Best Practices for Digital Health Outcomes

GOALS

The goals of this subgroup are to recommend: 1) Best practices for choice of connected sensor technology (digital technology) for digital health outcome measures for clinical research on Parkinson's Disease (PD) and 2) Guidance for Digital Data Sharing for clinical trials on PD. Connected sensor technologies use sensors, computing platforms, connectivity, and algorithms to measure clinical signs, behaviors, and events for clinical research. Outcomes generated by connected sensor technologies in this report include measures derived from prescribed activities/tests (e.g., PD signs during the UPDRS III or gait metrics from a 6-minute walk test) or unprescribed health behaviors during activities of daily living (e.g., PD signs, gait, sleep, heart rate variability, activity levels, etc.). These practices and guidance do not include electronically-collected, patient-reported outcomes about self-perceived feelings, observations, judgements (e.g., quality of life, medication or sleep diaries, etc.) or clinician-reported outcomes about signs and symptoms (clinical rating scales, etc.) that do not rely upon sensors for data generation.

BACKGROUND

At this time, all digital health outcomes for PD clinical intervention trials are generally considered EXPLORATORY. Although there is growing evidence that connected sensor technology can provide more accurate and reliable outcomes for PD compared to current clinical standards, the specific technologies (devices and algorithms) for measuring digital health outcomes are changing and improving rapidly. In addition, although desired digital health outcomes related to the specific signs and symptoms of PD are well known (see other Common Data Element Guidance Document for PD), outcomes related to the impact PD has on daily life are just starting to be understood. Digital measurement products are quickly being developed to measure many of these outcomes in ways that have not been possible before; either because the outcome was impossible to measure with existing tools or because the technology has enabled greater precision and resolution than existing clinician or patient-reported scales. The performance (accuracy, precision, reliability, etc.) and feasibility of a particular connected sensor technology outcome depends to a large extent on the particular hardware and software used to collect the data and these technologies are changing and improving so rapidly. As a result, digital outcomes for PD are currently in the exploratory stage.

A number of important recommendations have recently been published regarding the types of evidentiary evaluations to make when considering digital technologies for interventional clinical trials (Badawy et al., 2019; Digital Medicine Society, 2021; Espay et al., 2012; FDA, 2009; FDA, 2016; FDA, 2021; Goldsack et al., 2020; Manta et al., 2020; Manta et al., 2021; Stevenson et al., 2020; Walton et al., 2020). These recommendations apply also to studies in PD and begin with the identification of a critical unmet measurement need. The unmet need must be linked to a meaningful aspect of health for people living with PD and may represent either an existing gap in measurement capability or the recognition of an opportunity for improved measurement properties through the use of technology (e.g., by enabling higher assessment frequency, lower participant burden through remote assessment, or better measurement resolution; Espay et al., 2016; Manta et al., 2020).

The use of connected sensor technology for study outcomes has many advantages and several risks. A major advantage of connected sensor technology for clinical research in PD is the improved accuracy, resolution, sensitivity/specificity, and reliability of digital outcomes compared to traditional clinical rating scales or patient-reported outcomes. Another advantage is the

potential to transmit data captured remotely directly to investigators. This increases opportunities for more patients to participate in clinical trials without the burden of traveling to the trial site. Remote data collection during daily life also allows for more frequent, and even continuous, data collection unlike intermittent trial visits that may occur on a "good day" or "bad day". Measuring how people function in daily life can provide a clearer picture of what people actually do in their natural environments (e.g., home, community, work) without the 'white coat' effects of measuring people's potential ability under a particular set of instructions in a supervised environment.

Risks of using sensor technology for research outcomes includes clinical risks, accuracy risks and privacy-related risks. Investigators should evaluate risk of injury or discomfort with use of technology for their particular cohort (e.g., skin irritation, interrupted sleep, infection from reuse, etc.) with evidence of safety tested by the technology manufacturer. Accuracy risk can be associated with difficulty validating outcomes collected remotely in unknown contexts, such as abnormal measures of tremor, bradykinesia, or gait when subjects wear sensors while riding in a car or using a stationary bike. Accuracy can also be complicated by independent use of technology, such as when a subject wears a body-worn, inertial sensor too loosely or fails to charge or obstruct sensors. Cybersecurity risks could impact patient privacy depending on how safely data is stored and transmitted.

Investigators are encouraged to use connected sensor technology as exploratory outcomes in their investigational trials in order to improve our understanding of their feasibility and usefulness. If the purpose of a clinical study is to validate digital health outcomes for future studies, such as to determine their validity, reliability, and sensitivity to change, then they can be used as primary or secondary outcomes. Whether used as primary, secondary, or exploratory outcomes, digital health outcomes from connected sensor technology should include evidence of technical verification, analytic validation, and clinical validation for their particular research purpose (Goldsack et al., 2020). Technical verification is evidence that the sample-level sensor output is correct when measured against the appropriate standard (e.g., accelerometry is evaluated against gravity) and of suitable resolution for the algorithm and outcome (e.g., sampling frequency). Analytical validation evaluates the performance of an algorithm to convert sensor outputs into physiological metrics using a defined data capture protocol in a specific PD participant population. Critically, analytical validation should be conducted in a representative sample of the specific PD subject population to ensure that the algorithm performs equally well across all intended users of the technology. Clinical validation evaluates whether the physiological metric acceptably identifies, measures, or predicts a meaningful clinical, biological, physical state, functional state, or experience, in the specific context of use and specific PD population. Clinical validation also determines statistical parameters, such as minimally clinical important difference (MCID).

This digital health guidance document for PD research addresses the following topics:

- Types of digital health products: Active (Prescribed or Prompted) and Passive (Unprescribed or Unprompted)
- Validation of Digital Medical Products: Sensor Technology, Algorithms, and Outcomes
- Reporting digital health outcomes in research
- Recommended digital health outcomes for PD

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- Considerations on use of connected sensor technology for research in PD
- Emerging digital outcomes for PD in need of further development

TYPES OF DIGITAL OUTCOMES

Digital outcomes can be divided into two main types of measures: *Active Monitoring* and *Passive Monitoring*. Active Monitoring provides digital measures as outcomes of prescribed or prompted tasks, either supervised in a clinic or laboratory or unsupervised/supervised remotely at home (e.g., quantifying bradykinesia based on the speed and amplitude of a rapid alternating forearm rotation task or quantifying postural sway in standing). Active Monitoring also includes protocols in which the digital outcomes come from prescribed tests that patients perform independently at home or perform at home while supervised with virtual or actual meetings with test administrators.

In contrast to prescribed tasks/tests, *Passive Monitoring* is designed to be used (ideally, unobtrusively) in daily life, during normal activities of daily living that are not supervised or influenced by the presence of an observer. For example, the speed of walking down a particular hallway or transitions between rooms in a patient's home can be captured with in home-mounted or body-worn sensors and sleep quality can be estimated from pressure sensors under a mattress (Wu, 2021). The increased availability of connected sensor technology for medicine and consumers is transforming clinical research and medical care outcomes from occasional, clinical tests to longitudinal monitoring in real-work contexts. *Active Monitoring* during prescribed tests often provides digital outcomes related to what a patient CAN do (ability) when instructed and observed, whereas passive monitoring of unprescribed activities provides outcomes related to what a patient actually DOES (performance). However, active monitoring during some prescribed tests (e.g., standing for 30 seconds to measure postural sway or sitting to measure breathing) may also measure actual performance and not ability, although there is some risk that even automatic behaviors can be influenced by the specific instructions, the clinical/laboratory context or by the observation of professionals.

Whichever type of monitoring a clinical trial uses as an outcome, it should be consistent for the entire trial, if possible, because the same outcome will likely differ when collected actively during a prescribed and/or supervised task than when collected passively, over longer periods of time during daily life. For example, studies have shown that the same outcomes (e.g., gait speed, tremor, bradykinesia, etc.) collected during a prescribed test versus during daily life often produce different results in the same patients (Shah et al., 2020). For example, gait speed is significantly slower when monitoring passively at home (averaged over a week of normal walking) than during prescribed walking tests (25 foot, 2-minute or 6-minute walks) when supervised in people with PD (although not necessarily with people who have other neurological disorders; Shah et al., 2020).

VALIDATION OF DIGITAL MEASUREMENT PRODUCTS

Digital measurement products include three main components: *sensor technology* (hardware), *algorithms* (software that transforms sensor generated signals into clinically interpretable data or outcomes) and *outcome*s (meaningful measures for clinical trials based on measurable

characteristics affected by an individual's PD or by an intervention). Each component is critical for end-to-end validity and reproducibility of data.

Sensor technology: Some digital measurement products use medical devices that have been approved by the FDA (510K clearance or de novo documentation) for specific context of use and validated for technical accuracy, reliability, and sensitivity to PD. Recently, however, connected sensor technology also includes general purpose, commercial devices (phones, tablets, cameras, etc.) to measure how people move, behave, think, etc. and was not originally intended to use for outcomes for clinical research (FDA, 2021). Most new digital health outcomes from new technologies have not, yet, been fully validated for use in people with PD. Investigators using new technologies to collect data for clinical trials, need to provide evidence that these unvetted devices have the accuracy, reliability, and sensitivity to PD needed so that other studies can reproduce their results. For example, many consumer pedometers, designed to record step counts in young healthy people, likely do not provide accurate information about step counts in people with PD who have shuffling and freezing gait disorders, so additional validation is required. Thus, investigators should first complete technical verification and validate the clinical accuracy of a particular digital outcome for their study of people with PD. Since different devices likely will have different accuracy, resolution, etc. that can affect outcomes, the same device should be used throughout a clinical trial, if possible. If different sensor technologies are needed across the duration of a trial, the sensor technology needs to be verified that it generates sample level data that meets the specifications of the algorithm and comparisons should be made of usability across different devices (e.g., the effects of using different attachment fabrics for wearable devices).

Algorithms: Connected sensor technology use algorithms to translate raw data into patient characteristics or events for clinical investigations. Algorithms for connected sensor technology can be embedded in the hardware/firmware as well as within the code, in computers/tablets /phone/servers used to collect the signals and translate them into meaningful outcomes. Software applications for algorithms can run on general-purpose computing platforms (e.g., phone, laptops, etc.) or on dedicated use devices (e.g., glucose monitoring device, smart pill, etc.). Not all algorithms produce accurate outcomes, and it is unlikely that two different algorithms will produce exactly the same outcomes. For example, the same gait measures (speed, stride length, etc.) may not be identical when measured in the same patient from two different mobile technologies placed in the same position on the body, because different algorithmic decisions (filtering, thresholding, sampling, definition of gait bouts, etc.) affect the outcomes. We recognize that some studies may use proprietary algorithms or machine learning models whose details cannot be shared (Loh, 2021). However, even when the algorithms or models are used as a black box, the details of the validation data and the validation procedure should be clear so that the results of the study can be reproduced using the same 'black box'. Thus, investigators should consistently use the same digital technology algorithms throughout a clinical trial and report enough information about the technology, so the results are reproduceable.

Outcomes: Outcomes can be either, or both, biomarkers and clinical outcome assessments (COAs) of performance. The usefulness of digital health outcomes in clinical trials depends upon several important statistical criteria. However, the relative importance of each criteria (below) needs to be weighted by investigators, depending on the goal and type of clinical trial. Decisions on which, specific outcome to select out of many potential digital outcomes should

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depend upon achieving the best statistical criteria, but it is likely that not one, single outcome will be superior to others. In that case, a combined, composite, digital score may improve overall performance. For example, a weighted sum of stride length, arm swing, and stride time variability may greatly improve performance of a "PD Gait Score" over any individual metric in discriminating people with PD from healthy controls in the clinic. When composite scores are used as digital outcomes, the details of how the score was derived should be included for other trials to reproduce. Statistical criteria for high quality, useful digital outcomes from connected sensor technology includes the following:

- *Technical verification*: accurate compared to laboratory gold standards (if applicable)
- *Sensitivity/Specificity to group*: Area Under Curve (AUC) of Receiver Operating Characteristics (ROC) versus age and sex-matched control subjects
- *Sensitive/Specific to mild or prodromal disease*: AUC of ROC
- *Clinical validity*: correlated with Movement Disorders Society United Parkinson Rating Scale (MDS-UPDRS) or other clinical evaluations of disease severity
- *Meaningfulness to patients*: correlated with Patient-Reported Outcomes (PRO); related to fall risk, hospitalizations, mortality, etc.
- *Construct validity:* correlated with physiological biomarkers
- *Sensitivity to change or progression:* if therapeutic goal is to slow progression
- *Sensitivity to motor fluctuations:* if therapeutic goal is to reduce fluctuations
- *Responsiveness:* to existing interventions (levodopa, agonists, etc.)
- *Effect size:* improvement compared to current, clinical primary outcomes
- *Reliability:* test-retest, inter-rater
- *Minimal Detectable Change (MDC):* how much the digital score needs to change to statistically detect a significant difference
- *Minimal Clinical Important Difference (MCID)*: how much the digital score needs to change for the patient with PD to notice a minimal difference

Useful and meaningful digital health outcome measures may depend upon the state/severity of PD. For example, in premanifest stage, digital health outcomes that measure physiological processes, such as heart rate variability or sleep disorder, may be very useful, although undetectable (and therefore not meaningful) to patients. In contrast, a useful digital health outcome in the early stage of manifest PD, prior to taking antiparkinson medication, may measure subtle, early signs such as tremor, bradykinesia, or gait quality (such as asymmetrical arm swing). Later in the disease, motor fluctuations related to dopaminergic medication, number of falls, and severity/frequency of freezing of gait may be more useful and meaningful to patients.

Clinical validation of outcomes is contingent on context of use, which includes setting (home, clinic, hospital room, work, outdoors, driving, etc.), active (prescribed) tasks or passive (unprescribed) activities, the particular patient population (newly diagnosed, experiencing freezing of gait), etc. Researchers should clearly state the context in which the digital measures they are developing have been validated. In addition, if researchers are selecting a digital measure that has yet to be validated in their context, they may need to perform their own clinical validation in this new context, although full technical verification and analytic validation may not be necessary.

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REPORTING DIGITAL HEALTH OUTCOMES FOR RESEARCH

All studies using digital health outcomes should at least report (see Manta et al., 2021 for details and Daneault et al., 2021 for example):

- Study design, power analysis, and sampling periods
- Gaps in the literature
- Study size (recruitment criteria, number of groups and individuals/group), indicating how it was assessed
- Ethics and Informed Consent (excluding verification studies)
- Participant flow (CONSORT diagram)
- Diagnosis criteria and severity grade, indicating how it was assessed
- Demographic and clinical data of participants
- Variables and outcome measures studied, statistical methods
- Specific for digital health outcomes:
  - Title or keywords: identify the study as proof of concept, verification, analytical validation, clinical validation, and/or utility and usability
  - State why connected sensor technology was chosen for the study
  - Setting (e.g., in clinic, laboratory, home, hospital, workplace, etc., since this can influence outcomes)
  - Description or publication of novel algorithms to allow reproducibility of results
  - Indicate testing periods (e.g., reference to antiparkinson medication)
  - Make and model of connected sensor technology and describe if the technology is a custom prototype or a product currently on the market
  - Sensor modalities (e.g., accelerometers, gyroscopes, touch screens, pressure, etc.) and sample-level data characteristics (e.g., units, sampling rate, etc.) used for data collection
  - Form factor (physical shape) and wear location (precise anatomic or environmental position) of devices
  - Software: Signal processing to translate from raw data to clinical outcome; description of the algorithm used to derive outcome and data analysis used for the study; version number and manufacturer of software for data collection and analysis
  - How outcome was derived (e.g., average, 95th percentile, excluding short gait bouts)
  - Data collection protocol and procedures
  - Training for staff and participants
  - Numbers analyzed and how the missing data was treated
  - Technical problems, utility, and usability
  - Intended use of outcome (e.g., diagnosis, prognosis, monitoring/treatment effect)
  - Feedback from participants and/or staff on technology, if relevant
  - Limitations of the connected sensor technology used

This checklist is a short summary from: The EVIDENCE (EValuatIng connecteD sENsor teChnologiEs) checklist that was developed by a multidisciplinary group of content experts from the Digital Medicine Society, representing the clinical sciences, data management, technology development, and biostatistics. The aim of EVIDENCE is to promote high quality reporting in studies in which the primary objective is an evaluation of the usefulness of a digital measurement product (Manta et al., 2021).

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RECOMMENDED DIGITAL OUTCOMES FOR PD

Based on available evidence to date, we recommend four digital outcomes for which a variety of technology solutions have been developed and tested in people with PD. However, in light of the complex and dynamic landscape of technology solutions available, it is currently not possible to recommend specific technology products as the "best" to quantify particular digital health outcomes. The majority of evidence for the following outcomes come from inertial sensors worn on the body during prescribed tests, although a growing number of studies are also investigating the clinical validity of these outcomes when used passively, during daily life. Evidence of accurately measuring parkinsonian gait, balance, bradykinesia, and tremor during daily life is evolving rapidly but they are difficult to validate because of lack of accurate gold-standards and because consensus has not been reached about the best practices, technologies, analysis or digital outcomes for these important signs of Parkinsonism during unprescribed activities of daily living (Garcia-Agundez et al., 2021).

GAIT: The digital outcomes with the most evidence for parkinsonian **gait disorders,** with demonstrated usefulness for clinical trials, include (Peterson, 2016; Brognara, 2019; Salarian, 2009):

- Stride length (meters)
- Arm swing range of motion (degrees)
- Angle of foot at heel contact (shuffling)
- Turn velocity (or number of steps to turn 180 degrees or 360 degrees; cm/sec)
- Trunk range of motion (degrees)
- Stride time (duration) variability (SD or CoV).

BALANCE: The digital outcomes with the most evidence for quantifying **postural control disorders** in PD using wearable sensors, feasible for clinical trials include (Mancini et al, 2020; Hasegawa et al, 2019; Hasegawa et al, 2021):

- Anticipatory Postural Adjustments (APAs) prior to step initiation (e.g., peak lateral and anterior acceleration of the trunk (L2) prior to first step)
- Postural Sway during stance (e.g., root mean square or jerk of horizontal trunk acceleration during at least 30 seconds of quiet stance on firm or foam surface, eyes open)
- Postural Responses (APRs) (e.g., first step length or height or time to achieve equilibrium after an external perturbation such as release of body lean)
- Limits of Stability (e.g., how far a subject can voluntarily lean forwards, backwards or sideways without taking a step).

BRADYKINESIA: Slowness of movements during prescribed tests, such as arm rotations, finger tapping, leg and foot tapping, etc. can be accurately measured with body-worn, inertial sensors (Gao et al., 2018).

TREMOR: Inertial sensors on the wrist or some non-attached sensors can accurately measure the amplitude and frequency (and duration/fluctuations in daily life) of resting tremor in the forearms of people with PD. However, tremor at rest (pill-rolling) associated with PD may be

most severe distally so the most sensitive measures of tremor may come from more distal technologies worn on the fingers (Vivar et al., 2019).

CONSIDERATIONS FOR USE OF CONNECTED SENSOR TECHNOLOGY FOR RESEARCH

Not all digital measurement products used to evaluate outcomes have the same quality control technical verification. Before using novel digital measurement products for clinical trial outcomes, researchers should document the manufacturer's published technical verification and demonstrate clinical validation for their PD population. Some consumer connected devices do not have high standards for technical verification on accuracy of sensors under a variety of conditions (like temperature changes). In addition, not all algorithms that transform sensor signals into usable outcomes have been developed for and tested for patients with disorders like PD. Therefore, they may not provide valid, accurate information if developed and tested only on young, healthy adults. Thus, investigators should take into account this issue and mitigate it in their study (i.e., include a control group to determine the sensitivity and specificity for PD).

Body-worn inertial sensors need to be securely attached to the body. Sensors used to measure abnormal movement quality (gait) or clinical signs (tremor) need to be firmly, yet comfortably, attached to the body to reduce extraneous noise. For example, sensors that are carried in a pocket or too loosely attached to the body will detect changes in accelerations and velocities unrelated to changes in actual body movements, resulting in inaccurate outcomes.

Position of body-worn sensors is critical. If parkinsonian gait disorders are to be quantified, sensors located on the feet, or at least on the ankles, will provide the most accurate data about foot motion. Important characteristics of PD gait include short strides, lack of dorsiflexion of the foot, long double support time, and excessive variability of stride time (Peterson et al., 2016). A change in orientation of the feet in space while walking can accurately calculate all of these metrics from feet-worn inertial measurement units (IMUs), whereas other body placements may not (Schlachetzki et al., 2017). Wrist-worn and waist-worn inertial sensors may be able to accurately measure a few gait quantity (e.g., steps per day) and quality (e.g., regularity) metrics if trained based on foot sensors on the same cohort (Keren et al., 2021) or if novel gait metrics are developed (Raykov et al., 2021).

Actigraphy does not measure quality of gait. PD causes stereotyped gait disorders (shuffling, short strides, slow turns, lack of arm swing, etc.) that can be accurately measured with body-worn IMUs on the feet or lower legs and arms. In contrast, actigraphy worn on the wrist, waist, or legs can measure whether and how much a person walks or is active versus sedentary, so it measures quantity, not quality of gait. Some studies have shown that quality of gait characteristics are very sensitive and specific markers of PD, whereas quantity of walking (length or number of gait bouts, number of steps or turns per hour, etc.) may not be sensitive to PD (Shah et al., 2020).

EMERGING DIGITAL OUTCOMES FOR PD IN NEED OF FURTHER DEVELOPMENT

Motor fluctuations
There is an unmet need to objectively measure motor fluctuations, continuously, in daily life in people with PD. Some progress has been made in estimating severity of tremor and

bradykinesia with wearable sensors in daily life, although they can be very context specific (Ancona et al., 2021). Dyskinesia, particularly the tonic type, is notoriously very difficult to measure with inertial sensors because it can occur across any muscles of the body and has a frequency spectrum that overlaps with normal movements. Rigidity can be measured while a clinician moves a patient's limbs, but remote, passive monitoring of rigidity has not been reported. Another challenge is that motor fluctuations are likely to be much more rapid than patient diaries are able to detect so a clinical gold-standard for validation is imperfect.

Freezing of gait
Freezing of gait (FoG) is notorious for being difficult to elicit in the clinic and clinical observation is generally limited to whether FoG is present (Yes or No), rather than rating the severity (or frequency) of FoG. An unmet need is quantifying the frequency and severity of FoG events during daily life. Inertial sensors on the legs have successfully been used to measure FoG during prescribed turning tasks in the laboratory or clinic (Mancini et al., 2020) and more validation of measures of FoG in daily life is needed (Silva de Lima et al., 2017).

Sleep
Sleep disturbances are one of the most commonly reported non-motor symptoms of PD. Rapid Eye Movement (REM) sleep behavior disorder (RBD), sleep fragmentation, short sleep duration and sleep-disordered breathing have been associated with an increased risk of neurodegeneration and cognitive decline in PD. Connected sensor technology provides longitudinal assessment without the biggest problems of the gold-standard sleep labs, which are an atypical sleeping environment and single-night snapshot. Although a large number of possible digital outcomes have been used to measure sleep quality in the home, most have not been validated against sleep laboratory gold standards (video-polysomnography) or for people with PD. Multimodal approaches that include monitoring movement with wearable or nearable devices, breathing, and brain signals hold the most promise for usefulness albeit with challenges of independent usability during daily life. There is an unmet need to determine how to unobtrusively, best measure sleep disorders in the homes of people with PD (Hanein and Mirelman, 2021).

Cognition
Another unmet need is how to measure functionally relevant cognitive function in daily life in people with PD. Most digital cognitive tests simply translate pen and paper cognitive tests to tablets or laptops. However, cognitive tests that are meant to be self-administered at home may not result in the same outcome as supervised cognitive tests in the clinic and are prone to more noise. Some newly developed tests use patients own behavior, such as typing speed and errors, but these have not been validated for PD patients who have motor disorders, such as bradykinesia, which could affect results.

Speech
Dysphonia is being evaluated for the potential of using voice as a population-based PD screening tool, such as during telephone conversations (Arora, 2021).

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CONCLUSIONS

There is great need to continue to develop and test digital outcomes for clinical research in people with PD. After technical verification, clinical validation requires testing novel outcomes in the specific type of participants (and often age-matched control participants) planned for a future intervention trial. Selecting outcomes that are meaningful to individuals with PD is paramount, so patient-reported outcomes and usability/meaningfulness questionnaires are encouraged in clinical research using connective sensor technology.

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