ORIGINAL ARTICLE: ANDROLOGY

Home sperm testing device versus laboratory sperm quality analyzer: comparison of motile sperm concentration

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Objective: To test the ability of the smartphone-based YO Home Sperm Test to accurately and precisely measure motile sperm concentration (MSC) versus the SQA-Vision, an automated laboratory semen analyzer.
Design: MSC compared for the YO device on Galaxy and iPhone smartphones versus the SQA-Vision in a double-blind manner.
Setting: Academic medical center.
Patient(s): Donor semen samples from 24 men in 144 aliquots.
Intervention(s): None.
Main Outcome Measure(s): Accuracy, precision, and agreement assessed between the YO device and the SQA-Vision for MSC results.
Result(s): The YO device demonstrated good correlation and good to moderate agreement with the SQA-Vision for MSC results up to a range of 94×10^6/mL with Pearson and concordance correlation coefficient above 0.92. The YO also showed a very high level of accuracy (97.8%) with positive and negative percent agreement above 94%. The difference in coefficient of variation between the YO and the SQA-Vision was low (between 9.4% and 11.2%) and not statistically significant. The precision among the YO phone devices was lower (16.0%) than the manufacturer's claim of $\leq 20\%$.
Conclusion(s): The smartphone-based device has a high level of accuracy and precision when compared with the SQA-Vision. It can detect samples with abnormally "low" MSC (below 6×10^6/mL cutoff), which supports its use as an effective home sperm test for screening "low" and "moderate/normal" MSC cases. In addition, the device effectively identifies varying levels of normal MSC in a precise manner over a wide range of normal MSC. Thus, the YO Score can improve patient satisfaction and empowerment. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Home sperm test, motile sperm concentration, semen quality analyzer, smart phone, sperm

The etiology of infertility, a condition that affects 15% of couples worldwide, is shared equally between men and women (1). Male factor infertility alone contributes 30% to 50% of the infertility cases in couples (2). Semen analysis, analyzing key sperm parameters such as concentration, motility, and morphology, is the standard diagnostic tool to evaluate male factor infertility (3–5). Based on criteria established by the World Health Organization (WHO) (6), abnormality in one or more of these parameters is significantly associated with male factor infertility (7).

In clinical diagnostic laboratories, conventional semen analysis is performed using both manual microscopic and automated testing systems, including computer-assisted semen analysis or sperm analyzers such as the integrated visual optical system (IVOS) and SQA-Vision (Medical Electronics Systems) (2, 6). Inherent in each technology are the limitations that inhibit widespread point-of-care use (2, 8). Manual semen analysis involves skilled technicians and labor-intensive sample inspection using a microscope, and often the results are subjective and prone to human error. On the other hand, automated sperm analyzers, which serve as an alternative approach to

Received June 14, 2018; revised August 19, 2018; accepted August 21, 2018.
A.A. has nothing to disclose. M.K.P.S. has nothing to disclose. R.S. has nothing to disclose. K.M. has nothing to disclose. A.S. has nothing to disclose. S.G. has nothing to disclose. R.H. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.08.049

manual semen analysis, require expensive equipment, which limits their widespread use (8, 9).

The process of semen analysis itself has prevented its widespread acceptance as the first diagnostic test for suspected infertility. Among couples presenting for infertility assessment, 18% to 27% of men will not be tested (10). Many men find the process of collecting a semen sample in a sterile, clinical setting to be stressful; they may not agree to deliver a sample for testing or will fail to obtain a sample under such conditions (2, 11, 12). In the absence of a clear-cut evaluation and diagnosis of the male partner, the female partner may undergo unnecessary and unsuccessful medical interventions (8, 10). This highlights the need for an at-home semen screening test that is relevant, accurate, easy to use, and affordable.

In response to the growing awareness of the challenge of male semen analysis testing, affordable at-home sperm analysis screening has been introduced to the consumer market (9). This home approach to sperm testing presents an attractive solution for men, allowing them to perform a screening test privately at their own discretion. Several home-based male fertility assays have been cleared by the U.S. Food and Drug Administration (FDA), such as SpermCheck (Princeton BioMeditech) and the Trak Male Fertility Testing System (Sandstone Diagnostics) (13–15). However, these tests report only sperm concentration, one of the three key parameters for assessing sperm quality (8, 13, 15).

The emerging use of mobile phones as testing devices has established the smartphone as a powerful platform for home diagnostic testing. Smartphones process information quickly, have adequate memory, transmit data and information, display user-friendly interfaces in the form of software applications (apps), and include high-resolution cameras as well as other functions. These unique characteristics, coupled with the secure and private nature of individual mobile phones, makes the smartphone a very attractive platform for home testing (8). If the onboard camera is fitted with an external optical attachment to allow proper image magnification for semen analysis, the smartphone has great potential to provide affordable, easily accessible point-of-care fertility diagnostic assays (16, 17).

In 2017, the YO Home Sperm Test (Medical Electronics Systems) entered the consumer market as the first FDA-cleared (K161493), video-based smartphone platform for home sperm testing. The YO measures motile sperm concentration (MSC), a composite of concentration (number of cells/mL) and motility (percentage of moving sperm). It uses the smartphone's camera and light source and the YO Clip (a mini-microscope) to capture a moving sperm video. Using the manufacturer's proprietary algorithms, the YO app analyzes the light fluctuations caused by sperm movement in the video and translates these movements into MSC. The MSC results are dichotomized and reported to the end user as "low" or "moderate/normal" MSC based on the established 6×10^6/mL cutoff, derived from the 2010 WHO guidelines (6). We evaluated the performance of the YO Home Sperm Test by comparing the MSC results obtained by this smartphone-based device with the results obtained by the SQA-Vision, an automated laboratory analyzer that accurately and directly measures MSC (18, 19).

MATERIALS AND METHODS

Study Design

After approval by the institutional review board at Cleveland Clinic in Cleveland, Ohio, semen samples were obtained from healthy male donors. Written consent was obtained from all the donors. A total of 24 donors were enrolled in the study, and each provided multiple semen samples after an abstinence period of 2 to 3 days. All samples were tested, irrespective of the semen quality.

After liquefaction, a total of 144 aliquots were prepared from the 24 donors; the samples were split into three equal aliquots to evaluate MSC results simultaneously on three devices in a blinded manner. The YO devices were tested with the apps for iOS (iPhone 7; Apple) and Android (Galaxy S7; Samsung) operating-system smartphones versus the SQA-Vision, an automated laboratory semen analyzer. The analysis was performed in duplicate on all devices following the manufacturer's guidelines. Of the 144 semen samples, 55 samples demonstrated abnormal MSC values below 6×10^6/mL.

YO Device Overview and Testing Procedure

The YO Home Sperm Test kit consists of a YO Clip, fixed coverslip slide, collection cup, liquefaction powder (<5 mg α-chymotrypsin), and a fixed volume transfer pipette (Supplemental Fig. 1, available online). To begin testing, 20 μL of liquefied semen is loaded into the fixed coverslip slide, using the transfer pipette. The YO Clip is slid over the top of the smartphone and precisely aligns with the phone's camera. The filled slide is inserted into the clip for testing. The smartphone's autofocus automatically brings the sample into focus, and a video is captured for analysis. The YO app guides the user through all these steps using both check-off, step-by-step instructions and animations that emphasize the key processes.

During testing, the YO Clip functions as a microscope that uses the smartphone's camera and light source to capture a 30-second sperm video. The software then analyzes the sperm video by identifying light signal and color changes in pixels to detect moving cells, translating this movement into MSC via proprietary algorithms. For study purposes, the MSC results were retrieved directly from the YO device with no further interpretation steps (i.e., dichotomizing the MSC values into low or moderate/normal results).

Smartphones and YO Application

Each test on the YO device was conducted on two types of smartphones, a Galaxy S7 and iPhone 7. The YO application was download from the Google Play or the iPhone App Store and was properly installed on the relevant iOS or Android operating system. Before reporting the test results, the YO app performed internal quality control to ensure the precise alignment of the clip on the phone, proper sample loading of the slide, and correct slide insertion into the clip.

Reference Method

The YO device was compared with results from the SQA-Vision, an FDA-cleared automated laboratory semen quality analyzer that performs a direct measurement of MSC. The SQA-Vision technology, which is widely used in hospital laboratories and in vitro fertilization centers, is based on the detection of electro-optical signals combined with spectrophotometry, interpreted by proprietary algorithms. The performance of SQA-Vision technology has been discussed and validated in previous studies (18, 19). For quality control purposes, QwikCheck Beads (Medical Electronic Systems), which include two known concentration levels of latex beads and a negative concentration/motility control solution, were tested daily on the SQA-Vision before testing the semen samples.

Semen Sample Handling

The liquefaction powder provided with the YO kit was added to the semen samples immediately after collection and was allowed to liquefy the sample for 10 minutes at room temperature. After testing, samples were reconstituted in seminal plasma to obtain various MSC levels. The semen samples were individually centrifuged at 600 × *g* for 15 minutes to separate the seminal plasma from the pellet. The seminal plasma was then used to reconstitute the sperm pellet to obtain varying concentrations of spermatozoa. In total 144 samples were tested in duplicate on all three devices, covering MSC up to a range of 94 × 10^6/mL.

Statistical Analysis

The performance of the YO Home Sperm Test on both smartphones—the Galaxy S7 and iPhone 7—was evaluated by comparing the median and 95% confidence interval for MSC results obtained by the YO device for the Galaxy and iPhone with each other and with the SQA-Vision. Normality was determined by D'Agostino-Pearson test. The data were statistically evaluated using MedCalc software (version 17.8) to calculate the precision, accuracy, agreement of the YO device and YO Score.

Precision. To evaluate the repeatability of the YO system, coefficients of variance (CV%) were calculated within each device (SQA-Vision, YO iPhone, and YO Galaxy) by comparing duplicate measurements of all 144 samples. The averaged CV% was calculated within and between the YO devices to determine each device's precision. To avoid misinterpretation of low-end numbers, MSC values that fell below the lower detection limit of 1.5 × 10^6/mL were excluded from the CV% calculation. The precision between the two smartphone devices was analyzed in the same manner.

Accuracy. To examine the clinical agreement between a smartphone-based test and the SQA-Vision, the positive percent agreement (PPA) and negative percent agreement (NPA) were calculated between the MSC results obtained on the YO smartphone devices and on the SQA-Vision as the comparator method. An MSC of 6 × 10^6/mL was set as the cutoff between positive and negative results. Vertical scatterplot diagrams were created to represent the qualitative performance of the YO device to measure MSC.

Agreement of YO device and SQA-Vision. To evaluate the level of agreement of the YO device to accurately calculate the MSC compared with the SQA-Vision, a regression line including Pearson and concordance correlation coefficients was calculated. In addition, analysis of covariance (ANCOVA) was used to determine whether there were differences in the slopes of the YO devices.

YO Score (MSC ranking). To provide further ranking, the MSC results were converted into a "YO Score," a YO feature that categorizes MSC levels into ordinal groups. The series of YO Scores, expressed in steps of 10, were established based on the WHO distribution of values for semen parameters from fertile men whose partners had a time-to-pregnancy of 12 months or less. A polynomial relationship was generated between the corresponding WHO study centiles and the MSC values through multiplication of concentration and percentage of motility. The average MSC and standard deviation for each YO Score was calculated. In addition, analysis of variance and post hoc Scheffé analysis were performed to determine whether there were statistically significant differences between the YO Scores.

RESULTS

The main focus of this study was to evaluate the performance of the YO device in determining the MSC above and below the 6 × 10^6/mL cutoff level with a maximum limit of 94 × 10^6/mL. The MSC results of the YO devices were compared with results from the SQA-Vision in a double-blinded manner. Overall, the study demonstrated the accuracy of the YO devices (on a Galaxy S7 and iPhone 7) to correctly identify abnormal MSC values and to accurately rank normal values of MSC up to a range 94 × 10^6/mL.

Methods Comparison

Table 1 displays the repeatability, precision, and correlation coefficients of MSC obtained by the YO devices versus the SQA-Vision. The median and the 95% confidence interval (CI) are in close alignment, demonstrating minimal to no systematic discrepancies. The intra-device CV% was found to be lower than 11.2% and in close alignment between the YO devices and the SQA-Vision. No statistically significant differences were found between the devices when the SQA-Vision and YO devices were compared for CV%.

The inter-phone (iPhone vs. Galaxy) precision was slightly higher and found to be less than 16.0%. The comparison of MSC results obtained using the automated sperm analyzer to those obtained by both smartphone devices resulted in highly statistically significant ($P<.001$) regression lines, with Pearson and concordance correlation coefficients above 0.92 (Fig. 1A and B; see Table 1). Both YO devices showed a positive slope in the regression, with a higher slope for the YO Galaxy compared with the YO iPhone. The statistical significance tests refer to analyses of covariance (ANCOVA) showed that the slopes were statistically different ($P<.0001$).

TABLE 1

Repeatability, precision, and correlation coefficient of motile sperm concentration ($\times 10^6$/mL) obtained by YO device with two types of smartphone (iPhone 7 and Galaxy S7) versus SQA-Vision (n = 144, duplicate measurements).

	Motile sperm concentration ($\times 10^6$/mL)		Precision (CV%)		Correlation coefficient: SQA-Vision versus	
Device	**Median**	**95% CI**	**Intra-device**	**Inter-device**	**Concordance**	**Pearson**
YO iPhone 7	11.95	6.90–19.99	10.2	16.0	0.96	0.96
YO Galaxy S7	15.08	6.43–27.41	11.2		0.92	0.97
SQA-Vision	15.58	8.05–22.54	9.4	NA	1	1

Note: CV = coefficient of variation; CI = confidence interval.

Agarwal. Evaluation of home sperm testing kit. Fertil Steril 2018.

Clinical Performance

Comparison of the results of the YO devices with those of the SQA-Vision on the MSC threshold above and below 6×10^6/mL is presented in Table 2. The PPA and NPA of the smartphones are further illustrated in a vertical scatterplot (Fig. 2). The results demonstrate accuracy above 97% for both the YO iPhone and YO Galaxy. The overall accuracy of both devices was 97.8%. The high PPA and NPA results indicate the ability of the YO device to accurately identify the MSC of semen samples above and below the threshold of 6×10^6/mL. The overall false-positive cases were low for both YO devices (<3%).

YO Score

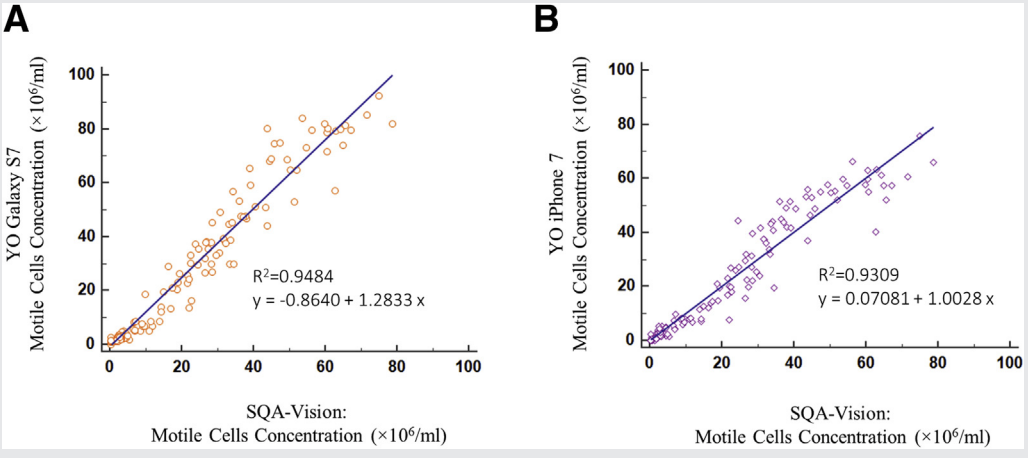
The MSC up to a range of 94×10^6/mL was categorized into different YO Scores based on the centiles published by the WHO for concentration and percentage of motility. Each level of YO Score was found to be in the expected MSC range and statistically significantly different from other YO Score levels ($P<.05$) (Supplemental Fig. 2A and B, and Supplemental Table 1, available online).

DISCUSSION

Until relatively recently all semen analysis technologies were restricted to the laboratory setting for use by experienced, trained professionals. To fully and precisely determine a diagnosis of infertility many characteristics of semen must be evaluated; by contrast, for screening purposes value, a home sperm test must accurately and effectively report on a single semen parameter. In addition, this test must be easy enough for the lay user to perform at home. The challenge of developing a home sperm test that meets these criteria has affected the widespread use of current home sperm tests. However, the global issue of increasing male infertility and the reluctance of men to be tested in a clinical setting has continued to fuel the quest for such home tests.

The emerging use of mobile phones as testing devices has established the smartphone as a powerful platform for home diagnostic testing. This portable platform encompasses the technology for processing vast amounts of information, for communication, and for onboard sensing modalities with engaging human interactive interfaces (8, 16, 17). Ultimately, an effective home test platform should provide the consumer with sufficient clinically accurate and

FIGURE 1



Scatter diagram and regression line comparing motile sperm concentration values measured by SQA-Vision versus (**A**) YO with Galaxy S7 and (**B**) YO with iPhone 7 (n = 144).

Agarwal. Evaluation of home sperm testing kit. Fertil Steril 2018.

TABLE 2

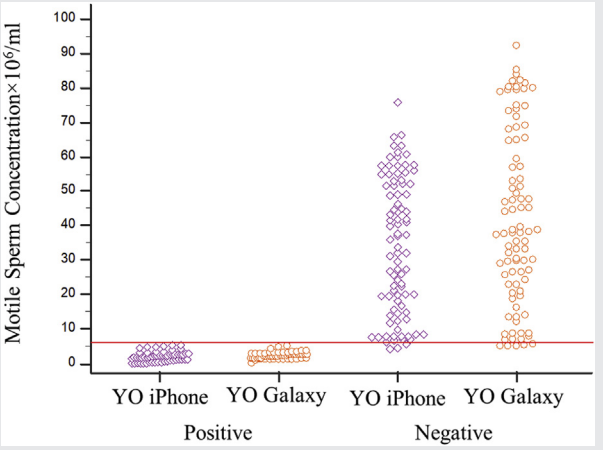
Positive and negative percent agreement between the YO devices and SQA-Vision.

Device	N	PPA	NPA	FP cases	Accuracy
YO iPhone 7	144	100.0%	96.6%	3	98.3%
YO Galaxy S7	144	100.0%	94.4%	5	97.2%
Overall	288	100.0%	95.5%	8	97.8%

Note: FP = false positive; PPA = positive percent agreement; NPA = negative percent agreement.

Agarwal. Evaluation of home sperm testing kit. Fertil Steril 2018.

FIGURE 2



A vertical scatterplot illustrates the positive percent agreement (PPA) and negative percent agreement (NPA) of the YO with iPhone and YO with Galaxy devices in detecting samples with motile sperm concentration below and above 6 × 10^6/mL cutoff (red line).

Agarwal. Evaluation of home sperm testing kit. Fertil Steril 2018.

relevant information that he can make a determination about whether to seek further professional medical advice.

In the current study, we evaluated the performance of the YO Home Sperm Test, a smartphone-based device that was introduced into the market in 2017. The performance of the YO Home Sperm Test was evaluated by comparing the MSC results obtained by the smartphone-based assay with the results obtained by the SQA-Vision, an automated laboratory analyzer that directly measures MSC (18, 19). The YO device measures the concentration of motile spermatozoa in a semen sample, which is an integrated parameter of concentration and motility. Although there is no widespread agreement on a single threshold value for predicting male fertility potential (20–23), concentration and motility are considered to be two of the three most important sperm parameters, along with morphologic characteristics (24, 25). Therefore, an over-the-counter device that measures these two important semen parameters in a composite test provides optimal fertility screening that could not be obtained by reporting on concentration or motility alone (14, 16).

To optimize the interpretation of the MSC test results, one must define the proper reference cutoff/threshold for differentiating fertile from subfertile males. The latest edition of the WHO laboratory manual for examination of human semen has determined the 5th percentile as a lower reference limit, recommending thresholds for interpreting semen analysis (6, 26). In the YO Home Sperm Test, the cutoff for differentiating between low or moderate/normal MSC was calculated based on the established clinical thresholds of the WHO guidelines through the multiplication of the reference values of concentration and percentage of total motility, resulting in a 6 × 10^6/mL cutoff. This was substantiated with statistical simulation, providing estimates of the MSC at the 5th percentile. The simulation of MSC was performed by independently generating more than 100,000 MSC values, based on the WHO published distributions for concentration and percentage of total motility (data not shown). The calculated cutoff was further supported with other publications that sought to determine values for semen measurements that best discriminate between fertile and infertile men by using the same 5th percentile approach (27–29).

The reported reference values result in varying MSC thresholds that are similar to the calculated MSC cutoff of the YO. For example, in a recent study, Tang et al. (29) examined 1,213 fertile Chinese men and reported 5th percentiles for sperm concentration as 20 × 10^6/mL and percentage of total motility of 39%, resulting in a MSC of 7.8 × 10^6/mL. Similarly, in another study Redmon et al. (28) examined 763 fertile from various ethnic groups among American fertile men. The 5th percentile concentration was 12 × 10^6/mL, and sperm motility was 28% with an MSC threshold of 3.4 × 10^6/mL (28). These values are similar to those found in the study by Jørgensen et al. (30), who showed that the calculated MSC threshold values vary from 4.0 to 9.3 × 10^6/mL based on 1,082 fertile men from four European cities.

Recent studies have suggested that the WHO guidelines for normal semen quality should be used with caution, especially in the lower normal (moderate) range. This concern is based on the fact that some men whose test results are reported as normal (above WHO recommended cutoffs) may in fact be subfertile because there exists a transitional rather than a clear-cut delineation of fertility when assessing the probability of conception. For example, Bonde et al. (23) showed a direct relationship between the probability of conception and an increase in sperm concentration up to 40 × 10^6/mL without any significant increase in the likelihood of pregnancy above this value. A more clinically meaningful classification system was suggested by Guzick et al. (3) in which men were subdivided into three groups designated as fertile, indeterminate, and subfertile. The results from our study indicated that subdividing MSC values into different groups of YO Scores provides reliable data about the MSC level (i.e., level of normality): the higher the YO Score, the higher the MSC value. Each YO Score was found to be statistically significantly different from other YO Score levels and in the expected MSC range (see Supplemental Table 1), providing reliable information to the end user about his MSC level of normality. This information can be further

used by a fertility specialist to assist couples in initiating further fertility investigation, diagnosis, and treatment.

In our current study, we have demonstrated that the results of this new model of smartphone-based device performs well compared with an SQA-Vision laboratory analyzer, with accurate and consistent measurement of MSC. In terms of precision, both the inter-device (Galaxy vs. iPhone YO devices) and intra-device (YO vs. SQA-Vision) CV% were found to be lower than the manufacturer's claim ($\leq$20%). The intra-device CV% was found to be in the range of 9.4% to 11.2% without any statistically significant difference between the YO devices and the SQA-Vision (see Table 1). The inter-phone type YO device (iPhone vs. Galaxy) precision was established at 16.0%. The low CV% was mainly attributed to design of the optical attachment, the fixed coverslip slide, and the YO application, all requiring very minimal input or judgment from the lay user.

The accuracy of the YO device is high, up to a range of 94 $\times$ 10^6/mL MSC. This compares positively with SQA-Vision based on Pearson and concordance correlation coefficient >0.92 (see Table 1). Although the slopes for both YO devices statistically significantly differed, the overall accuracy was not compromised because the assessed reportable range of MSC is quite high and well above the 6 $\times$ 10^6/mL cutoff. Our findings established an optimal MSC agreement between the YO device and SQA-Vision, thus rendering the YO device an attractive screening device with positive correlation to the SQA-Vision, a high-end laboratory device.

One of the study's limitations was the use of specimens from healthy donors and not from infertile men. An additional limitation was that lay users were not included in this study, so its usability by the consumer was not examined.

In the present study, the YO Home Sperm Test was found to be useful as a screening device for distinguishing samples with normal versus abnormal MSC values, so men can rely on the recommendation by the YO to seek medical advice. The YO can accurately detect abnormal MSC values below 6 $\times$ 10^6/mL with high PPA and NPA values (100% and 95.5%, respectively) (see Table 2). It provides a relevant, accurate, and convenient home screening option that permits men to assess their MSC status (normal/abnormal) privately and follow up with a physician for a complete semen evaluation. Considering that many men are only clinically examined for fertility problems at a relatively late stage, the use of such smartphone-based devices might improve patient care. In other fields of medicine, such as obstetrics, pediatrics, hematology, or ophthalmology, smartphone technologies are already used in the context of eHealth to improve efficiency, patient satisfaction, and empowerment (31, 32).

CONCLUSION

In conclusion, the tested smartphone-device allows users to accurately detect an abnormal sperm MSC level, a valuable parameter for screening fertility potential, in the convenience and privacy of their home environment. The reporting of normal/abnormal test results provides men with an early warning of a potential underlying fertility issue. This can serve as a motivation for men seeking medical intervention at an earlier stage and therefore greatly improve patient satisfaction, clinical efficiency, and management. Wide usage of such home sperm testing may be of potential interest for clinicians/physicians to engage reluctant men in the fertility assessment process.

Acknowledgments: The authors thank the andrology laboratory technologists for their help with recruitment of subjects for this study. The study was supported by the American Center for Reproductive Medicine.

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