A review of portable quantitative and semi-quantitative devices for measurement of vitamin A in biological samples

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ABSTRACT

Background: We catalog and summarize evidence of the analytical performance of portable quantitative and semi-quantitative devices for the assessment of vitamin A status and vitamin A deficiency (VAD) in various biological samples—including whole blood, plasma, serum, and milk—in addition to VAD determination by functional indicators such as pupillary response.

Methods: We searched the literature for published research articles, patents, and information from manufacturers of mobile devices, particularly those appropriate for low-resource settings. The included devices were required to be portable (lightweight and ideally not needing a power outlet) and to measure vitamin A as well as define VAD. Eligible studies compared a portable device to a reference standard of high-performance liquid chromatography for blood and milk, or a Goldmann-Weekers dark adaptometer for eyes/vision. Where available, identified devices were compared with reference methods across several performance criteria. When possible, we compared the device’s performance reported in published studies against the stated performance criteria from the manufacturers’ websites.

Results: We catalogued 25 portable devices for measuring vitamin A and/or VAD via biological samples. We also identified 18 comparison studies (plus associated reports) assessing nine methods: the iCheck Fluoro, iCheck Carotene, CRAFTi, Tidbit with or without the HYPER filtration system, custom field-friendly immunoassays, and microfluidic assays for blood; the iCheck Fluoro and iCheck Carotene for milk; and the Scotopic Sensitivity Tester-1 for eye function.

Conclusions: The iCheck Fluoro and iCheck Carotene are commercially available for use and are acceptable for measuring vitamin A in blood and milk samples, according to the available validation data. Many of the other identified devices, including other portable fluorometers, photometers, immunoassays, microfluidics-based devices, and dark adaptometers, were proofs of concept and not yet commercially available. Furthermore, none of these other devices included manufacturer-described device performance criteria to compare with descriptions from experimental studies. Several gaps remain, including studies comparing the other portable devices against a reference standard, particularly for functional indicators of vitamin A status/deficiency; available manufacturer-reported device performance criteria against which to compare future results of investigations; and more comprehensive reporting of validation metrics including sensitivity, specificity, precision, and Bland-Altman analysis.

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Introduction/background

Vitamin A deficiency (VAD) continues to be a major global health issue leading to poor health outcomes, including night blindness, greater severity of measles infection, and higher mortality risk from infectious diseases (Tanumihardjo et al., 2016). Most existing analytical techniques to assess vitamin A status by measuring serum retinol or retinol binding protein require access to a sophisticated laboratory and equipment such as high performance liquid chromatography (HPLC) (de Pee and Dary, 2002). These methods require extensive sample preparation, are time-consuming, and are potentially prohibitively expensive, depending on the number of samples to be analyzed. Furthermore, VAD is more prevalent in lower income countries, where such laboratory resources may be limited or might not yet exist; in recent vitamin A surveys, <20% of pregnant women at risk have been covered by population surveys globally, possibly partly because of a lack of diagnostics (WHO, 2009).

Portable, field-friendly devices and tools for assessing vitamin A status in populations have the potential to overcome some of the limitations of traditional, laboratory-based testing. These methods may differ in their cost, accuracy, reliability, ease of use, and required consumables/reagents for performing the testing.

A review cataloguing the range of portable tests for vitamin A status and VAD in biological samples, and summarizing these devices’ performance with respect to a reference standard method, is not available. Therefore, the goal of this review was to enable current manufacturers to modify and improve their products according to the gaps identified herein, and to set design goals for new products meeting the current demands of industry, regulators, and other stakeholders.

Materials and methods

In December 2020, we conducted a standardized search of the literature indexed in five databases (MEDLINE, EMBASE, World Health Organization Global Index Medicus, Scopus, and Web of Science) with no restrictions on language, location, or date of publication. We designed a search strategy for MEDLINE (PubMed) (Supplementary Table 1) and translated the search strategy for the remaining databases with guidance from the evidence synthesis specialists at Mann Library, Cornell University. We also used an online search engine to search for other sources such as manufacturers’ websites and patents, and we consulted with subject matter experts within our organizations to gain more information.

We catalogued any portable devices measuring vitamin A or vitamin A deficiency in biological samples, either as reported in studies or provided on manufacturers’ websites. We included both portable devices/methods measuring vitamin A status and devices/methods that indicated VAD. Initially, we considered devices measuring skin carotenoids, as shown in our search strategy; however, because of the lack of established guidance or consensus regarding the conversion of skin carotenoid measurements via Raman resonance spectroscopy (e.g., BioPhotonic Scanner (Pharmanex/Nuskin Enterprises, 2018)) to blood carotenoid measurements and overall vitamin A status (von Lintig, 2020), we determined that these devices were beyond the scope of the review.

The inclusion criteria for our analysis of device performance included certain study designs such as proof-of-concept development studies, method comparison studies, and diagnostic test accuracy studies; studies involving human participants (e.g., observational studies or randomized controlled trials) were considered if the authors described using a portable method for analyzing vitamin A in biological samples. Animal studies were also included. Eligible studies were required to measure vitamin A in any biological sample, including blood, eyes, or breast milk, with a portable device and to compare the device performance with that of a reference method, such as HPLC, depending on the sample type. Studies detailing field friendly methods of sample collection (e.g., dried blood spots) necessitating the use of a non-portable device or a laboratory for analysis were considered beyond the scope of this review.

We contacted the authors to request raw data or more information as needed. We also re-analyzed raw data, when available, as needed.

Results and discussion

Catalog of portable devices

From our search (Fig. 1), we catalogued 25 portable devices, kits, and/or field-friendly assays able to assess a variety of biological sample and vitamin A biomarker types in Table 1a (blood, milk) and Table 1b (eyes/vision assessment).

Vitamin A deficiency biomarkers

In Table 2, we list definitions of VAD used across studies for a variety of biological sample types, from humans or cattle, including cows, calves, and bulls (Table 2). We also note which studies used particular definitions (e.g., VAD measured as RBP ≤ 0.70 µmol/L was measured by Hix et al. 2004). A previous review by Tanumihardjo (2016) has outlined the utility of biomarkers for vitamin A nutrition status (Tanumihardjo et al., 2016), which we adapted for Table 2. We outline the biomarkers of vitamin A as identified in our literature search below.

Vitamin A liver concentration (µmol vitamin A/g liver) is the gold standard for vitamin A status but requires invasive techniques such as biopsy to be measured (Tanumihardjo et al., 2016). Sampling blood enables the quantification of serum retinol, serum retinol-binding protein (RBP), or provitamin A in the form of beta-carotene; however, each measure has trade-offs. Serum retinol reflects liver stores only at extremes of deficiency (<0.07 µmol/g liver) or elevation (>1.05 µmol/g liver) (WHO, 2011), because serum retinol is homeo-
sitionally regulated by the body. The World Health Organization defines VAD as serum retinol ≤ 0.70 µmol/L (WHO, 2011). RBP is commonly assumed to have a 1:1 ratio with serum retinol, and therefore the same cut-offs are sometimes used for both retinol and RBP. However, this ratio can be affected by the extent of VAD, zinc deficiency, acute phase response, protein-energy malnutrition, liver disease, acutely stressful situations, high fever, antibiotic use, or obesity (Tanumihardjo et al., 2016, de Pee and Dary, 2002). Therefore, previous studies have proposed other deficiency cut-offs, such as 0.69 µmol/L (Semba et al., 2002) or 0.83 µmol/L (Engle-Stone et al., 2011, Gorstein et al., 2008). Recently, the Global Alliance for Vitamin A has recommended analysis of a subsample by HPLC to confirm the cut-off point for VAD; furthermore, given the acute phase response, inflammation markers such as C-reactive protein and alpha-1-acid glycoprotein must also be measured (Global Alliance for Vitamin A, 2019).

Beta carotene is one of several dietary provitamin A carotenoids, a plant-derived form of vitamin A. The body converts dietary provitamin A carotenoids into retinol with the following conversion factors: 1 µg retinol activity equivalent (RAE) equals 1 retinol equivalent (RE), 1 µg retinol, 2 µg β-carotene in oil, 12 µg β-carotene in mixed foods, or 24 (12–26) µg other provitamin A carotenoids in mixed foods (Institute of medicine, 2001, Combs and McClung, 2017, Blaner, 2014). The conversion efficiency ratio of beta carotene to RAE is still debated. For example, the European Food Safety Authority suggests that the conversion is 6:1 rather than 12:1 (EFSA Panel on Dietetic Products, Nutrition Allergies, 2015). Carotenoids can be measured in blood, milk, or skin, and several studies have found a positive association of skin carotenoid concentrations with serum or plasma carotenoid status (Zidichouski et al., 2009, Aguilar et al., 2014, Morgan et al., 2019, Hayashi et al., 2020). However, a consensus has not been reached regarding a conversion factor or how the measurements equate to vitamin A status (von Lintig, 2020). Because carotenoids tend to reflect recent dietary intake rather than long-term status, recommended serum carotenoid deficiency cut-offs have not been established in humans (von Lintig, 2020). Deficiency in β-carotene in cow’s blood has been defined as 0.6–1.5 mg/L (Klein et al., 2013, De Ondarza and Al, 2009, Schweigert and Immig, 2007).

In breast milk, retinol may be measured to estimate both the maternal vitamin A status and intake, and the infant intake of vitamin A (Engle-Stone et al., 2014, Tanumihardjo et al., 2016). Additionally, breast milk retinol measurement is influenced by the stage of lactation, time of day, “fullness” of the breast, feeding status if milk from both breasts is analyzed, and whether the milk is hindmilk compared with foremilk (Tanumihardjo et al., 2016). VAD is defined as a milk retinol concentration ≤ 1.05 µmol/L, or ≤ 8 µg/g milk fat (Tanumihardjo et al., 2016). In cows, milk β-carotene levels are often measured and linked to bovine fertility and health.

Because of vitamin A’s role in in producing rhodopsin, the visual pigment of rods in the eyes, VAD can cause ocular manifestations resulting in poor vision (World Health, 2014). These include night blindness, conjunctival xerosis, Bitor’s spots, corneal xerosis, and keratomalacia. Impaired adaption to the dark is among the first symptoms of VAD, and it can be used as a screening tool (World Health, 2014). Tests such as pupillary and visual thresholds can assess dark adaptation by determining the lowest-intensity level of light required to cause pupillary dilation or to visualize an image (World Health, 2014, Labrique et al., 2015).

Comparison studies

From 3230 studies (after de-duplication), we identified 18 studies (19 reports) comparing nine portable methods/devices (index 1) to a reference standard method (Fig. 1); we were unable to retrieve an additional two reports (Craft, 2005, Fujita, 2007). No studies compared two portable methods (i.e., index 1 vs. index 2). Thirteen studies (15 reports) measured human or cattle blood samples (BioAnalyt, 2020; Chaimongkol et al., 2011; Ciaiolo et al., 2015; Elom et al., 2015; Ghaffari et al., 2019; Hix et al., 2004, 2006; Lee et al., 2016; Lu et al., 2017, 2018, Raila et al., 2012, 2017; Schweigert et al., 2017).
## Table 1a
Catalog of all portable devices quantifying vitamin A and vitamin A deficiency: blood, milk.

| Device (manufacturer) | Vitamin A biomarker | Pricing | Technical requirements | Portability | Consumables: Reagents required | Operational range | Target setting |
|-----------------------|---------------------|---------|------------------------|-------------|--------------------------------|-------------------|---------------|
| **# Tests per kit**   |                     |         |                        |             |                                |                   |               |
| iCheck Fluoro (BioAnalyt GmbH, Teltow, Germany) (BioAnalyt, 2021) | Retinol, retinyl palmitate, retinyl acetate and other esters | Pricing not published | Fluorescence | 100 tests per kit | Compact and lightweight (11 × 4 × 20 cm); 0.45 kg | Optional: 50 mL conical tubes, weighing dishes, reference samples | 50–3000 µg RE/L | Lab and field |
|                       |                     |         |                        |             |                                |                   |               |
|                       |                     |         |                        |             |                                |                   |               |
| iCheck Carotene (BioAnalyt GmbH, Teltow, Germany) (BioAnalyt, 2021) | Beta-carotene | Pricing not published | Photometry | 100 tests per kit | Compact and lightweight (11 × 4 × 20 cm); 0.45 kg | Optional: 50 mL conical tubes, weighing dishes, reference samples | 0.15–15 mg/L | Lab and field |
|                       |                     |         |                        |             |                                |                   |               |
|                       |                     |         |                        |             |                                |                   |               |
| CRAFTI (Eurofins CRAFT Technologies Inc., Wilson, NC, USA) (Chaimongkol et al., 2011; Eurofins Craft Technologies, 2020) | Retinol | Pricing not published | Fluorescence | NR | Minimal training | Compact and lightweight (13 × 16.5 × 35 cm); 2.1 kg | + + | Fluorometer cuvettes or Durham tubes | 0.5–1.5 µmol/L | Lab and field |
|                       |                     |         |                        |             |                                |                   |               |
|                       |                     |         |                        |             |                                |                   |               |
| Tidbit (Lu and Erickson, 2017, Lu et al., 2017), ± HYPER filtration system (Lu et al., 2018) (Cornell University, Ithaca, NY, USA) | RBP | Estimated: $95 manufacturing cost; $1.50 per test; Using HYPER platform, ~$1 per test | Fluorescence, multi-color lateral flow | NR | Mean for consumer, clinical, and research use | Tidbit reader, disposable test strip(s) | + + | Lightening-Link Conjugation Kits (Innova Bioscience Ltd., HF180 cards (EMD Millipore); Running buffer (60 µL)) | 2.2–20 µg/mL (0.10–0.95 µmol/L) | Lab and field |
|                       |                     |         |                        |             |                                |                   |               |
|                       |                     |         |                        |             |                                |                   |               |

### Notes
- “NR” indicates not required.
- “+” indicates required.
- **“++”** indicates strongly recommended.
- **“+++”** indicates highly recommended.

### Technical Requirements
- **Sample volume, preparation and setup:** Includes all necessary steps for sample preparation and setup.
- **Overall time required:** The total time required for the test, including sample preparation and analysis.

### Portability
- **Power source:** Indicating whether the device requires a power source, such as battery or Wi-Fi.

### Consumables
- **Reagents required:** Details on the type and amount of reagents needed for the test.

### Operational Range
- **Quantification:** The range of values that the device can accurately measure.

### Target Setting
- **Manufacturer support available:** Indicates whether the manufacturer provides support for the device.
- **Global availability:** The geographic availability of the device.

### Other Details
- **Results:** Includes result formats and storage options.
- **Manufacturer:** Indicates the company that produces the device.
- **Corresponding authors:** Provides contact information for further inquiries.

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| Device (manufacturer) | Vitamin A biomarker | Pricing | Technical requirements | Portability | Consumables: Reagents required | Operational range | Target setting |
|----------------------|---------------------|---------|------------------------|------------|-------------------------------|------------------|---------------|
| Principle/method     |                     |         |                        |            |                               |                  |               |
| # Tests per kit      |                     |         |                        |            |                               |                  |               |
| Overall time required|                     |         |                        |            |                               |                  |               |
|                       | + +                 |         |                        |            |                               |                  |               |
| RID plate reader (The | RBP                 | Pricing not published | Meant for researchers | Compact and lightweight (22 × 14 × 16 cm, 1.14 kg) | + +                | + +            | + +           |
| Binding Site, San    |                     |         |                        | + +        |                               |                  |               |
| Diego, CA, USA) (Hix | RBP                 | Pricing not published | Serum: 5 µL requires serum separation | User guide and installation CD, USB-A to USB-B cable, power supply, plate reader calibration plate | + +                | + +            | + +           |
| et al., 2004, 2006;  |                     |         |                        |            |                               |                  |               |
| The Binding Site, 2020) |                     |         |                        |            |                               |                  |               |
| Radial immunodiffusion of antigen-antibody precipitin rings | + + | | + + | + + | + + | + + | + + |

(continued on next page)
### Table 1a (continued)

| Principle/method | Device (manufacturer) | Vitamin A biomarker | Pricing | Technical requirements | Portability | Consumables: Reagents required | Operational range | Target setting |
|------------------|-----------------------|---------------------|---------|------------------------|-------------|-------------------------------|-------------------|---------------|
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |
|                  |                       |                     |         |                        |             |                               |                   |               |

#### Notes:
- EIA, enzyme immunoassay; HPLC, high-performance liquid chromatography; NR, not reported; RBP, retinol-binding protein; RID, radial immunodiffusion.
- ++ = best.
- +++ = acceptable.
- + = not acceptable.

2011a; Chaimongkol et al., 2008; Lu and Erickson, 2017); four studies measured human or cattle milk samples (Schweigert et al., 2011b, Schweigert et al., 2011a, Engle-Stone et al., 2014, Abebe et al., 2019); and one study measured eye function (Peters et al., 2000). Study details are listed in Table 3. We also re-analyzed the data presented in supplemental Tables S1 and S2 in one publication to calculate the descriptive statistics for plasma and whole blood retinol in samples analyzed by HPLC and iCheck Fluoro (Raila et al., 2017).

We also identified many studies that used a portable device for assaying samples but did not compare the results to those of a reference method and instead cited previous validation studies. Although the devices used are catalogued and described (Tables 1a and 1b), these studies are not further detailed in this review.

Study populations were mostly from the US and Germany, in addition to Thailand, Italy, France Ireland, Japan, Ethiopia, Morocco, Cameroon, Papua New Guinea, Nicaragua, Cambodia, and Oman. Portable fluorometers, photometers, enzyme-based assays or immunoassays, microfluidics-based approaches, and a dark adaptometer for eye function were assessed and compared with their respective reference standards.

Table 4 compares the stated performance criteria described by the device manufacturers' websites to reporting from individual studies using the devices, according to the WHO Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users (ASSURED) criteria for diagnostic tests in resource-limited settings (Kosack et al., 2017). Only the iCheck Fluoro and iCheck Carotene stated performance criteria on the BioAnalyt website and are included in this table. No studies described the cost of the devices. Most devices did not have published cost information, aside from some of the slit lamps showing list prices. Other devices described by the studies were developed as proofs of concept and are either not on the market or are on the market, but lacking performance criteria on the manufacturer’s website.

We note that the study by Ghaffari et al. (2019) reported both measurements of retinol in whole blood and beta carotene in plasma, but only directly references the iCheck Fluoro device and not the iCheck Carotene (Ghaffari et al., 2019). Whereas the iCheck Carotene requires 0.4 mL of sample, the iCheck Fluoro requires 0.5 mL; the authors stated using only 0.5 mL of sample.

Additionally, the manufacturer (BioAnalyt) lists only “colostrum, cattle whole blood, and serum” as appropriate sample types for the iCheck Carotene; however all studies using the iCheck Carotene, including a BioAnalyt report, also analyzed plasma for beta carotene content (BioAnalyt, 2020; Ghaffari et al., 2019; Raila et al., 2012).

A major gap across all devices is the lack of reporting on sensitivity and specificity compared with a reference standard method.

Most studies compared a portable device to a reference method. Tables 5a-5g show the performance of these devices against their reference standards for measuring vitamin A and VAD. Additional analyses conducted with other index (e.g., index 2) tests are described in the text.

In human blood samples, both the iCheck Fluoro and the CRAFTi portable fluorometers were used to measure retinol (Table 5a). The iCheck Fluoro studies showed a high correlation (0.98) and an R-squared value over 0.95 with respect to HPLC. Both CRAFTi studies found a mean difference in serum retinol of ~0.07 μmol/L, and the 2011 study found moderate sensitivity and specificity in identifying VAD at either ≤ 0.70 μmol/L or ≤ 1.05 μmol/L. Few additional comparative data were available between studies. Bias analysis indicated an acceptable level of agreement (within two SDs or 95% acceptability limits) between these devices’ performance and HPLC.

Of note, we identified an additional report examining “vitamin A... in plasma” as measured by the CRAFTi compared with HPLC (Craf, 2005). The correlation between methods was 0.82. However, these data came from a summary of a poster submitted to a conference, and we were unable to find the full version of the poster; therefore,
Table 1b: Catalog of all portable devices quantifying vitamin A and vitamin A deficiency: eyes.

| Device (manufacturer) | Vitamin A biomarker | Pricing (estimated, list price from manufacturer website) | Technical requirements | Portability | Power source | Slit lamps: Magnification | Dioptric range | Interpupillary range | Slit image width(s) | Target setting | Manufacturer support available | Global availability |
|-----------------------|---------------------|-----------------------------------------------------------|-------------------------|-------------|--------------|---------------------------|----------------|---------------------|---------------------|---------------|--------------------------------|---------------------|
| BA 904, BA 904C (Haag-Streit, Harlow, Essex, UK) Haag-Streit, 1900 | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | “Lightweight” | Batteries and chargers | 10 ×, 16 × | – 8 to + 8 | 53-95 mm | | | | |
| Slit lamp | | | Anterior segment; 4-5 h | BA 904: head and chin rest stand, two energy packs, charger, power supply and large case; BA 904C: two energy packs, charger, power supply, parking unit and small case | 45 min | | | | | Field, clinic | | |
| | | | | | | | | | | |
| Hand-held digital slit lamp (HSL-100, HSL-150) Portable slit lamp (Heine®) (Melo et al., 2004; Heine Optotechnik GmbH, 2018) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | 70 g | Rechargeable or battery handle | 10 ×, 16 × | Field, clinic | | | Yes | | |
| Slit lamp | | | Anterior segment; NR | BETA4 SLIM NT rechargeable handle and NT4 table charger (included reducer insert), spare bulb, hard case | | | | | | | |
| | | | | | | | | | | | |
| Portable slit lamp (SL-17) (Kowa Ophthalmic Diagnostic Products, Torrance, CA, USA) (KOWA New Lighter) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | <800 g; 220 × 95 × 220 mm | 4 AAA batteries, dust cover, stand, instruction manual; optional: forehead rest, camera connection adapter | 10 ×, 16 × | Field, clinic | | | Yes | | |
| Slit lamp | | | Anterior segment; NR | 4 AAA batteries, dust cover, stand, instruction manual; optional: forehead rest, camera connection adapter | | | | | | | |
| | | | | | | | | | | | |
| Binocular hand held biomicroscope slit lamp (PSL One, PSL Classic) (Keeler, Malvern, PA USA) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | 900 g; 238 × 116 × 210 mm | Base charger unit, power supply, user instructions, lens cloth | 10 ×, 16 × | Field, clinic | | | Yes | | |
| Slit lamp | | | Anterior segment; 2.5 h | 900 g; 238 × 116 × 210 mm | Base charger unit, power supply, user instructions, lens cloth | 10 ×, 16 × | Field, clinic | | | | |
| | | | | | | | | | | | |
| Handheld Slit Lamp S200 (Digital Eye Center, Miami, FL, USA) (Digital Eye Center, 2021; Digital Eye Center, 2021) | Ocular morbidities | $2090 | Meant for researchers and ophthalmologists | 40 g; NR | Rechargeable battery | 10 ×, 16 × | Field, clinic | | | | |
| Slit lamp | | | Anterior segment; NR | 40 g; NR | Rechargeable battery | 10 ×, 16 × | Field, clinic | | | | |

(continued on next page)
| Device (manufacturer) | Vitamin A biomarker | Pricing (estimated, list price from manufacturer website) | Technical requirements | Portability | Power source | Slit lamps: Magnification | Dioptic range | Interpupillary range | Slit image width(s) | Filters | Target setting | Manufacturer support available | Global availability |
|----------------------|---------------------|-------------------------------------------------|-------------------------|-------------|-------------|--------------------------|---------------|---------------------|---------------------|---------|----------------|-------------------------------|---------------------|
| **Handheld Slit Lamp**<br>S2 (Digital Eye Center, Miami, FL, USA)<br>(Digital Eye Center, 2021; Digital Eye Center, 2021; Digital Eye Center, 2021) | Ocular morbidities | $1500 | Meant for researchers and ophthalmologists<br>Anterior segment; NR | 750 g; 19 × 105 × 230 mm | Rechargeable battery | + + + 10 ×, 16 × | 5 to + 5 | 45–70 mm | 0–10 mm | Heat-absorption, gray, red-free, cobalt blue | Field, clinic | | |
| **Digital portable slit lamp**<br>Microclear Hyperion<br>(Digital Eye Center, Miami, FL, USA)<br>(Digital Eye Center, 2021; Digital Eye Center, 2021; Digital Eye Center, 2021) | Ocular morbidities | $3800 | Meant for researchers and ophthalmologists<br>Anterior segment; NR | 600 g; NR | Rechargeable battery | + + 10 × | NR | NR | 0–10 mm | Heat-absorption, gray, red-free, cobalt blue | Field, clinic | | |
| **Hand held slit lamp**<br>(SL280) (Opticlar, Poole, Dorset)<br>(Optical Visionmed) | Ocular morbidities | $3900 | Meant for researchers and ophthalmologists<br>Anterior segment; 2 h | 880 g; fits in palm of hand<br>Two batteries, battery charger | Rechargeable batteries | + + 10 ×, 16 × | −7 to + 7 | 50–78 mm | 0.15/0.5/0.8/1.6 mm. Circle 12 mm dia. 1 mm square | Green (red free), cobalt blue, neutral density 0.8, clear | Field, clinic | | |
| **Portable slit lamp (PSL)**<br>(Reichert Technologies Inc., Depew, NY, USA)<br>(Reichert Technologies, 2021) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists<br>NR | 680 g; fits in palm of hand<br>Two batteries, battery charger | Rechargeable batteries | + + 10 ×, 16 × | −7 to + 7 | 50–70 mm | 0–11 mm | Cobalt blue, red free, color temperature conversion | Field, clinic | | |
| **Handy Slit Lamp XL-1**<br>(Shin-Nippon by Rexxam Co., Ltd.)<br>(Rexxam, 2021) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists<br>Anterior segment; NR | 700 g (195 × 105 × 230 mm)<br>Carrying case, one battery, battery charger, forehead support, diopter adjustment bar, instruction manual | Rechargeable battery | + + 10 ×, 16 × | −7 to + 7 | 50–70 mm | 0–11 mm | Cobalt blue, green, conversion | Field, clinic | | |
| Device (manufacturer) | Vitamin A biomarker | Pricing (estimated, list price from manufacturer website) | Technical requirements | Portability | Power source | Slit lamps: Magnification | Target setting |
|-----------------------|---------------------|----------------------------------------------------------|------------------------|------------|-------------|--------------------------|----------------|
| Portable slit lamp S150 (Medi-Works, Shanghai, China) (Mediworks, 2021) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | + + + | Rechargeable batteries | 6 × | Field, clinic |
| Slit lamp, attachment for phone | | | | | | | |
| Portable slit lamp SK-LS-1B portable slit lamp (Coburn Technologies, Inc. South Windsor, CT, USA) (Coburn Technologies Inc.) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | + + | Rechargeable batteries | + + + | Field, clinic |
| Slit lamp | + | + + + | + + + | + + + | + + | 0–12 mm | |
| RetEval (LKC Technologies, Gaithersburg, MD, USA) (Technologies, 2019) | Ocular morbidities | Pricing not published | Meant for researchers and ophthalmologists | + + | Rechargeable batteries | + + | Field, clinic |
| Non-mydriatic flash and flicker ERG/VEP device | + | + + + | + + + | + + + | + + | + + | |
| Mobile eye testing unit (Agrawal and Sahu, 2020) | Ocular morbidities: conjunctival xeritis with Bitot’s spot (X1B) or keratomalacia (X3B) (World Health, 2014) | Pricing not published | Meant for researchers, optometrists, ophthalmologists | + + + | Hand-held | N/A | Field |
| Vision drum, trial box, retinoscope, slit-lamp bio-microscope, applanation tonometer, and non-mydriatic fundus camera | + | + + + | + + | + + | + + | + + | |
| Scotopic Sensitivity Tester-1 (LKC Technologies, Gaithersburg, MD, USA) (Congdon et al., 1995, Congdon et al., 2000, Sanchez et al., 1997) | Visual score/threshold | Pricing not published | Meant for researchers and ophthalmologists | + + + | Hand-held | N/A | Field |
| Dark adaptor | + | + + + | + + + | + + | + + | + + | |

(continued on next page)
| Device (manufacturer) | Vitamin A biomarker | Pricing (estimated, list price from manufacturer website) | Technical requirements | Portability | Power source | Slit lamps: Magnification | Diop tic range | Interpupillary range | Slit image width(s) | Target setting | Manufacturing support available | Global availability |
|-----------------------|---------------------|----------------------------------------------------------|------------------------|------------|-------------|--------------------------|----------------|-----------------------|------------------|---------------|-----------------------------|---------------------|
| Portable field dark adaptometer (custom) (Labrique et al., 2015, Palmer et al., 2015, Palmer et al., 2016) Dark adaptometer | Visual score/ threshold Pupillary score/ threshold Pupillary dynamics | Pricing not published | Meant for researchers and ophthalmologists Retina; binocular partial bleaching with camera flash (>3400 cd-s/m²) | Portable: “Its size and weight allowed it to be carried long distances to areas unreachable by car.” | Laptop-powered | 10 tests per day | + | + | + | + | Field, lab | N/A; not commercially available |
| Emtech A meter V.01 (custom) (Mehta, 2018, Mehta, 2019b, Mehta, 2019a, Mehta and Mehta, 2018, Banerjee, 2019) Dark adaptometer | Dark adaptation; identify pictorial representation of objects at low light intensity | Pricing not published | Meant for researchers and ophthalmologists Retina; NR | Handheld | NR | Results output to microSD card | + | + | + | + | Field, lab | N/A; not commercially available |
| Custom-built portable field dark adaptometer (Steven and Wald, 1941, Wald, 1941) Dark adaptometer | Visual threshold Dark adaptation | Pricing not published | Meant for researchers and ophthalmologists Retina; NR | 8.4 kg; 21.6 × 21.6 × 29.2 cm; “approximate size and shape of a pocket lamp” Eyepiece, test unit, cord, cabinet | Three 2-volt discharge storage cells | Results in log units | + | + | + | + | Field, lab | N/A; not commercially available |
| Reference method: Goldmann-Weekers dark adaptometer (Haag-Streit) Dark adaptometer | Visual threshold Dark adaptation | Not available for purchase | Meant for researchers and ophthalmologists; some models require conversion table for a calibration error (Maggiano et al., 1978) Retina, with pupils dilated; NR | Requires external power source N/A | Results: luminance in units of log microapostilbs, which requires conversion to the more contemporary unit of luminance, cd/m² | + | + | + | + | Clinic | No |

Notes: NR, not reported. + + + = best. + + = acceptable. + = not acceptable.
Table 2
Definitions of vitamin A deficiency, by sample type and device.

| Blood (whole, serum, plasma)* | Typeb | Device (studies using) | Deficiency or insufficiency definitions usedc |
|------------------------------|--------|------------------------|---------------------------------------------|
| Retinol                      | Status | iCheck Fluoro (BioAnalyt)4 (Boateng et al., 2018, Elom et al., 2015, Ghaffari et al., 2019, Raiha et al., 2017, Schweigert et al., 2011a, Bechir et al., 2012, Crump et al., 2017, Schweigert et al., 2011b, Whang et al., 2012, Zambo et al., 2012) | Severe/clinical deficiency: ≤0.35 µmol/L (10 µg/dL) (WHO, 2011) |
|                              |        | Spectrophotometer model 450 (Sequoia-Turner) (Marinovic et al., 1997) | Low/subclinical deficiency: ≤0.70 µmol/L (20 µg/dL) (WHO, 2011) |
|                              |        | CRAFTI (Craft Technologies) (Chaimongkol et al., 2011) | Insufficiency: ≤1.05 µmol/L (30 µg/dL) (de Pee and Dary, 2002) |
| RBP                          | Status | Custom REI (Jix et al., 2004) | Deficiency: ≤0.70 µmol/L (Jix et al., 2004) |
|                              |        | EEµPAD (Lee et al., 2016) | Deficiency: <16.3 µg/mL (Lee et al., 2016) |
|                              |        | Tidbit (Lu and Erickson, 2017, Lu et al., 2017) ± HYPER filtration (Lu et al., 2018) | Deficiency: <14.7 µg/mL (correlated with retinol ≤ 0.70 µmol/L) (Lu et al., 2017) |
| Beta-carotene                | Not defined | Custom Ag-Ab reaction (Ciaiolo et al., 2015) | Not defined (Ciaiolo et al., 2015) |
| Milk Biomarker Retinol       | Typeb  | iCheck Carotene (BioAnalyt)4 (Ghaffari et al., 2019, Hye et al., 2020, Klein et al., 2013, Livingston et al., 2020, Meinke et al., 2016, Raiha et al., 2012, Madureira et al., 2020) | Humans: No official cut-off defined (von Lintig, 2020) |
|                              |        | (no studies) | Cattle: not defined (Blaner, 2020) |
|                              |        | (no studies) | Cattle: not defined |
| Eyes Biomarker Visual score/threshold | Typeb  | Device (studies using) | Deficiency or insufficiency definitions usedc |
|                              | Function | Scotopic sensitivity hand-held illuminator (LKC Technologies, Inc.) (Congdon et al., 1995, Sanchez et al., 1997, Reilly et al., 2006) | Humans: Inadequate: <1.05 µmol/L (Bliner, 2020) |
|                              |        | EmTech A meter V.01† (Mehta, 2018) | or milk fat < 8 µg/g (Bliner, 2020) |
|                              |        | Portable visual adaptometer (Wald, 1941, Steven and Wald, 1941) | Cattle: not defined |
|                              |        | Scotopic Sensitivity Tester-1TM (SST-1) (Peters et al., 2000) | Humans: not defined |
|                              |        | Portable field dark adaptometer (PFDA) or digital pupillometer (Labrique et al., 2015, Palmer et al., 2015, Palmer et al., 2016) | Cattle: not defined |
| Dark adaptation: pupillary score/responsiveness | Function | Portable field dark adaptometer (PFDA) or digital pupillometer (Labrique et al., 2015, Palmer et al., 2015, Palmer et al., 2016) | (continued on next page) |
Table 2 (continued)

| Blood (whole, serum, plasma) | Type | Device (studies using) | Deficiency or insufficiency definitions used |
|-----------------------------|------|-----------------------|---------------------------------------------|
| to post-stimulus divided by number of frames per second (Labrique et al., 2015) | Function | Scotopic Sensitivity Tester-1™ (SST-1) (Peters et al., 2000) | No official cut-off defined |
| Rod function (dark-adapted rod full-field electro-retinogram responses (Peters et al., 2000)) | Function | Mobile eye unit (comprised of vision drum, trial box, retinoscope, slit-lamp bio-microscope, application tonometer, non-mydriatic fundus camera) (Agrawal and Sahu, 2020) | Night blindness, conjunctival xerosis with Bitot’s spots (XIB), keratomalacia (XIB), ocular lesions (Agrawal and Sahu, 2020) (stages as designated by World Health Organization grading system (World Health, 2014)) |
| Ocular morbidities | Function | Heine HSL-100 biomicroscope equipped with portable slit lamp (Melo et al., 2004) | Ocular lesions (Melo et al., 2004) |

Notes: Ag-Ab, antigen–antibody; EE-µPAD, electronics enabled microfluidic paper-based analytical device; HYPER, High-yield paper-based quantitative blood separation system; RBP, retinol-binding protein; REI, rapid enzyme immunoassay.

h cd/m² is the SI unit of luminance (Congdon et al., 2000).

* Adapted from reference (Tanumihardjo et al., 2016).
† Whereas serum or plasma is required to measure circulating vitamin A, some devices can use whole blood as the sample input.
‡ Defined by global standards (e.g., World Health Organization) or by study authors.
§ An earlier version of this device is referenced as iCheck Ret 435–1 (Bechir et al., 2012).
¶ Correlated with retinol < 0.70 µmol/L, when sandwich ELISA is used for RBP measurement (Erhardt et al., 2004).
‖ An earlier version of this device is referenced as iCheck Ret 515–2 (Bechir et al., 2012).
* Device also referenced as “dark adaptometer” (Banerjee, 2019) or “In-Direct method and system for Vitamin A deficiency detection” (Mehta, 2019b, Mehta, 2019a, Mehta and Mehta, 2018).

We identified two microfluidics-based devices, the EE-µPAD (Lee et al., 2016) and the Tidbit with HYPER filtration (Lu and Erickson, 2017, Lu et al., 2017, Lu et al., 2018), both of which were able to separate whole blood into serum, detect VAD at high sensitivity and specificity with respect to the reference ELISA test, and send results to a mobile device (Table 5d). We note that the ELISA test may not be a suitable reference method for assessing VAD, owing to inherent problems with antibodies to RBP. Neither device is currently on the market.

Although we identified several portable dark adaptometers (Table 1b), we found only one validation study between a portable dark adaptometer, the Scotopic Sensitivity-Tester 1 by LKC Technologies, and a reference standard, the Goldmann-Weekers dark adaptometer used in clinical settings (Peters et al., 2000) (Table 5e). The portable device was comparable to the reference standard in its sensitivity in identifying elevated final thresholds for dark adaptation, with a correlation (R²) of 0.77. However, this study was performed in the US in an eye clinic, and it remains to be tested and compared with the reference standard in field settings.

The iCheck Fluoro, a portable fluorometer, was used to measure bovine blood samples for retinol (Table 5f). Compared with HPLC, mean differences in whole blood, plasma, or serum retinol ranged from −0.01 µmol/L to 26.5 µmol/L, and the iCheck generally displayed higher values than HPLC. The correlation between the iCheck Fluoro and HPLC was positive, ranging in R² values from 0.61 to 0.96. Weaker correlations were observed in cows (range: 0.78–88) than calves (0.90–0.96).

Raila et al. (2017) also compared the correlation between bovine whole blood retinol (n = 10) and plasma retinol (n = 10), both measured by the index test iCheck Fluoro, and found a significant positive correlation (R² = 0.87) (Raila et al., 2017). No studies reported sensitivity and specificity, or distinguished specific %CVs. Bias analysis indicated acceptable agreement between the device performance and HPLC.

The iCheck Carotene, a portable photometer, was used to measure carotenoids in bovine whole blood and plasma. Mean differences in beta-carotene concentration ranged from −0.29 mg/L to 0.26 mg/L in plasma samples in cows and calves (Table 5g). The correlation between iCheck Carotene and HPLC was high, with R² between 0.93...
Table 3
Description of included studies comparing a portable method against a reference standard method.

| Author          | Year  | Device            | Manufacturer                  | Sample tested | Biomarker | Study population           | Test location (field/laboratory, country) | Reference method | Ref.                  |
|-----------------|-------|-------------------|--------------------------------|---------------|-----------|-----------------------------|------------------------------------------|------------------|----------------------|
| Chaimongkol    | 2011  | CRAFTi            | Eurofin Craft Technologies     | Serum         | Retinol   | Study cohorts               | Thailand                                 | HPLC             | (Chaimongkol et al., 2011) |
| Chaimongkol    | 2008a | CRAFTi            | Eurofin Craft Technologies     | Serum         | Retinol   | Study cohorts               | Thailand                                 | HPLC             | (Chaimongkol et al., 2008) |
| Ciaiolo        | 2015  | Custom Ab-Ag reaction | Custom                        | Retinol Serum,| Patients | Italy                      | Nephelometry                             | (Ciaiolo et al., 2015) |
| Lee            | 2016  | EE-µPAD           | Custom                        | Serum         | RBP       | Commercial (ProMedDx)       | USA                                      | ELISA            | (Lee et al., 2016) |
| BioAnalyt report (year: NR) | 2012 | iCheck Carotene | BioAnalyt | Whole blood or plasma | Dairy cows and calves | NR | HPLC | (BioAnalyt, NR) |
| Raila          | 2017  | iCheck Fluoro     | BioAnalyt                     | Beta-carotene Plasma | Holstein-Friesian cows, local farm | Germany, Ireland, France | HPLC | (Raila et al., 2017) |
| Ghaffari       | 2019  | iCheck Carotene   | BioAnalyt                     | Beta-carotene Plasma | Holstein cows and calves from institutional farms | Germany | HPLC | (Ghaffari et al., 2019) |
| Schweigert     | 2011a | iCheck Fluoro     | BioAnalyt                     | Retinol Whole blood, serum | Dairy cows and bulls, institutional farms | Germany, Japan | HPLC | (Schweigert et al., 2011a) |
| Schweigert     | 2011b | iCheck Fluoro     | BioAnalyt                     | Retinol Milk | Study cohorts and local cows | Germany | HPLC | (Schweigert et al., 2011b) |
| Abebe          | 2019  | iCheck Fluoro     | BioAnalyt                     | Retinol Milk | Study cohorts | Ethiopia | HPLC | (Abebe et al., 2019) |
| Elom           | 2015  | iCheck Fluoro     | BioAnalyt                     | Retinol Serum | Study cohorts | Morocco | HPLC | (Elom et al., 2015) |
| Engle-Stone    | 2014  | iCheck Fluoro     | BioAnalyt                     | Retinol Milk | Study cohorts | Cameroon | HPLC | (Engle-Stone et al., 2014) |
| Peters         | 2000  | SST-1             | LKC Technologies               | RBP Eyes      | Patients of Retina Foundation of the Southwest | USA | Goldmann-Weekers Dark Adapometer | (Peters et al., 2000) |
| Lu             | 2017  | Tidbit, ± HYPER filtration system | Custom                        | RBP Serum      | Commercial (Research Blood Components LLC) | USA | ELISA | (Lu and Erickson, 2017, Lu et al., 2017, Lu et al., 2018) |

Notes: Ag-Ab, antigen-antibody; EE-µPAD, electronics enabled microfluidic paper-based analytical device; EIA, enzyme immunoassay; HYPER, high-yield paper-based quantitative blood separation system; RBP, retinol-binding protein; RID, radial immunodiffusion assay; SST-1, Scotopic Sensitivity Tester-1.

a Meeting abstract, therefore some details are not reported.
b RID may be considered a second index test, because it is not a reference standard; however, in the study, only the first index test, RBP-EIA was the assay undergoing development and validation.
### Table 4
Assessment of devices against manufacturer-reported performance, according to ASSURED* criteria. (Ghaffari et al., 2019; Raila et al., 2017; Schweigert et al., 2011b; Schweigert et al., 2011a; Abebe et al., 2019; Elom et al., 2015; Engle-Stone et al., 2015; Raila et al., 2012; Ghaffari et al., 2019.)

| Device, operational range, and sample types listed | Cost of device and consumables | Calibration and method training requirement | Sample volume and preparation | Time required for analysis | Special storage conditions for device and consumables | Equipment-free | Deliverable to end-users | Global availability and manufacturer support |
|--------------------------------------------------|-------------------------------|---------------------------------------------|---------------------------------|-------------------------|-------------------------------------------------|----------------|--------------------------|-----------------------------------------------|
| **Stated criteria**  
(1Check Fluorescence Website Accessed March 2, 2021)  
Vitamin A (retinol) as retinol phosphate, retinol acetate and retinol esters, operational range: 50-4000 μg RSL/L  
Breast milk, whole blood, serum | NR | Factory set (standards included for controls)  
1 day training | 0.5 mL  
If solid: dilute and homogenize in distilled or bottled water | ≤10 min  
20-25°C, no direct sunlight, 13-month shelf-life, upright | Devices: 11x4x40 cm, 0.45 kg  
Test kit: 28x14.5x16.5 cm  
All required consumables and equipment included in kit | Yes | Yes |
| Ghaffari et al. (Sheffett et al., 2019)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Germany |
| Raila et al. (Raila et al., 2017)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Germany and Japan |
| Schweigert et al. (Schweigert et al., 2011)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter  
(“can camp out analysis on the spot”) | Test done in Germany |
| Schweigert et al. (Schweigert et al., 2011)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in “low resource setting” |
| Abebe et al. (Abebe et al., 2019)  
Tested retinol in breast milk | NR | “low-cost” | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter  
(“User-friendly”) | Test done in Ethiopia |
| Even 2015 (Elom et al., 2015)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Morocco |
| Engle-Stone et al. (Engle-Stone et al., 2015)  
Tested retinol in breast milk | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Cameroon |
| **Stated criteria**  
(1Check Carotene Website Accessed March 2, 2021)  
Total carotenoids, operational range: 0.1–15.0 mg/l  
Caulisium, cattle whole blood and serum | NR | Factory set (standards included for controls)  
1 day training | 0.4 mL  
<10 min  
20–25°C, no direct sunlight, 13-month shelf-life, upright | Devices: 11x4x40 cm, 0.45 kg  
Test kit: 28x14.5x16.5 cm  
All required consumables and equipment included in kit | Yes | Yes |
| Bioreflex report (BioAnalyx)  
NR | NR | NR | 0.4 mL | ≤5 min  
20–25°C, no direct sunlight, 13-month shelf-life, upright | Devices: 11x4x40 cm, 0.45 kg  
Test kit: 28x14.5x16.5 cm  
All required consumables and equipment included in kit | Yes | Yes |
| **Stated criteria**  
(1Check Carotene Website Accessed March 2, 2021)  
Tested beta-carotene content in bovine plasma | NR | NR | NR | 0.4 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Germany, Ireland, France |
| Raila et al. (Raila et al., 2012)  
Tested beta-carotene content in bovine whole blood and plasma | NR | NR | NR | 0.4 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Germany, Ireland, France |
| Ghaffari et al. (Sheffett et al., 2019)  
Tested beta-carotene content in bovine plasma | NR | NR | NR | 0.5 mL | ≤5 min | NR | Field-portable fluorimeter | Test done in Germany |

**Notes:** HPLC: high-performance liquid chromatography; n/a, not available; NR, not reported; RE, retinol equivalents (units reported by manufacturer). However, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of Food Technologists, 2001).

*ASSURED Criteria: adapted from (Koesma et al., 2017)

*Corresponding 1Check values were corrected by subtracting the mean difference between 1Check and HPLC from the actual reading

*Ranges given as 95% confidence interval
Table 5a
Portable fluorometers: device performance in human blood samples.

| Portable device vs. reference | iCheck Fluoro vs. HPLC | iCheck Fluoro vs. HPLC | CRAFTi vs. HPLC | CRAFTi vs. HPLC |
|------------------------------|------------------------|------------------------|----------------|-----------------|
| **Vitamin A biomarker**      | Retinol\(^a\)          | Vitamin A\(^a\)        | Retinol\(^a\)  | Retinol\(^a\)   |
| **Sample type**              | Plasma                  | Serum                   | Serum           | Serum           |
| **Study population**         | 89 children             | 56 samples              | 38 women        | 75 women, 143 children |
| **Concentration difference** | MD: 0 min: 1.9 | µg/L ± 23.2          | NR              | MD: −0.07       |
|                             | MD: 15 min: −8.0 | µg/L + 22.7          | NR              | MD: −0.07       |
| **Correlation coefficient**  | 0 min: 0.98            | NR                     | NR              | 0.77            |
|                             | 15 min: 0.98           | NR                     | NR              |                 |
| **R\(^2\)**                  | NR                     | >0.95                  | NR              |                 |
| **Regression equation**      | NR                     | Slope = 0.81           | NR              |                 |
| **Operational range**        | NR                     | NR                     | NR              | 0.5–1.5 µmol/L  |
| **VAD or VAI (%), index vs. ref** | Not defined: N = 2/89 vs. NR | NR                     | NR              | <0.7 µmol/L: 9.2% vs. 2.8% |

**Precision**
- **Sensitivity**
  - NR
  - NR
  - NR
  - NR
- **Specificity**
  - NR
  - NR
  - NR
  - NR
- **Intra-assay %CV**
  - NR
  - 2.5–6.4 %\(^b\)
  - Agreement noted but not quantified
  - 3.97% vs. 3.45%
- **Inter-assay %CV**
  - NR
  - NR
  - NR
  - NR
- **Inter-observer %CV**
  - NR
  - NR
  - NR
  - NR
- **Bland Altman analysis comments**
  - No commentary. At 0 min, 3 values fell outside 2 SDs. At 15 min, 4 values fell outside 2 SDs
  - No systematic bias
  - No systematic bias; most values within ± 0.5 with normally distributed serum retinol values

**Reference**
- Elom et al., 2015
- Schweigert et al., 2011
- Chaimongkol et al., 2008
- Chaimongkol et al., 2011

Notes: MD, mean difference; NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of medicine, 2001)); SD, standard deviation; VAD, vitamin A deficiency; VAI, vitamin A insufficiency.

\(^a\) Units: µg/L or µg RE/L.

\(^b\) Specific %CVs not distinguished.

\(^c\) Study abstract, lacking some details.

Table 5b
Portable fluorometers: device performance in human and bovine milk samples.

| Portable device vs. reference | Human milk | Bovine milk |
|------------------------------|------------|------------|
|                              | iCheck Fluoro vs. HPLC | iCheck Fluoro vs. HPLC | iCheck Fluoro vs. HPLC | iCheck Fluoro vs. HPLC |
| **Vitamin A biomarker**      | Retinol\(^a\), milk fat\(^c\) | Retinol\(^a\), milk fat\(^c\) | Retinol\(^a\) | Retinol\(^a\) |
| **Study population**         | 104 women              | 75 women, 154 samples | 1 woman, 154 samples | 1 woman, 16 samples |
| **Concentration difference** | MD: 0.01 µmol/L, 0.03 µg/g fat | −0.83 ± 0.14 µmol/L, −5.6 ± 0.7 µg/g fat | 103% ± 13 | 105% ± 9 |
| **Correlation coefficient**  | 0.57 (unadj), 0.59 (adj) | 0.85 (unadj), 0.79 (adj) | NR | NR |
|                             | 0.32 (unadj), 0.35 (adj) | 0.72 (unadj), 0.62 (adj) | NR | NR |
| **Regression equation**      | NR | NR | NR | NR |
| **Operational range**        | 50–3000 µg RE/L | 50–3000 µg RE/L | NR | NR |
| **VAD or VAI (%), index vs. ref** | <1.05 µmol/L: 87% vs. 76% | <1.05 µmol/L: 3.9% vs. 2.60% | <8 µg/g fat: 9% vs. 2% | 21 cows |
| **Precision**                | Sensitivity
  - NR
  - Too few VAD cases to examine
  - NR
  - NR
  - NR
| **Specificity**              | NR
  - Too few VAD cases to examine
  - NR
  - NR
  - NR
| **Intra-assay %CV**          | 1.1% vs. 1.5–1.6% | 0.6% | NR | NR |
| **Inter-assay %CV**          | NR | NR | NR | NR |
| **Inter-observer %CV**       | NR | NR | NR | NR |
| **Bland Altman analysis comments** | Used to present mean difference between measurements; mean difference not significantly different from zero | Plotted but no conclusion drawn; appears to show 8 values outside of 2 SDs (µmol/L retinol) and 8 values outside of 2 SDs (µg/g fat) | NR | NR |
| **Reference**                | Abebe et al., 2019 | Engle-Stone et al., 2014 | Schweigert et al., 2011b | Schweigert et al., 2011b |

Notes: MD, mean difference; NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of medicine, 2001)); VAD, vitamin A deficiency; VAI, vitamin A insufficiency.

\(^a\) Units: µg/L or µg RE/L.

\(^b\) Units: µg/g fat.

\(^c\) Adjusted for breast milk fat content.

\(^d\) Not reported but based on previous studies using same device.

\(^e\) Specific %CVs not distinguished.
and 0.99. No studies reported sensitivity, specificity, or specific %CVs. Bias analysis revealed an acceptable level of agreement between the device performance and that of HPLC.

Future perspectives and recommendations

Gaps and recommendations

On the basis of our review of the literature, portable devices fell into five categories:

1. Portable fluorometers
2. Portable photometers
3. Field-friendly immunoassays and/or microfluidics-based devices
4. Slit lamps
5. Dark adaptometers

We found that, although many portable devices for quantifying vitamin A have been developed and described, only a few devices appear to be currently on the market or commercially available; of these, only two had easily accessible performance criteria information on the manufacturers’ websites related to vitamin A measurement. Studies tended not to report on portable device characteristics. Some major gaps involve the lack of data reported by studies. Few studies have reported the portable device’s sensitivity and specificity in detecting VAD compared with the reference standard method—a necessary metric for validation and adoption by randomized trials. Furthermore, only the iCheck devices were assessed in more than two studies; other devices should be analyzed further for validation.

Minimal set of criteria for point-of-need devices

See Fig. 2.

The device should:

1. Be lightweight with a small form factor for easy transport to the necessary location as needed.
2. Be standalone without needing additional equipment and self-powered, and should pre-store all the required reagents for the test, and use common reagents that are available on the market.
### Table 5d
Portable microfluidics-based methods: device performance in human blood.

| Portable device vs. reference | EE-µPAD, vs. ELISA | Tidbit with HYPER platform, vs. ELISA<sup>a</sup> | Tidbit without HYPER platform, vs. ELISA |
|-------------------------------|---------------------|-----------------------------------------------|------------------------------------------|
| **Vitamin A biomarker<sup>f</sup>** | RBP<sup>b</sup> | RBP<sup>b</sup> | RBP<sup>b</sup> |
| **Sample type** | Whole blood | Whole blood | Serum |
| **Study population** | 95 adults (commercial) | 12 adults | 43 adults (commercial) |
| **Concentration difference** | NR | NR | NR |
| **Correlation coefficient** | NR | NR | 0.75 |
| **R<sup>2</sup> (index, unless specified)** | NR | Index: 0.81 vs. ref: >0.99 | 0.56 |
| **Regression equation** | NR | Slope = 0.99 | Slope = 0.97 |
| **RMSE, index vs. ref** | NR | 3.75 vs. 1.3 µg/mL | 4.34 µg/mL vs. NR |
| **Operational range** | <~10–70 µg/mL (graph) | <~5-20 µg/mL (graph) | 2.2–20 µg/mL (0.10–0.95 µmol/L) |
| **VAD or VAI (%), index vs. ref** | <16.3 µg/mL: AUC = 0.7139 vs. 17.2% | NR | <14.7 µg/mL (≤0.70 µmol/L): NR vs. 9.3% |

**Precision**

| | Sensitivity | Specificity | Intra-assay %CV | Inter-assay %CV | Inter-observer %CV | Bland Altman analysis comments |
|---|---|---|---|---|---|---|
| **Vitamin A biomarker<sup>f</sup>** | 75% at MFR cutoff, 0.831 | 62.3% at MFR cutoff, 0.831 | 10.8% vs. 3.9% | NR | NR | NR |
| **Operational range** | NR | NR | 20.3% deviation per test strip, recommend taking average of 3 test strips | NR | NR | Bias at ~0.05 µg/mL (~2.3 nmol/L) |
| **VAD or VAI (%), index vs. ref** | NR | NR | NR | NR | NR |

**Reference**

(Lee et al., 2016) (Lee and Erickson, 2017, Lu et al., 2017, Lu et al., 2018) (Lu and Erickson, 2017, Lu et al., 2017)

**Notes:** MD, mean difference; MFR, multi-faceted ratio i.e., the ratio of the light transmission in the test area to that in the background control area, calculated for RBP for each sample repeat. NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of medicine, 2001); RMSE, root mean squared error; VAD, vitamin A deficiency; VAI, vitamin A insufficiency.

<sup>a</sup> Reference ELISA utilized samples that were filtered using HYPER system.

<sup>b</sup> Units: µg/mL, mg/L, or µmol/L.

### Table 5e
Other portable devices: device performance in for assessing eye function (vision).

| Eyes Index 1<sup>1</sup> vs. reference<sup>bc</sup> | SST-1 vs. Goldmann-Weekers dark adaptometer<sup>d</sup> |
|---|---|
| **Validation of portable device** | Dark adaptation final threshold<sup>2</sup> |
| **Vitamin A biomarker** | 87 patients<sup>e</sup> and 24 healthy children and adults |
| **Study population** | NR |
| **Concentration difference** | 0.88 (adjusted for ceiling effect) |
| **Correlation coefficient** | 0.77 |
| **R<sup>2</sup> (index, unless specified)** | “intercept close to zero” |
| **Regression equation** | 0–30 dB stimulus intensity range (0-3 log units) |
| **Operational range** | Elevated final thresholds: 75% vs. 82% |
| **VAD or VAI (%), index vs. ref** | Final threshold elevated: 74.7% |

**Precision**

| | Sensitivity | Specificity | Intra-assay %CV | Inter-assay %CV | Inter-observer %CV | Bland Altman analysis comments |
|---|---|---|---|---|---|---|
| **Vitamin A biomarker** | NR | NR | NR | NR | NR | NR |
| **Operational range** | NR | NR | NR | NR | NR | NR |

**Reference**

(Peters et al., 2000)

**Notes:** MD, mean difference; MFR, multi-faceted ratio i.e., the ratio of the light transmission in the test area to that in the background control area, calculated for RBP for each sample repeat. NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of medicine, 2001); RMSE, root mean squared error; VAD, vitamin A deficiency; VAI, vitamin A insufficiency.

<sup>a</sup> Reference analyte is dark adaptation final threshold.

<sup>b</sup> Units: log units.

<sup>c</sup> Patients had retinal degeneration with mild to severe loss of rod function from full-field ERG results.

<sup>d</sup> Reference analyte is dark adaptation final threshold.

<sup>e</sup> Reference analyte is dark adaptation final threshold.
### Table 5f

Portable fluorometers: device performance in bovine blood samples.

| Portable device vs. reference | iCheck Fluoro vs. HPLC<sup>a</sup> | iCheck Fluoro vs. HPLC<sup>a</sup> | iCheck Fluoro vs. HPLC<sup>a</sup> | iCheck Fluoro vs. HPLC<sup>a</sup> | iCheck Fluoro vs. HPLC<sup>a</sup> |
|-------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Vitamin A biomarker           | Vitamin A<sup>a</sup>              | Vitamin A<sup>a</sup>              | Vitamin A<sup>a</sup>              | Vitamin A<sup>a</sup>              | Vitamin A<sup>a</sup>              |
| Sample type                   | Whole blood                        | Whole blood                        | Whole blood                        | Whole blood                        | Whole blood                        |
| Study population              | 28 cows                            | 11 calves                          | 10 cows                            | 28 cows                            | 11 calves                          |
| Concentration range           | 184–336                            | 0.78                               | 0.90                               | 0.78                               | 0.90                               |
| Correlation coefficient R²    | 0.61                               | 0.81                               | 0.92                               | 0.77                               | 0.94                               |
| Regression equation           | y = 0.77 + 11.26                    | NR                                 | NR                                 | NR                                 | NR                                 |
| Operational range             | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| VAD or VAI (µg)               | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| Precision                     | NR                                 | NR                                 | States test is sensitive and specific but does not quantify these | States test is sensitive and specific but does not quantify these | States test is sensitive and specific but does not quantify these |
| Sensitivity                   | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| Specificity                   | NR                                 | NR                                 | States test is sensitive and specific but does not quantify these | States test is sensitive and specific but does not quantify these | States test is sensitive and specific but does not quantify these |
| Intra-assay % CV              | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| Inter-assay % CV              | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| Inter-observer %CV            | NR                                 | NR                                 | NR                                 | NR                                 | NR                                 |
| Bland-Altman analysis comments| Good level of agreement and no systematic error. 5% of total values fell outside 95% acceptability limits (Ghaffari et al., 2019) | Good level of agreement and no systematic error. 4% of total values fell outside the 95% acceptability limits (Ghaffari et al., 2019) | Good level of agreement and no systematic error. 1% value fell outside of 95% acceptability limits (Ghaffari et al., 2019) | Good level of agreement and no systematic error. 1% value fell outside of 95% acceptability limits (Ghaffari et al., 2019) | Good level of agreement and no systematic error. 4% of values fell outside the 95% acceptability limits |
| Reference                     | Ghaffari et al., 2019              | Ghaffari et al., 2019              | Ghaffari et al., 2019              | Ghaffari et al., 2019              | Ghaffari et al., 2019              |

**Notes:** MD, mean difference; NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer)—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of medicine, 2001); VAD, vitamin A deficiency; VAI, vitamin A insufficiency.

<sup>1</sup> Reference sample is in plasma.

<sup>2</sup> Reference sample is serum.

<sup>3</sup> Units: µg RE/L.

<sup>4</sup> Units: µmol/L.

<sup>5</sup> Reported value from this study appears to be a repeated value for cow whole blood beta carotene content given as 2.09–8.15 mg/L, instead of the calf whole blood vitamin A reported in µg RE/L.

<sup>6</sup> Values appear to be an average of intra- and inter-assay %CV.

3. Be easy to use with minimal processing steps in the protocol, and should require minimal training effort.

4. Have analytical performance (e.g., %CV < 5% or within Bland Altman 95% limits of agreement) comparable to those of the current laboratory standards, with a capability to test various biological samples.

5. Be affordable and capable of scaling up with locally available consumables where needed.

6. Be able to connect to the internet or an external hard drive with a built-in data management system to allow the test results to be reliably stored and transferred.

7. Be able to output test results quickly and present in a format that is easy to interpret.

### Conclusions

In this review, we identified 25 portable methods or devices for a variety of biological sample types including those of human (blood, milk, and eye/vision) and animal (blood and milk) origin. These included nine methods measuring biochemical markers of vitamin A or VAD (serum retinol, RBP, milk retinol, retinyl palmitate, and retinyl esters) and 17 portable methods measuring functional biomarkers (measures of eye health, for example dark adaptation).

The iCheck devices, including iCheck Carotene and iCheck Fluoro—for measuring total carotenoids or beta-carotene, or for measuring retinol, retinyl palmitate, retinyl acetate, or other esters, respectively, in blood or milk—were the only devices with manufacturer-reported
### Portable photometers: device performance in bovine blood samples.

| Portable device vs. reference | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> | iCheck Carotene vs. HPLC<sup>a</sup> |
|-----------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| **Vitamin A biomarker**     |                                      |                                      |                                      |                                      |                                      |                                      |                                      |
| Sample type                 | Whole blood                          | Whole blood                          | Whole blood                          | Plasma                               | Plasma                               | Plasma                               | Plasma                               |
| Study                       | 28 cows                              | 11 calves                            | 23 cows                              | 28 cows                              | 11 calves                            | NR, cows and calves                  | 166 cows                             |
| Concentration difference    | NR                                   | NR                                   | MD: 0.21                             | MD: −0.29                            | MD: 0.02                             | NR                                   | MD: 0.26                             |
| Correlation coefficient     | 0.98                                 | 0.98                                 | 0.99                                 | 0.97                                 | 0.98                                 | NR                                   | 0.99                                 |
| R<sup>2</sup>               | 0.97                                 | 0.99<sup>b</sup>                     | 0.99                                 | 0.93                                 | 0.96<sup>c</sup>                     | 0.97                                 | 0.98                                 |
| Regression equation         | y = 0.97x + 0.17<sup>d</sup>         | NR                                   | y = 0.97x + 0.40<sup>e</sup>         | y = 0.90x + 0.17<sup>f</sup>         | y = 0.98x + 0.31<sup>g</sup>         | y = 0.98x + 0.31<sup>g</sup>         | y = 0.98x + 0.31<sup>g</sup>         |
| Operational range           | NR                                   | 0.4–18 mg/L                          | NR                                   | NR                                   | NR                                   | NR                                   | 0.4–18 mg/L                          |
| **Precision**               |                                      |                                      |                                      |                                      |                                      |                                      |                                      |
| Sensitivity                 | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   |
| Specificity                 | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   |
| Intra-assay% CV             | NR                                   | NR                                   | 5.5% vs. 2.3%<sup>f</sup>           | NR                                   | NR                                   | NR                                   | NR                                   |
| Inter-assay% CV             | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   |
| Inter-observer % CV         | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   | NR                                   |
| **Bland Altman analysis**   | A good level of agreement and no systematic error for β-carotene and vitamin A; only 5% of the differences in measured values fell outside the 95% acceptability limits for β-carotene in dairy cows<sup>h</sup> | A good level of agreement and no systematic error for β-carotene and vitamin A; only 5% of the differences in measured values fell outside the 95% acceptability limits for β-carotene in dairy cows<sup>h</sup> | Graph presented, no comment (appears to have good agreement) | Systematic error did not occur between methods: 4% of differences outside 95% limits<sup>i</sup> | Systematic error did not occur between methods: 4% of differences outside 95% limits<sup>i</sup> | Systematic error did not occur between methods: 4% of differences outside 95% limits<sup>i</sup> | Systematic error did not occur between methods: 4% of differences outside 95% limits<sup>i</sup> |
| Reference                   | (Ghaffari et al., 2019)              | (Raila et al., 2012)                 | (Ghaffari et al., 2019)              | (BioAnalyt, NR)                      | (BioAnalyt, NR)                      | (BioAnalyt, NR)                      | (BioAnalyt, NR)                      |

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### Notes:

- MD: mean difference; NR, not reported; RE, retinol equivalents defined as the sum of retinol and retinyl esters, equal to 3.3 International Units (IU) of vitamin A or as 1 µg (units reported by manufacturer—however, retinol activity equivalents (RAE) are the preferred unit for reporting (Institute of Medicine, 2001).
- Reference sample is in plasma.
- Units: mg/L.
- Average from reference analyses done in Germany and Switzerland.
- Reference analysis done in Germany.
- Reference analysis done in Switzerland.
- Appears to represent the average CV for both whole blood and plasma samples.

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The performance metrics as well as the most information and data available to ascertain the method’s accuracy and precision with respect to those of a gold standard such as HPLC. These methods, in addition to the CRAFTi portable fluorometer, as compared with HPLC, were thus considered acceptable for measuring both blood and milk for biochemical biomarkers of vitamin A and detecting vitamin A deficiency.

In measuring human or cow milk samples’ retinol concentration, the iCheck Fluoro had variable performance across studies, including both lower and higher values than the gold standard HPLC, thus leading to weaker correlation values than those calculated for blood samples. However, the mean differences were < 1 µmol/L, and the values were considered to be within the expected variance. Correlation was improved by diluting the samples; dilution may be required for higher accuracy when the portable method is used.

Several portable immunoassays (RBP-REI, RID, general immunoassay) and microfluidics-based methods (EE-microfluidics, TIDBIT with or without HYPER platform) for measuring RBP in human blood had acceptable correlations with HPLC reference methods and similar detection of VAD. However, these assays appeared not to be commercially available.

One study has measured eye function with a portable dark adapter (Scotopic Sensitivity Tester-I), which had comparable results to the gold standard, a Goldmann-Weekers dark adapterometer. However, field studies using this device in comparison to a reference remain to be performed. Given the importance of eye health as a functional indicator of vitamin A deficiency, this gap in the literature is substantial.

Finally, the iCheck Fluoro was used for measuring bovine blood samples for retinol. Generally, the retinol values were higher than those in samples tested by HPLC. Retinol measurements in calves appeared to have stronger correlations than retinol in cow’s blood.

Several studies examined the accuracy of the iCheck Carotene, as compared with HPLC, in determining carotenoid content in cow’s blood. Strong correlations with acceptable levels of agreement were observed between device performance and HPLC performance.

In summary, the iCheck devices are commercially available and are acceptable for measuring vitamin A in blood and milk, on the basis of the available data. Many of the other identified devices were proofs of concept and not yet commercially available. Several gaps remain, including studies comparing the other portable devices against a gold standard.
standard, particularly for functional indicators of vitamin A status/deficiency; available manufacturer-reported device performance criteria against which to compare the results of future investigations; and more comprehensive reporting of sensitivity, specificity, precision, and other validation metrics.

CRediT authorship contribution statement

Samantha L. Huey: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Jesse T. Krisher: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. David Morgan: Project administration, Supervision, Writing – review & editing. Penjani Mkambula: Project administration, Writing – review & editing. Bryan M. Gannon: Conceptualization, Methodology, Writing – review & editing. Mduudi N.N. Mbuya: Writing – review & editing. Saurabh Mehta: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crbiot.2022.04.003.
