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REVIEW ARTICLE

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Emerging technologies for home-based semen analysis

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SUMMARY

With about 70 million cases of infertility worldwide, half of which are caused by male factors, sperm analysis is critical to determine male fertility potential. Conventional semen analysis methods involve complex and manual inspection with a microscope, and these methods are labor intensive and can take several days. Due to unavailability of rapid, convenient, and user-friendly semen analysis tools, many men do not seek medical evaluation, especially in resource-constrained settings. Furthermore, as conventional methods have to be conducted in the laboratories, many men are unwilling to be tested as a result of social stigma in certain regions of the world. One solution can be found in at-home sperm analysis, which allows men to test their semen without the hassle of going to and paying for a clinic. Herein, we examine current at-home sperm analysis technologies and compare them to the traditional laboratory-based methods. In addition, we discuss emerging sperm analysis approaches and describe their limitations and future directions.

INTRODUCTION

Around 40–50% of the 70 million cases of infertility worldwide are caused by male factors (Center for Disease Control and Prevention (CDC) Infertility FastStats, 2013; Knowlton *et al.*, 2015; Garolla *et al.*, 2014; Ghaleno *et al.*, 2014; Huang *et al.*, 2014; Nosrati *et al.*, 2014; Tung *et al.*, 2014). Male infertility is caused by abnormal characteristics in several parameters, including sperm motility, morphology, velocity, semen volume, sperm concentration, and sperm count (Hammoud *et al.*, 2008; Safaee *et al.*, 2012; Aitken *et al.*, 2013a,b; Brown *et al.*, 2013; Chen *et al.*, 2013; Lewis *et al.*, 2013; Worrilow *et al.*, 2013; Zahedi *et al.*, 2013; Nosrati *et al.*, 2016). To determine male fertility potential, sperm analysis of these main parameters is necessary. Each of these parameters can be assessed through standard sperm analysis methods using microscopes and counting chambers. Motility is scored by evaluating each individual spermatozoa in a given sample, counting the numbers of progressive, non-progressive, and immotile spermatozoa, and comparing the values to find an average percentage of motility. Morphology is assessed by visual analysis through microscopy. Spermatozoa are counted, numbered, and then assessed based on head shape, midpiece shape, and tail (principle piece) (WHO, 2010). The velocity of progressive spermatozoa is determined by measuring the speed in μm per second. Semen volume is largely measured by calculating the weight of the semen, assuming the density of 1 g/mL. It can also be quantified using direct measurement with a marked vessel, although transfer between different vessels is not recommended due to volume loss. Sperm concentration is determined by counting the number of spermatozoa per aliquot of sample. Dilutions may need to be made in order to ensure that there are 200 sperm cells per replicated aliquot. A given volume can then be used in calculations to determine the concentration. Finally, sperm count is calculated by multiplying the sperm concentration by semen volume (WHO, 2010).

As these conventional sperm analysis methods involve complex, manual inspection with a microscope, they are labor intensive and can take several days. Additionally, the results of these methods are subjective and prone to human error (Henkel, 2012; Nosrati *et al.*, 2016). Other methods, such as computer-assisted semen analysis (CASA), which uses algorithms to automatically track spermatozoa, are also effective and are able to present qualitative information on sperm motility. However, CASA-

based methods still have to use large, expensive, and high maintenance equipment, which hinders widespread use (Su *et al.*, 2010). Both traditional methods and CASA are also limited by small field of view, which prevents large numbers of spermatozoa being analyzed at the same time (Zhang *et al.*, 2011; Fennell & Asghar, 2017). Furthermore, as both methods have to be conducted in the laboratories, many men are unwilling to be tested as a result of social stigma in certain regions of the world (Nosrati *et al.*, 2016). Conversely, at-home analysis of male fertility is a cost-effective, private, and rapid solution to male fertility-based inquiries, making it beneficial to men who are hesitant to seek medical evaluation. Most at-home systems will provide rudimentary analysis of a sample, giving the person an idea of whether or not to pursue further testing. In addition to men wanting to assess their fertility potential, vasectomy patients who want to confirm the success of their procedure and test for the presence or absence of sperm cells can also find at-home tests useful. Herein, we review current methods of home-based sperm analysis and compare these methods to WHO standards of semen analysis to determine which device provides the most accurate and complete analysis. We discuss the limitations of home-based sperm analysis devices, and future directions are highlighted.

STANDARD SEMEN ANALYSIS

The World Health Organization (WHO) has set standards for Sperm Analysis in WHO Laboratory Manual (WHO, 2010). According to WHO, the motility of sperm cells is categorized into three types of movement, progressive motility (PR), non-progressive motility (NP), and immotility (IM). Progressive motility is defined by active motion in a large circular pattern or in a forward linear pattern and is not dependent on speed, while non-progressive motility is defined by movement without progression. Immotility is defined by no observable movement. While total motility has a lower reference limit of 40%, progressive motility has a lower reference limit of 32% (WHO, 2010).

The morphology of spermatozoa is greatly varied, and most of both fertile and infertile men have a range of 0–25% observed normal sperm morphology. This value is further reduced by the selection of cells by the zona pellucida, which chooses a set of morphologically similar spermatozoa. These 'zona-preferred' morphologies only contribute to 8–25% of all motile spermatozoa. Although sperm cells are composed of head, neck, midpiece, principle piece, and endpiece, it is difficult to observe the endpiece. As a result, the spermatozoon is considered to have a head and tail, which includes the midpiece and principle piece. Both components must be normal in order for the entire cell to be classified as normal. Generally, the head must be smooth, contoured, oval in shape, and without excessive vacuoles and the midpiece must be around the same length as the head and be in line with the major axis of the head. The principle piece must be thinner than the midpiece and about 10 times the length of the head. It can also be looped around itself, but cannot have any sharp angle, which indicates a break. Some of the more common defects include wrong sized or shaped heads, heads with vacuoles, double heads, improperly inserted midpieces, midpieces or principle pieces with abnormal width or length, broken or bent principle pieces, or any combination of these abnormalities. In addition, excessive residual cytoplasm (ERC) is another notable defect. ERC is characterized by excessive irregular cytoplasm and is often related to defective midpieces. The lower reference limit is 4% morphologically normal spermatozoa within a single ejaculation. This rate is calculated by multiplying the normal forms by the total number of spermatozoa within the ejaculate (WHO, 2010).

The velocity of PR spermatozoa is varied but can be categorized into fast and slow based on whether its velocity is greater or lesser than 25 μm/sec. Semen volume is the amount of semen produced in a single ejaculate, while the concentration of spermatozoa is the number of spermatozoa per unit of volume. Both volume and concentration are critical due to the fact that they are used to calculate total sperm count, which refers to the total number of spermatozoa in an entire ejaculate (WHO, 2010). Although other factors contribute to and are associated with male infertility, sperm count is one of the leading causes for it (Zhang *et al.*, 2011). According to the WHO, the lower reference limits for semen volume, sperm concentration, and sperm count in a single ejaculate are 1.5 mL, 15×10^6 spermatozoa per mL, and 39×10^6 spermatozoa per ejaculate, respectively (Table 1) (WHO, 2010).

As semen quality has a number of characteristics, male infertility can be caused by different factors or a combination of factors. Infertility trends also vary across regions. According to one study, 34.14% of the male partners of infertile couples in central India were abnormal in sperm concentration and had less than 15 million sperm/mL. A total of 19.35% of tested men were azoospermic, meaning they lacked spermatozoa in their semen completely. In addition, 10.70% had less than 30% motility and over 60% abnormal morphology (Kumar *et al.*, 2015). A study performed in Los Angeles, California, found that 18% were abnormal in concentration with under 20 million sperm/mL, only 4% were azoospermic, 51% of men were abnormal in motility, and 14% had abnormal morphology (Acacio *et al.*, 2000). Comparatively, in Punjab, only, 11.11% of men had a sperm concentration below 20 million sperm/mL, while 14.89% of men were azoospermic. Only, 25.81% of those men had reduced sperm motility, and 3.26% had abnormal morphology (Butt & Akram, 2013). At another instance, in Abakaliki, Nigeria, 70% of men had sperm concentrations of below 10 million sperm/mL and, like in LA, 4% had no spermatozoa at all (Table 2) (Ugwuja *et al.*, 2008). Although the distribution of abnormal characteristics varied across areas, abnormal concentration and motility seem to be the most prominent. Comparing the results of different studies, the concentration of progressively motile spermatozoa seems to be the most predictive factor regarding outcome, but, still, no individual parameter can be considered single best predictor of fertility (Tomlinson *et al.*, 2013).

Table 1 Normal semen parameters and standard reference values (WHO, 2010)

Parameter	Lower reference unit
Motility	40% for total motility 32% for progressive motility
Morphology	4% of normal forms
Velocity	25 μm/sec
Volume	1.5 mL
Concentration	15×10^6 spermatozoa per mL
Count	39×10^6 spermatozoa per ejaculate

Table 2 Comparison of the percentages of men with abnormal characteristics in India, Los Angeles, Punjab, and Nigeria

	Abnormal concentration (%)	Absence of spermatozoa (%)	Abnormal motility	Abnormal morphology
India (Kumar *et al.*, 2015)	34.14	19.35	10.70% (grouped together)	
Los Angeles (Acacio *et al.*, 2000)	18	4	51%	14%
Punjab (Butt & Akram, 2013)	11.11	14.89	25.81%	3.26%
Nigeria (Ugwuja *et al.*, 2008)	70	4	Not available	Not available

Figure 1 Devices for home-based sperm analysis. (a) SpermCheck Fertility Test Kit with instructions for use, SpermCheck device, collection cup, semen transfer device, and SpermCheck solution bottle. (b) Micra Sperm Test, which includes a microscope with which to analyze the spermatozoa. (c) Trak device. (i) Few drops of sample are added on the Trak disposable test chip. (ii) Sample is centrifuged to isolate and quantify sperm cells. (iii) The height of sperm pellet is related with concentration of sperm cells. (d) Fertell Male Fertility Home Test. (i) Device with sample. (ii) Hyaluronic acid solution released to sample (iii) Sample heated up and spermatozoa swim up through hyaluronic acid. (iv) Motile spermatozoa react with antibody and collect on strip, producing visible red line. (e) SwimCount Sperm Quality Test with device, collection cup, and syringe. Reprinted with permissions from Bjorndahl et al. (2006), and weblinks from SpermCheck, Micra, Trak, and SwimCount.

DEVICES FOR HOME-BASED SEMEN ANALYSIS

SpermCheck Fertility

The SpermCheck Fertility Test is a product that tests semen for sperm concentration at the threshold of 20 million per milliliter. The white, plastic device has a sample well and a strip that allows users to read the results (Fig. 1a). The kit includes the SpermCheck device, a collection cup, a transfer device, and the SpermCheck solution bottle. As per company guidelines, the results are ready in around 10 min and are indicated with two lines telling whether the concentration per mL is greater or lesser than 20 million/mL. Designed as a first step to determine if further clinical evaluation is required, it retails for $39.99 USD and claims to be 98% accurate (Table 3) (SpermCheck® Fertility). Although results of the SpermCheck test are quick and easy to interpret, it only indicates if sperm concentration is above or below the given threshold, preventing users from knowing the exact concentration and determining if their spermatozoa are normal or abnormal in other parameters, such as morphology and motility.

Micra Sperm Test for Sperm Count and Motility

The Micra Sperm Test is a commercially sold product that screens for three major male fertility factors, sperm count, motility, and semen volume. The product calls for the user to collect

Table 3 Comparison of home-based sperm analysis devices

Test	Materials	Parameters tested	Time until results	Price	Accuracy
SpermCheck	Antibody reaction for color change	Concentration	10 min	$39.99	98%
Micra	Microscope kit	Count, motility, volume	30 min	$85	Not available
Trak	Centrifuge, smartphone application	Concentration	36 min	$199.99	97%
Fertell	Antibody reaction for color change	Motile concentration	1 h	Not available	95.3%
SwimCount	Antibody reaction for color change	Motile concentration	1 h	€49.99 = $58.5	95%
Paper-Based	Antibody reaction for color change	Concentration, motility, viability	10 min	Not available	100%
Microfluidic by YA Chen	Microfluidic device with resistive pulse	Motile concentration, motility	12 min	Not available	9% difference
Microfluidic by CY Chen	Microfluidic device, centrifuge	Total and motile count	20 min	Not available	5% difference
YO	Smartphone	Motile concentration	13 min	$49.95	97%
Smartphone	Microfluidic chip, smartphone	Concentration, motility, velocity, volume, count	Depends on phone model, mean processing time <5-sec	Not available	97.71%
ReproSource	Mail-in for manual evaluation	Concentration, motility, morphology, more	1–2 days	Varies depending on provider	Not available
Episona	Mail-in for genetic evaluation	Genetic abnormalities	2 weeks	$895	Not available

and dilute an ejaculate (Fig. 1b). This sample is then placed on the device, which has a gridded surface so that motility can be calculated by the user. The product claims to provide results quickly and easily with only 30 min of waiting in between ejaculation and interpreting results. The kit includes a microscope and provided slides with which the user will analyze the spermatozoa. Also provided in the kit are instructions that allow the user to accurately interpret the data exhibited by the spermatozoa and provide ranges for normal and abnormal sperm count, motility, and sperm volume. The device retails for approximately $85 USD. Although the Micra device is able to examine three parameters, it is prone to human error and makes it hard to receive accurate and qualitative data on a semen sample because it requires the user to observe the sample manually.

Trak

Trak is a small portable device that uses centrifugal motion to determine sperm concentration. A sample is loaded into a disposable microfluidic chamber and centrifuged (Fig. 1c). The company claims to give an estimate of cell concentration based on the size of the cell pellet after the 6-min centrifugation is complete. The device categorizes sperm concentration as Low, Moderate, or Optimal for conception with two marks of delineation noting 15 and 55 million/mL. On its website, it claims to show 97% accuracy when compared to standard laboratory evaluations. In addition, the device also comes with an app that allows users to enter data and track their sperm count. The corresponding app, made available in 2015, claims to aid the user in making more health-conscious decisions that could positively affect their sperm count. The app has sections to specifically assess as user's wellness, diet, exercise, stress, exposure to heat sources, and toxins to identify risk factors and areas for improvement. It also lets users log the result of clinical semen analysis performed by a third-party laboratory. That section includes areas to log the date, days abstained, the volume, viscosity, and pH of semen, as well as sperm count, motility, and morphology. FDA cleared in May 2016 and becoming available in October 2016, the Trak device is under the parent company of Sandstone Diagnostics and retails for $199.99 USD for the device and four tests (Information Obtained from Weblink). A 2-test refill pack retails for $49.99 USD. Similar to other home-based sperm tests, the Trak System only roughly indicates if the sperm concentration is within a certain range and fails to analyze other important parameters.

Fertell Male Fertility Home Test

Fertell Male Fertility Home Test is a device that estimates motile sperm concentration and produces an easy to interpret, visual result of a red line appearing on the device (Fig. 1d). It only detects positive or negative results, based on a detection limit of 10×10^6/mL. The device works by separating spermatozoa with progressive motility from liquefied semen using hyaluronic acid solution. Once the motile spermatozoa swim up through the solution, they react with an antibody and collect at a strip, producing the red line that indicates a positive concentration. A negative result shows no line and alerts the user so that he can seek more comprehensive testing. For ease of use, a light-emitting diode (LED) provides feedback to the user at various stages to show if the device is functioning properly. The device was found to have an accuracy of 95.3% compared to a CASA test and a hyaluronate migration test (HMT) and was sold under the parent company of Genosis Ltd (Björndahl *et al.*, 2006). Again, the Fertell device is unable to provide more data than a simple positive/negative result, not giving users much information on their fertility potential and requiring them to seek further testing.

SwimCount Sperm Quality Test

SwimCount Sperm Quality Test is another home-based kit that tests the concentration of progressively motile sperm cells. The kit includes a collection cup, a syringe, instructions for use, and the device itself (Fig. 1e). Users collect a sample in collection cup, wait for about 30 min, stir the sample ten times with the syringe, collect 0.5 mL of the sample with the syringe, and transfer it to the device. As an add-on, users may also get the SwimCount Non-Spermicide Condom to collect the sample. Then, a slider on the side must be pushed forward to activate the device, which has three chambers: the sample chamber in which the semen is deposited by the user, the separation chamber to which

only progressively motile spermatozoa can swim into, and finally, the detection and result window to which the progressively motile spermatozoa, now stained with dye, are captured onto. After another 30 min and pulling the slider back, the results are interpreted by the final color in the results window compared to the reference colors printed next to the window on the device. If similar to the lightest color, the concentration is below 5 million motile sperm/mL. If similar to the darkest color, the concentration is above 20 million motile sperm/mL. If similar to the middle color, the concentration is in between the other values, near at the normal level for fertile men according to WHO. SwimCount Sperm Quality Test has an accuracy of 95% compared to manual microscope methods and retails for €49.99 (Information Obtained from Weblink). Like the other products, this test is also unable to provide information on parameters other than progressively motile concentration, meaning that further testing is still required.

PAPER-BASED SEMEN ANALYSIS

Paper-based devices are also beginning to emerge in various fields of biomedical engineering including microfluidics, diagnostics, and POC testing (Asghar *et al.*, 2014a, 2016a; Rappa *et al.*, 2016; Sher *et al.*, 2017). These paper-based devices overcome some of the limitations of currently available at-home sperm analysis kits, such as their need for multiple steps, subjectivity, high cost, and ability to only measure one parameter. For example, a paper-based device has been developed with the ability to measure three semen parameters, sperm viability, sperm concentration, and sperm motility, in about 10 min (Fig. 2). Additionally, the paper-based device can be produced cost-effectively. It is made of one laminate layer and two wax-printed paper layers bound together with double-sided tape. Results are returned with a change in the device's color, which results from a reaction between yellow tetrazolium dye and the diaphorase flavoprotein enzyme, which is present in active spermatozoa. The device determines concentration when the enzyme in the live spermatozoa reacts with the dye, causing a colorimetric change in the device from yellow to purple. Motility is determined in the same way, except that the motile spermatozoa must successfully swim through a viscous buffer and narrow pores of a membrane filter before being able to react with the dye. This device was found to show 100% agreement with results from CASA and dye exclusion vitality assays (Nosrati *et al.*, 2016). Like the currently available home-based devices, paper-based devices only estimate the quality of semen samples and are unable to provide specific, quantitative data. Although it can evaluate three parameters (viability, concentration, and motility), it cannot evaluate other important parameters that are critical to fertility potential, such as sperm morphology.

MICROFLUIDIC DEVICES FOR HOME-BASED SEMEN ANALYSIS

Microfluidic devices are being developed for various applications in medicine including disease diagnosis, tissue culture, and cryopreservation (Asghar *et al.*, 2012, 2014b, 2016b; Hafeez *et al.*, 2012; Miki & Clapham, 2013; Seiringer *et al.*, 2013; Tasoglu *et al.*, 2013a,b; Islam *et al.*, 2014; Shafiee *et al.*, 2015; Safavieh *et al.*, 2016; Adenmosun *et al.*, 2017; Coarsey *et al.*, 2017; Kanakasabapathy *et al.*, 2017a). Like paper-based devices, these microfluidic devices also provide a quick way to evaluate semen with a simple readout. A microfluidic device has been designed to measure motile sperm concentration and motility by producing a flow field for the spermatozoa to swim against (Fig. 3). The spermatozoa that are able to successfully swim against the flow in a given time were then counted using resistive pulse measurement. With this method, the device only showed a 9% difference in sperm count from manual counting under a microscope. One of the main advantages of this device is that it does not require any labels or biomarkers (Chen *et al.*, 2011). At another instance, scientists have designed a microfluidic device that is able to quantify the total and motile sperm counts. In this device, motile spermatozoa must swim across a phase-guide barrier to mix with a buffer (Fig. 4). Afterward, the solution is centrifuged to determine sperm concentration. Results are found rapidly, easily, and accurately in few minutes. Additionally, the results are also found to agree within 5% with those of a manual evaluation with a microscope in a Makler chamber (Chen *et al.*, 2013). Although these devices provide many advantages, they also have some limitations. One of the main challenges is that these microfluidic devices require external peripheral equipment, including pumps and tubing, making them less portable and more expensive and, hence, may not be suitable for at-home testing at their current stage.

Another approach to making semen analysis more accessible with microfluidics is through one of the most common devices available, the smartphone. One commercially available smartphone-based at-home device is the YO Sperm Test, which tests for motile sperm concentration. The device works by attaching onto the phone and using the phone's camera and flash to record a video of the spermatozoa in the sample (Fig. 5a). The user must download the accompanying application, collect a sample in the provided container, add liquefying powder, and wait for 10 min. Then, they must attach the device to the phone, transfer the sample to a slide using a pipette, and then insert the slide into the device. Results are ready within 3 min and are explained in a report within the app. Users are also able to view and save the recorded video of their spermatozoa. The YO Sperm Test claims to have over a 97% accuracy and retails for $49.95 USD for two tests (Information Obtained from Weblink). Like other home tests, it is unable to perform a full analysis and can only return information on motile sperm concentration. In addition, it is only available for certain phone models and each version is specific to a particular model, meaning if a user does not have one of the offered models or purchases a new phone, they will be unable to use the test.

Another device that evaluates sperm concentration, motility, velocity, volume, and count has been developed (Kanakasabapathy *et al.*, 2017b). An on-phone image analysis is performed on a semen sample with a microfluidic device and a modular wireless weight scale. It uses a lightweight optical attachment for the smartphone, which provides the appropriate lighting and positioning for proper image magnification. The attachment has a specific opening for the microchip to fit into so that it positioned correctly at the proper distance away from the smartphone. The microchip itself employs a polydimethylsiloxane (PDMS) bulb for power-free mechanical pumping that creates a negative pressure chamber (Fig. 5b). A smartphone application that accompanies the device guides users through the steps to complete a test and then stores the results for long-term monitoring. When compared to CASA testing, the device was found to have an accuracy of 97.71% (Kanakasabapathy *et al.*, 2017b). Although

Figure 2 Paper-based Device. (a) Breakdown of device. (b) Assembled device before and after sample is applied. (c) Colorimetric signal is produced after semen sample is applied to dry device. (d) To test motility, spermatozoa must pass through buffer and pores on membrane filter before producing a color change. Reprinted with permission from Nosrati *et al.* (2016).

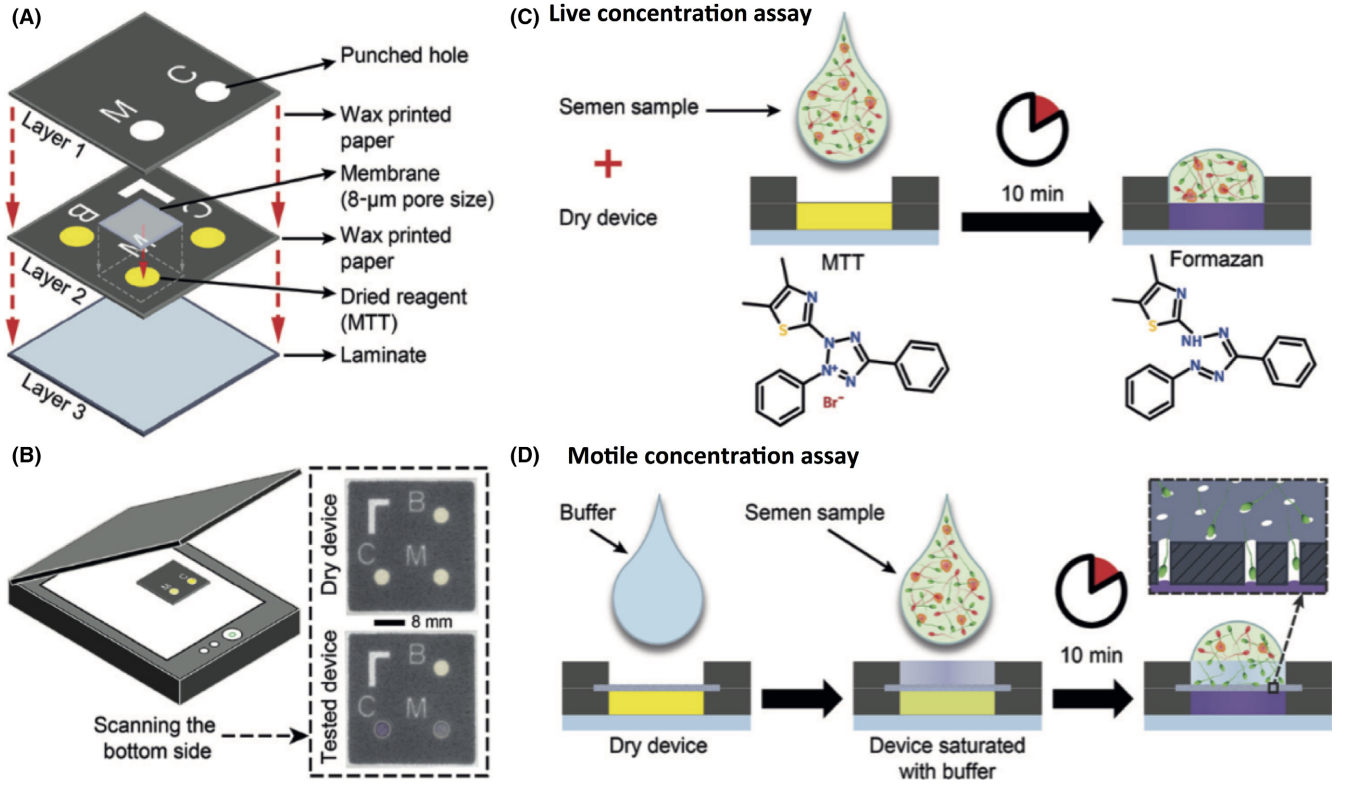
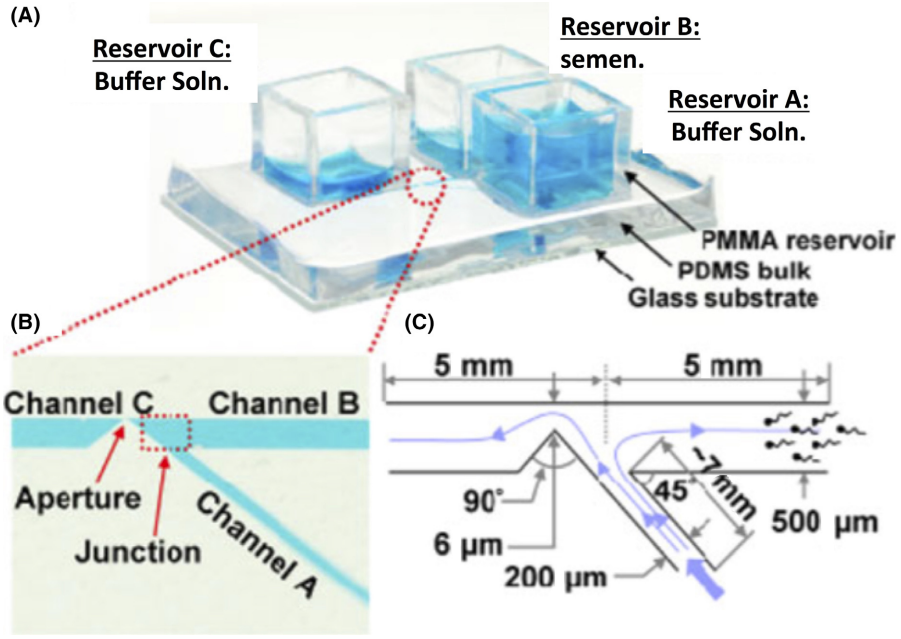
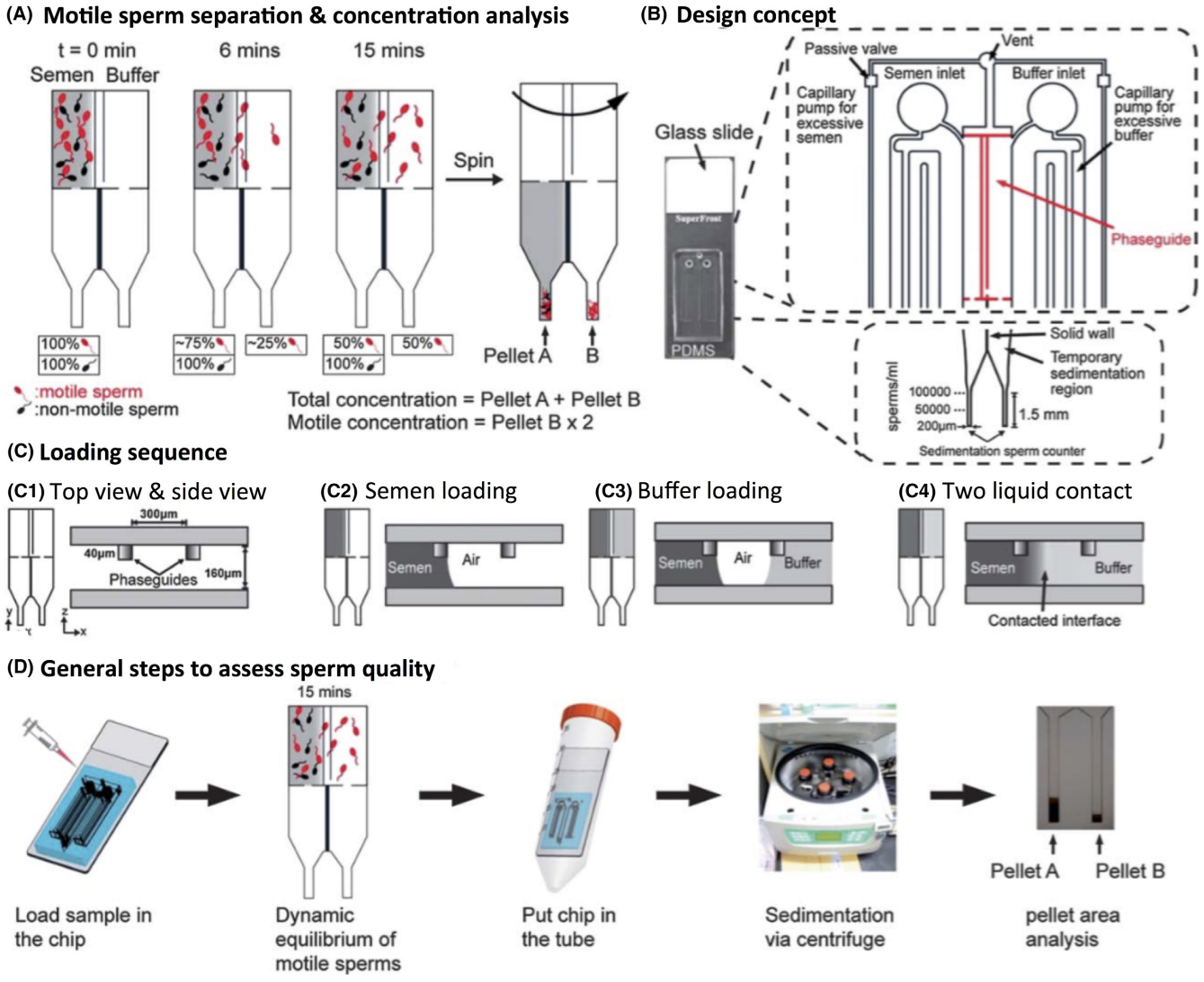


Figure 3 Microfluidic Device created by YA Chen *et al.* (a) Actual device with glass substrate, polydimethylsiloxane (PDMS) bulk, and reservoirs for semen and buffer solution. (b) Microchannels where motile spermatozoa swim through flow of buffer. Motile spermatozoa are able to swim through Channel B and avoid being flushed through the aperture and Channel C. (c) Microchannel dimensions. Reprinted with permission from YA Chen *et al.* (2011).



this device has certain advantages, such as requiring minimal user handling and measuring multiple parameters, it still is unable to assess sperm morphology. In addition, it is sometimes prone to error when it identifies non-sperm cells as spermatozoa (Kanakasabapathy *et al.*, 2017b). Further, changing smartphone type and model may significantly skew the results.

Figure 4 Microfluidic device created by CY Chen *et al.* (a) Motile spermatozoa swimming across barrier and calculation of sperm concentrations after centrifugation. (b) Schematic of device design. (c) Semen and buffer loading sequence. (d) Steps followed to assess sperm quality. Reprinted with permission from CY Chen *et al.* (2013).



MAIL-IN SEMEN ANALYSIS ASSAYS

In addition to home-based methods of sperm analysis, mail-in sperm analysis kits in which users collect a sample at home and then send it to the provider for analysis are also available. ReproSource's @Home Collection Kit contains a shipping container that is able to maintain semen quality enough for a proper evaluation within 26 h. It also includes a preservative tube, a pipette, a biohazard bag, ice packs and cooling gels to keep the sample cold, and labels to ship it back. It offers a standard evaluation of concentration, motility, and morphology, as well as inflammatory markers and accessory gland health. Its reliability was tested by performing semen analysis on samples collected with the kit 26 h apart, finding only a 15% coefficient of variation between the two tests. With the kit, patients are able to collect a sample at home and then send it to ReproSource, which will then send results to their physician within 1–2 days (Information Obtained from Weblink).

Mail-in epigenetic male fertility tests also exist. Instead of testing the basic parameters, Episona's Seed test analyzes individual genes in sperm DNA and provides clients with information on genetic abnormalities that may affect both male factor infertility risk and poor embryo development risk, which may help to determine which treatment is most appropriate for a particular case. The kits consist of instruction cards, a collection tube, a funnel, and a biohazard bag. Patients must have a kit ordered from their doctors before being able to collect a sample at home, sending it back to Episona's laboratories for analysis, and receiving the results online. The service is currently being offered for $895 USD (Information Obtained from Weblink).

LIMITATIONS OF HOME-BASED SEMEN ANALYSIS METHODS AND FUTURE DIRECTIONS

Although at-home, paper-based, and microfluidic sperm analysis products are a step ahead of the traditional methods for semen analysis, they still have many limitations. The primary issue is the fact that current non-conventional sperm analysis methods are best used only for indicating whether a user should or should not pursue further testing. Most can only provide

Figure 5 Smartphone-based devices. (a) YO Sperm Test attached to smartphone with slide inserted. Once the test is complete the application will report the concentration of motile spermatozoa and indicate if it is within the normal range, as well as show the user a recorded video of their spermatozoa. (b) Device by Kanakasabapathy *et al.* (i) A comparison of steps of the smartphone-based device and traditional methods. Semen sample is loaded onto smartphone-based device using bulb and then the microchip is separated from the loading end and placed in the optical attachment. Sample loaded into counting chamber and microscope and then evaluated manually or with a CASA system. (ii) Actual device with smartphone, microchip, and attachment. (iii) Side view of device. Reprinted with permission from Medical Electronic Systems (Information Obtained from Weblink) and Kanakasabapathy *et al.* (2017b).

information on one or a few parameters at a time. While this information can be helpful, only having data on some, but not all, factors can lead to false negatives for male infertility, as spermatozoa can be simultaneously considered normal in one characteristic, but abnormal in another. A single parameter does not define whether an individual is fertile or infertile, but whether or not a natural pregnancy occurs within a year does. As a result, these methods are not yet a replacement for laboratory analysis. Formal confirmation from a fertility specialist is still recommended even after the use of a home-based test, which can actually delay getting a full clinical evaluation. Semen analysis from a clinic is much more detailed and can provide information on many more parameters simultaneously. Although not as quick or inexpensive as current home-based kits, clinics and laboratories can usually return results within a few days and are fairly affordable at around $100 USD for each test.

Because of these reasons, at-home testing may be more useful to vasectomy patients. As over 33 million men undergo vasectomy procedures as a safe and inexpensive contraceptive solution, it is important for them to retest their semen to ensure the surgery's success. However, the number of patients who actually follow up is very low because of the inconvenience, but the ease of home-based testing has the potential to improve patient compliance. For these patients, the main parameter to test for is sperm concentration, which should be below 100,000 sperm/mL eight to sixteen weeks after undergoing the procedure, meaning the tests that are only able to test concentration can still be valuable to them (Kanakasabapathy *et al.*, 2017b).

New approaches to sperm analysis are seeking ways to overcome the challenges of current technology. Lensless on-chip microscopes and imaging systems have been introduced. Researchers were able to create a lens-free on-chip microscope using digital holography that could automatically analyze spermatozoa and process count, speed, and direction of motile spermatozoa without the need for any bulky and expensive lenses, lasers, or other components (Su *et al.*, 2010; Sobieranski *et al.*, 2015; Fennell & Asghar, 2017). Furthermore, a lensless charge-coupled device (CCD) imaging system that can both quickly analyze and sort spermatozoa in a microfluidic channel has also been developed. Both these devices are able to quantitatively track larger numbers of spermatozoa as a result of larger fields of view and are also portable and more compact (Zhang *et al.*, 2011). Moving forward, even more improvements in sperm analysis and imaging can be made. Some potential advances could include improved systems that can measure multiple parameters automatically and possibly analyze sperm morphology and distinguish between normal and abnormal spermatozoa. With the ability to automatically, accurately, and quantitatively evaluate all parameters tested in traditional analysis, but without the drawbacks of bulky, expensive equipment, lengthy wait times, lack of skilled technicians, and inconvenience, these systems would have the potential to become a common alternative to or even replacement for the current conventional sperm analysis methods.

CONCLUSION

At-home sperm analysis is a valuable tool for determining fertility potential, especially for couples struggling with infertility, as well as vasectomy patients. Men who are reluctant to seek conventional clinical testing due to high cost, long wait time, inconvenience, or social stigma might be more willing to use home-based sperm analysis kits, which overcome those problems. With these kits, men are able to rapidly evaluate their fertility potential with ease at a low cost from the comfort and

privacy of their own homes, unlike the traditionally used methods. Although currently available home systems only provide rudimentary results, they can give users a basic idea of their fertility potential based on few parameters and motivate them to pursue more comprehensive testing. This inability of home-based sperm analysis systems to test fertility based on all sperm functional parameters that are usually analyzed in the laboratory limits their use and makes them prone to false-negative results, which may actually delay men from seeking more thorough evaluation. Nevertheless, at-home sperm analysis devices are still relevant as they encourage hesitant men to take a first step in investigating their fertility potential and should continue being improved. Recent advances in microfluidics and imaging technologies should be further investigated for their application in designing more reliable home-based sperm analysis devices.

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CONFLICT OF INTERESTS

The authors declare no financial conflict of interest.

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