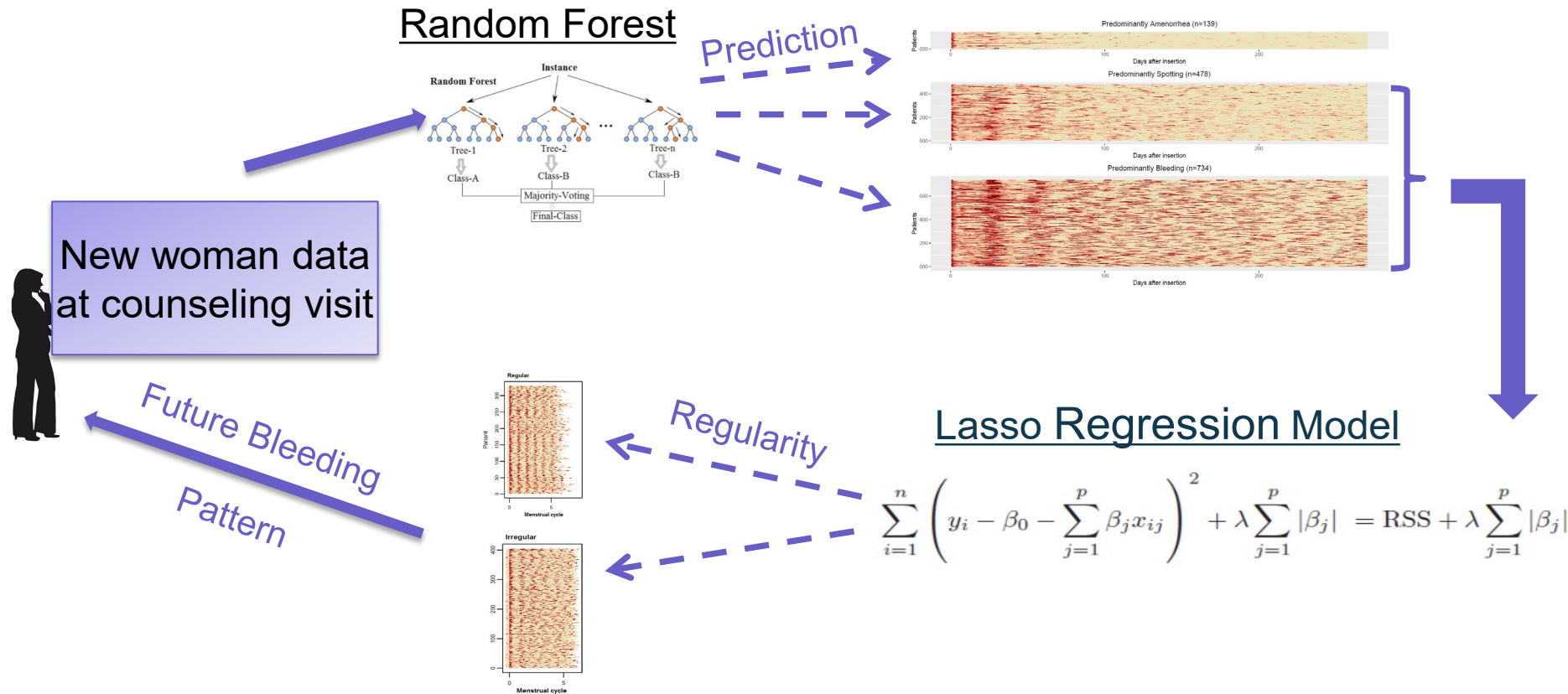Predominantly Bleeding (n=734)
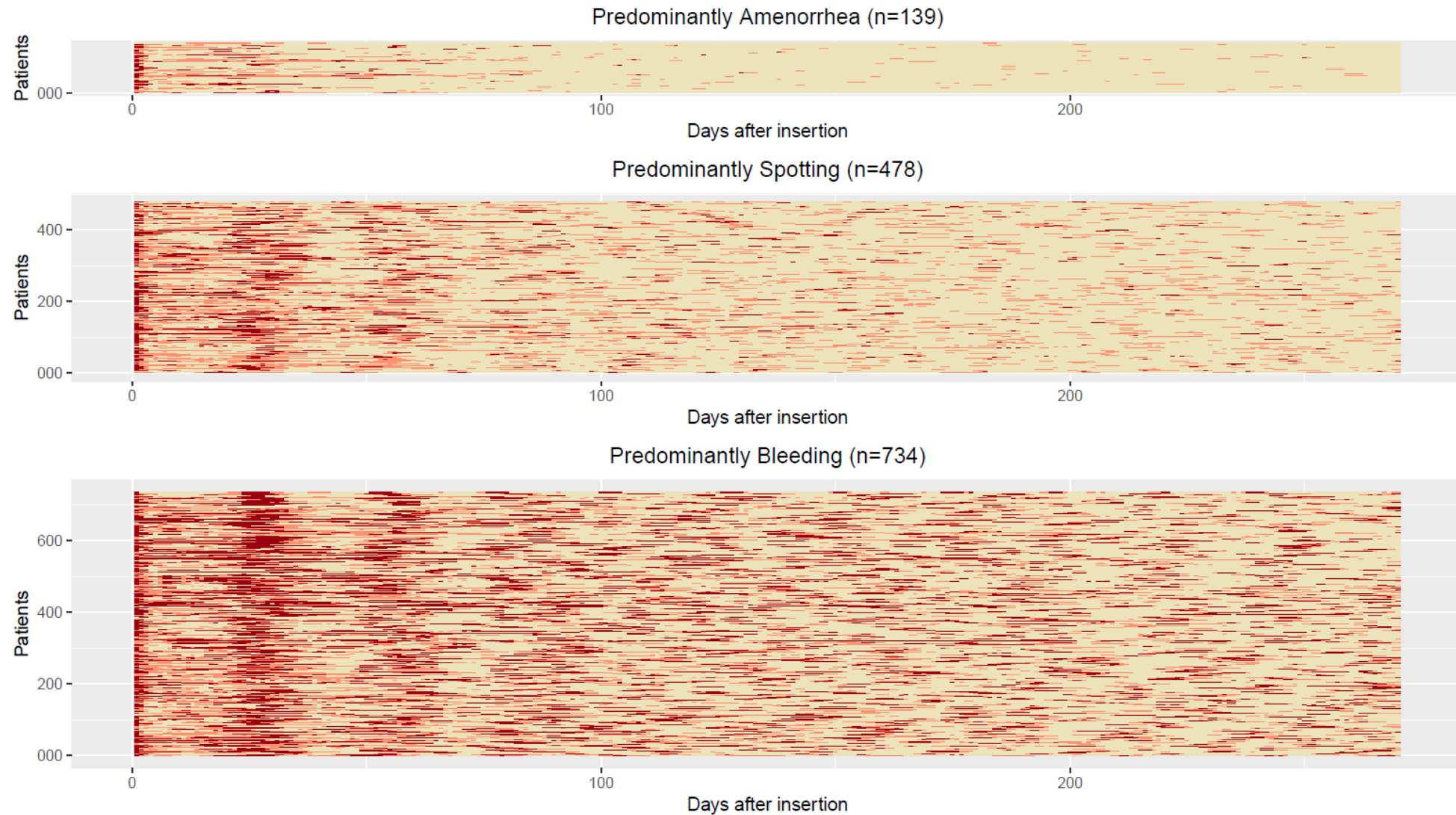
Assessment of Menstrual Cycle Regularity

// very complex due to individually varying and unknown cycle lengths of women

// state-of-the-art time series methodology to identify regularity

Artificial Intelligence Prediction Model

Random Forest

Prediction

New woman data at counseling visit

Future Bleeding Pattern

Regularity

Lasso Regression Model

$$\sum_{i=1}^{n} \left(y_i - \beta_0 - \sum_{j=1}^{p} \beta_j x_{ij} \right)^2 + \lambda \sum_{j=1}^{p} |\beta_j| = \text{RSS} + \lambda \sum_{j=1}^{p} |\beta_j|$$

// prediction of future bleeding pattern by applying data science, machine learning and state -of-the-art time series statistical methodology

Medical device app – now in an appstore near you

MyIUS – your IUS/hormonal coil companion

A certified companion to track your bleeding, predict future bleeding profile and get information around your hormonal coil (IUS).

KNOW YOUR IUS

Agenda

// Menstrual cycle

    // Introduction for the layMEN

// Measurement of menstrual bleeding

    // Bleeding pattern

    // Measurement in ml

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Volume of menstrual blood

// For some diseases it is important to measure the menstrual blood loss accurately

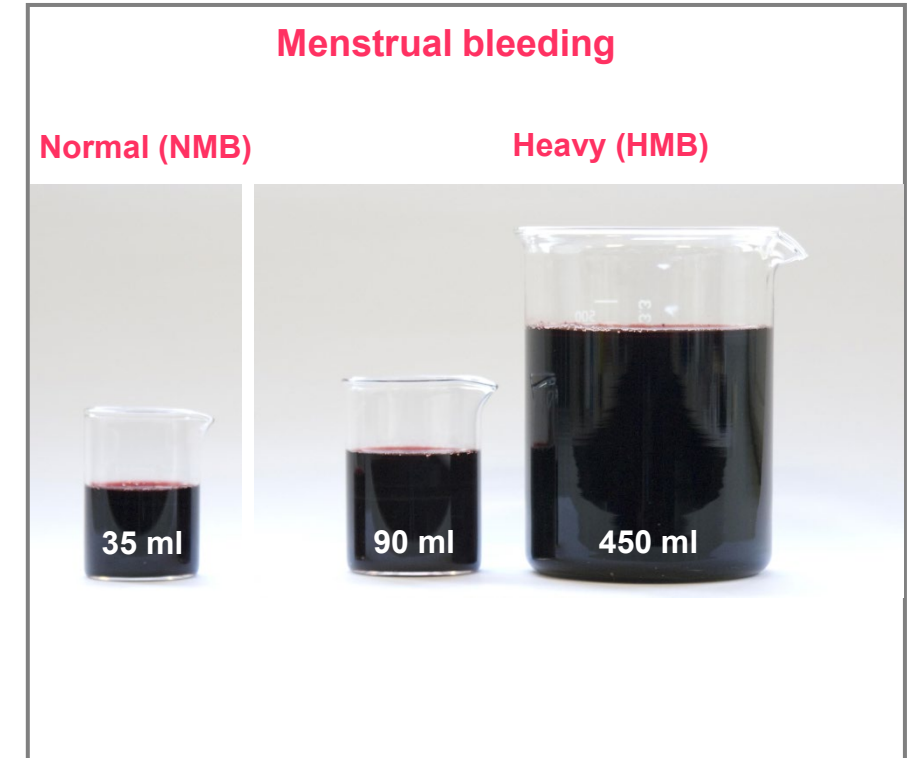 // „normal" blood loss is ~ 35 ml/cycle

  // „abnormal" menstrual blood loss is > 80 ml

// For comparison

  // „normal" ~ 1.23 imp. fl. oz. or 1 shot of liquor

 // „abnormal" ~ >2.82 imp. fl. oz. or 1 cup of tea

  // Blood donation is 470 ml or 16.5 imp. fl. oz. in the UK

Menstrual bleeding

Normal (NMB)   **Heavy (HMB)**

35 ml   90 ml   450 ml

https://www.blood.co.uk/the-donation-process/what-happens-on-the-day/

Gold standard measurement of menstrual blood loss

// All used sanitary items in a cycle are collected and shipped to the laboratory (in cooling bags!)

// Not perfect as, e.g., blood loss while showering is missed

// Blood content is determined by the alkaline-hematin method

// Rather cumbersome for the woman and rather expensive
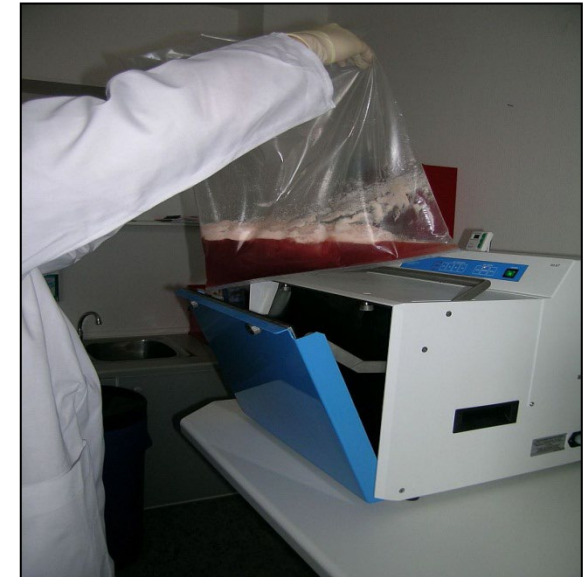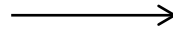
// Need a simpler method for clinical practice and for pragmatic trials

How to make it simpler?

// First idea: menstrual cup

// Only some 20% of removals without spilling

// Second idea: measure weight of used sanitary items

// Variation in weight of unused items

// Weight also affected by, e.g., sweating

// Third idea: Pictogramm

Witchbox -Own work
https://en.wikipedia.org/wiki/Menstrual_cup#/media/File:%D0%9C%D0%B5%D0%BD%D1%81%D1%82%D1%80%D1%83%D0%B0%D0%BB%D1%8C%D0
%BD%D1%8B%D0%B9_%D0%B4%D0%B8%D1%81%D0%BA_%D0%B8_%D0%BC%D0%B5%D0%BD%D1%81%D1%82%D1%80%D1%83%D0%B0%D
0%BB%D1%8C%D0%BD%D0%B0%D1%8F_%D1%87%D0%B0%D1%88%D0%B0_(cropped).jpg CC BY-SA 4.0

Pictogram

// A woman compares each used product to the icons

// Each icon has a value in ml attached

// Easy to use

// Challenges:

  // Different products (brands) show different stains for the same blood volume

  // How to determine the ml per icon?

  // How to validate the pictogram results?
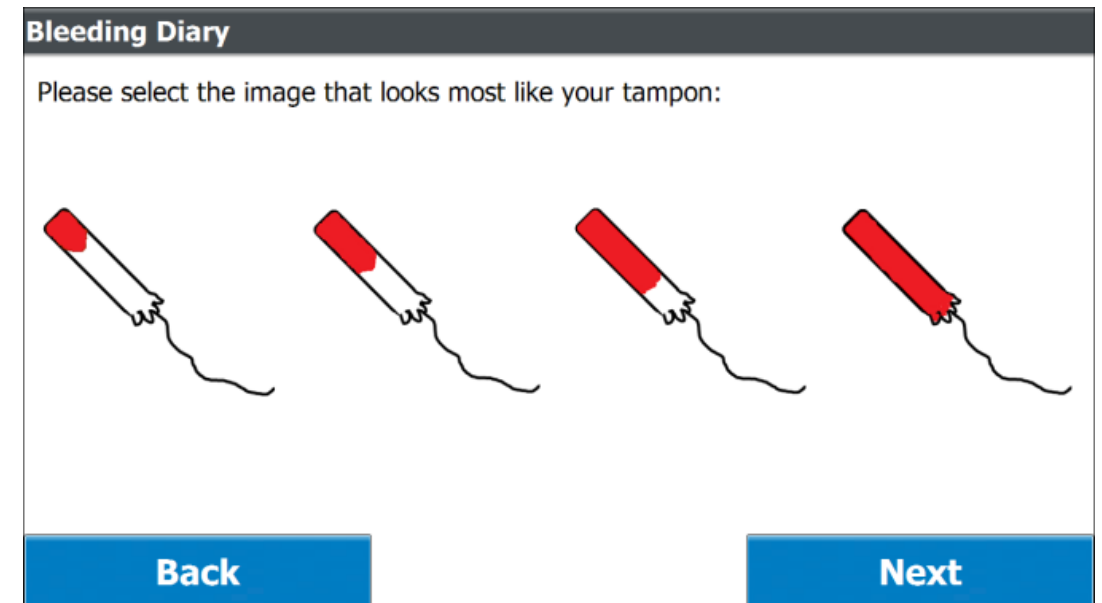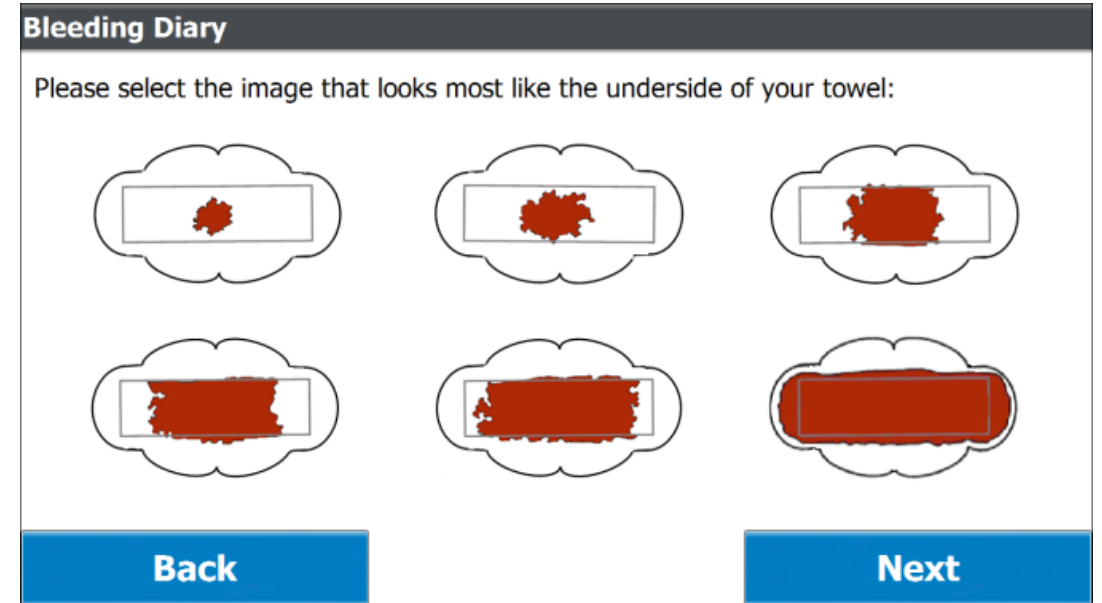
Pictogram – 2

// Long history of different pictograms and their validation vs. alkaline-hematin method

// Need to re-do the work with new sanitary items!!

// When we started our program, there was a validated pictogram available,

// but the products were no longer on sale.

Magnay et al. BMC Women's Health (2018) 18:142
https://doi.org/10.1186/s12905-018-0627-8

BMC Women's Health

RESEARCH ARTICLE   **Open Access**

A systematic review of methods to measure menstrual blood loss

Julia L. Magnay[1], Shaughn O'Brien[1,2], Christoph Gerlinger[3,4] and Christian Seitz[3*]

Pictogram – 3

// Our pictogram was validated, especially for the detection of excessive bleeding (> 80ml)

Schumacher *et al.* BMC Women's Health 2012, **12**:24
http://www.biomedcentral.com/1472-6874/12/24

Table 5 Comparison of assessment of bleeding episodes as excessive

Classification according estimated MBLV	Classification according measured MBLV		Total
	Excessive	**Not excessive**	
excessive	380 (58.6%)	64 (9.9%)	444 (68.5%)
	87.4% of excessive	30.0% of not excessive	
not excessive	55 (8.5%)	149 (23.0%)	204 (31.5%)
	12.6% of excessive	69.9% of not excessive	
Total	435 (67.1%)	213 (32.9%)	648 (100%)

(n = 648 episodes; excessive means Sum MBLV of episode > 80 ml).

Haberland *et al. Journal of Patient-Reported Outcomes* (2020) 4:97
https://doi.org/10.1186/s41687-020-00263-0

Journal of Patient-Reported Outcomes

RESEARCH   **Open Access**

Validation of a menstrual pictogram and a daily bleeding diary for assessment of uterine fibroid treatment efficacy in clinical studies

Claudia Haberland[1*], Anna Filonenko[2], Christian Seitz[3], Matthias Börner[4], Christoph Gerlinger[5,6], Helen Doll[7,8] and Dorothea Wessiepe[9]

Recommended reading

// Amelia C. L. Mackenzie, et al.
   Consensus recommendations for measuring the impact of contraception on the menstrual cycle in
   contraceptive clinical trials
   medRxiv 2024.04.04.24305350; doi: https://doi.org/10.1101/2024.04.04.24305350

// Frenz AK, Ahlers C, Beckert V, Gerlinger C, Friede T.
   Predicting menstrual bleeding patterns with levonorgestrel-releasing intrauterine systems.
   Eur J Contracept Reprod Health Care. 2021 Feb;26(1):48-57. doi: 10.1080/13625187.2020.1843015

// All cited URLs were accessed between 2024-05-02 and 2024-05-15