Review Article

Thyroid Stimulating Hormone (TSH) Estimation using Point of Care Testing Devices: Pitfalls and Opportunities for Improvement

Mark Onyemaechi Ezegbogu[1,2], Clement Uchenna Ugwoke[3], Zainab Ibrahim[4], Kabiru Abdulsalam[4]

[1]Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Nigeria, [2]Molecular Biology Unit, Clina-Lancet Laboratories, Lagos, Nigeria, [3]Department of Clinical Chemistry, Clina-Lancet Laboratories, Lagos, Nigeria, [4]Department of Chemical Pathology and Immunology, Bayero University, Kano, Nigeria

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Abstract

Since the development of the first Point-of-care Testing device (POCT) in 1962, POCTs have found their way into nearly every facet of laboratory diagnostics due to their rapid turn-around-times, testing convenience, ease of use, and relatively lower costs. This review provides an update on the progress in the development of POCTs for TSH assays while highlighting the challenges of these methods and suggesting ways of overcoming them. To achieve this, a literature search of the appropriate databases (Google Scholar, MEDLINE, Science Direct, and PubMed) was conducted using the keywords: POCT, TSH, hyperthyroidism, and hypothyroidism. Relevant articles were identified, duplicates eliminated, then critically analyzed, and discussed in terms of their relevance to the research questions. The different sensitivities of the POCTs reported in the scientific literature are traceable to the peculiarities of the detection technique adopted and the sensitivity of the immune complex recognition, i.e., labelled versus unlabeled immunoassay methods. The main factors limiting the wide acceptance of POCTs are concerns over their clinical usefulness, accuracy, and data (in)security. Routine assessment of the technical competence of POCT operators and regular quality checks of the performance of these devices are critical to maintaining the clinical usefulness of POCTs in TSH measurement. Finally, further research is required to understand the dynamic expectations of clinicians regarding POCT use in diagnosing thyroid dysfunction especially in low- and middle-income countries where data on this subject is lacking.

Keywords: Hyperthyroidism, hypothyroidism, point-of-care testing, thyroid stimulating hormone

Introduction

Disorders of the thyroid gland are challenging to diagnose because their symptoms are often non-specific.[1,2] However, marginal changes in systemic thyroid hormone concentrations are usually accompanied by correspondingly remarkable changes in blood TSH levels. This correlation, therefore, makes TSH measurement a critical tool for diagnosing thyroid disorders, especially subclinical conditions.[3] The usefulness of serum TSH analytical methods lie in their ability to differentiate between hyperthyroid and euthyroid status, which is essentially, an index of the clinical sensitivity of the test method. Over the years, four generations of serum TSH methods have been developed,[4] and the analytical goal of these methods is to improve the accuracy, specificity, and sensitivity of these assays [see Table 1].[5-7] The decision to categorize TSH assay methods into different generations based on their functional sensitivity was first introduced by Nicoloff and Spencer in 1990.[8] Functional sensitivity, which essentially represents the limit of detection of TSH assay methods, summarily, describes the lowest concentration of an analyte (TSH) that can be reliably measured within a 20% coefficient of variation or less.[9]

Access this article online

Quick Response Code:

Website: www.njbcs.net

DOI: 10.4103/njbcs.njbcs_47_21

Address for correspondence: Mark Onyemaechi Ezegbogu, Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Nigeria. Molecular Biology Unit, Clina-Lancet Laboratories, Lagos, Nigeria. E-mail: markezegbogu@gmail.com

Submitted: 14-Sep-2021 **Revised:** 19-Jan-2022
Accepted: 20-Jan-2022 **Published:** 12-Jul-2022

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How to cite this article: Ezegbogu MO, Ugwoke CU, Ibrahim Z, Abdulsalam K. Thyroid Stimulating Hormone (TSH) estimation using point of care testing devices: Pitfalls and opportunities for improvement. Niger J Basic Clin Sci 2022;19:8-14.

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Methodology

An electronic search of relevant databases including Google scholar, Medline, Science direct and PubMed was done using the keywords; POCT, TSH, hyperthyroidism and hypothyroidism. Duplicates were eliminated and relevant articles identified using the inclusion criteria discussed below. Since this review was done using publicly available information, no ethical approval was required.

Inclusion criteria

Scope: This review focused on relevant articles published during the past decade. However, classical articles from outside this period were included to provide a snapshot of the technological advances in the field.

Concepts: This review included research articles that addressed at least one of the following concepts: (a) POCTs – basic principles and technological advances (b) TSH as a diagnostic biomarker. Articles that focused on the basic biology or therapeutics of TSH were eliminated (c) biosensors for measuring human TSH levels (d) research gaps in human TSH measurements using POCTs.

Context: This review focused on studies that demonstrated (i) a novel proof-of-concept for POCTs for TSH measurement and (ii) critical appraisals of the prospects and drawbacks of existing POCT technologies.

Source of evidence: These included primary research, systematic reviews, commentaries, and verified instrument inserts that were originally published in English language.

Article selection

The screening and inclusion were done in a multi-stage process. First, the titles and abstracts of identified articles were screened for inclusion. Next, the titles and abstracts were again screened by another author to minimize the chances of excluding potentially useful articles and vice versa. The final stage involved the skimming of the full texts for relevance before inclusion in the final cohort.

Results

Out of the 1851 results initially retrieved, 712 duplicates were excluded. The rest were scrutinized using the inclusion and exclusion criteria discussed above. Seventy-nine texts matching the inclusion criteria were finally selected for this study [See Figure 1].

Discussion

POCT devices

Point-of-care (POC) or near-patient testing involves "laboratory" testing at the point where the patient receives medical care, away from a central laboratory. Common testing locations include the patient's bedside, physician's office, patient's home, ambulance, or emergency room.[11-14] The use of POCTs in clinical medicine dates to 1962 following the development of a biosensor for detecting glucose in human blood.[15] Since then, rapid technological advances in biosensing ranging from advanced electrochemical methods to nanotechnology and more recently, bioelectronics have permitted the incorporation of bulky and sophisticated pieces of equipment into small portable devices.[16,17] These devices, which are usually available as hand-held or bench-top analyzers are easy-to-use and require little or no technical assistance; and while some POCTs are programmed for the analysis of a single analyte, others can run more than one test at a time – the so-called multiplex POCTs. Bar a few notable limitations,[18-20] POCTs are extremely attractive to clinicians[12] and the global POC market value is projected to exceed $40 billion by the year 2022.[21] The primary reasons for the growing interest in POCTs in present-day medical care are the convenience of testing and rapidity of result generation which promises to improve clinical outcomes dramatically.

Table 1: Generations of Serum TSH Assay Methods[10]

Generation	Limit of Detection
First generation (now obsolete)	1-2 mIU/L
Second generation (Fast)	0.1-0.2 mIU/L
Third generation (Hypersensitive)	0.01-0.02 mIU/L
Fourth generation (Ultrasensitive)	0.001-0.002 mIU/L

Besides the very well-documented benefits of POCTs such as their low cost, ease of manipulation, rapid turn-around times, patient satisfaction, and significantly reduced sample volume requirement,[22-25] the reasons for POCT use vary across different centers. For example, in emergency departments, POCTs are preferred to lab-based methods because the timeliness of result generation will guide critical clinical decisions, while in resource-limited settings, the relatively low cost and ease-of-use of POCTs are crucial factors influencing the diagnostic approach a health facility adopts.[26] Similarly, while POCTs may make frequent testing in patients requiring regular monitoring (such as diabetics) much less technically cumbersome,[27] they serve an entirely different purpose in rural settings where a quick POC test may prevent needless referrals to specialized medical centers.[28] Quests to meet the criteria stipulated by the World Health Organization (WHO) for products for low-resource settings is the driving force behind current research activity in POCT development. The WHO requires that these devices be ASSURED i.e., Affordable, Sensitive, Specific, User-friendly, Rapid & robust, Equipment-free and Desirable to end-users.[26] Over the past five decades, the paradigm for research in POCT development has gradually shifted from the miniaturization of these devices, to cost reduction, and more recently, the incorporation of smart technologies into POCT devices.

As a result, lab-on-a-chip (LOC) technologies are now the main drivers of POCT-led research. LOCs are microdevices, usually less than a few square centimeters large that offer integrated laboratory functions on a single device.[29] The instrumental design of LOCs is based on microtechnology

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which summarily, involves the integration of microelectronic chips using semiconductors and the application of lithography for pressure creation while the Embedded Scaffold Removing Open Technology (ESCARGOT) is used for the fabrication of microfluidic devices.[30] The manipulation of fluid flow on these microchips is governed by microfluidics – a concept first used in the 1980s to denote the study of the behavior, control, and manipulation of fluids at the micro- and nanoscale. The technological advances, challenges, and prospects of microfluidic devices and their roles in advancing the clinical usefulness of POCTs are discussed in detail elsewhere.[31,32]

POCTs for TSH measurement

Traditionally, TSH measurement like most other proteins that cannot be estimated by direct photometry of the products of their reactions with chromogenic substances, is done using immunoassays with various detection methods.[33] The detection methods that have been used so far include labels such as enzymes, radioactive materials, fluorescent dyes, luminescence, electrochemiluminescence, and more recently, label-free detection platforms such as surface enhanced Raman spectroscopy[34,35] and surface plasmon resonance detection[36] methods. These immunology-based approaches have appreciably improved the sensitivity and rapidity of TSH assays. Moreover, while earlier POCT methods were predominantly qualitative, advances in signal recognition have permitted the incorporation of quantitative and semi-quantitative assays into POCTs for TSH measurement.

Immunoassay is intrinsically the method of choice for the measurement of thyroid hormones irrespective of the analytical approach adopted. For example, the running theme among the four generations of TSH assay methods highlighted earlier involved progressive modifications of the fundamental immunoassay technique. In the same way, the POCT approaches reported in the scientific literature so far have involved different manipulations of TSH-directed antigen-antibody complexes. The reason for this is the superior sensitivity of immunoassay and its ease of incorporation into different analytical platforms.[37,38] Immunoassay generally involves the use of specific antibodies raised against the analyte of interest. The binding of an antibody to its corresponding antigen is affected by the concentration of each reactant, the specificity of the antibody for the antigen, the affinity and avidity of the antigen-antibody complex, and the availability of favorable environmental conditions.[39]

The binding of an antibody to an antigen, or more accurately, a hapten, obeys the law of mass action, such that:

$$K_a = \frac{K_1}{K_2} = \frac{[Hp - Ab]}{[Hp][Ab]}$$

Where:

Ka = the affinity or equilibrium constant; it represents the reciprocal of the concentration of free Hp when 50% of the binding sites are occupied.

Ab = Antibody moiety.

Hp = Hapten; a low-molecular weight immunogenic substance having only one epitope.

Following the successful binding of an antibody to an antigen, the next step involves the development of an efficient means of recognizing the antigen-antibody complex. For this purpose, immunoassays are broadly classified as labelled and unlabeled immunoassays. A label is a biomolecule complexed to either the antigen or antibody in an immune complex to detect the binding of an antigen to its corresponding antibody.

i. Labelled Immunoassay: These methods involve the attachment of labels to the corresponding antibody (or antigen) which can then be used to recognize the antigen-antibody complex. The different sensitivities (measured by the limit of detection) of the labelled immunoassay methods reported in the scientific literature are mainly due to the responsiveness of the detection method employed and the choice of immune labels, such as the choice of monoclonal vs polyclonal antibodies and the relative inertness of the engineered antibody to interfering molecules in the sample matrix.[40] Selecting the right label with a high affinity for the antigen of interest and strong avidity of binding improves the likelihood of detecting low concentrations of antigen-antibody complexes; thus, improving the sensitivity of the reaction appreciably [see Table 2]. Another important consideration in selecting labels is the perceived safety of the taggant, and this point explains the recent paradigm shift away from potentially harmful molecules such as radioactive and carcinogenic labels.
ii. Unlabeled Immunoassay: Examples of these techniques include radial immunodiffusion and several electrophoretic approaches such as counterimmunoelectrophoresis, immunofixation electrophoresis, and rocket electrophoresis. Direct detection of immune complexes on a solid phase has also been achieved using turbidimetry, and nephelometry.[41] More contemporary direct detection methods include surface plasmon resonance[42] and several electrochemical methods.[43,44]

POCTs for TSH measurement: Challenges and opportunities for improvement

Research into the clinical usefulness of POCTs generally focus on improving the technical performance of these devices[54,55]; however, a systematic review on the implementation of POCTs in primary care revealed that the overwhelming focus on improving the technical performance of POCTs may be misleading. Primary care physicians are typically more interested in the clinical utility and the associated risks of POCTs rather than their analytical performance.[18] For example, doctors in the UK recognize that excessive workload, clinical utility, patient satisfaction, training, and maintenance are major factors preventing the use of POCTs in primary care.[20] Similarly, Dutch clinicians believe that clinical management and test reliability are critical to the use of POCTs

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Table 2: Classification of POCT assay methods for TSH

Type	Detection method	*LOD	Highlight	Reference
Un labelled Immunoassay				
Sandwich immunoassay	Förster resonance energy transfer (FRET)	NA	Used the dot blot approach for candidate antibody screening. Compared FRET and electrochemical cartridge approach to screen for appropriate antibody combinations. Qualitative method.	Wang *et al*. 2015[43]
Sandwich immunoassay	Electrochemical immunosensor	0.1±0.02 ng/mL	Detector comprises ionic liquids, gold nanoparticles, and graphite. Qualitative method.	Beitollahi *et al*. 2017[44]
Sandwich immunoassay	Chemiluminescence	1.9 µIU/mL	Employed a polymer lab-on-a-chip microfluidic device. Qualitative method.	Jung *et al*. 2013[37]
Sandwich immunoassay	Fluorescence	0.4-4.0 µIU/mL	Employed the lateral flow chromatographic immunoassay technology to quantitatively determine the amount of TSH in samples.	Bolodeoku *et al*. 2019[45]
Sandwich (competitive) immunoassay	Raman spectroscopy	0.025 mIU/mL	Employed Raman active gold nanoparticles (AuNPs) in antibody conjugation. Platform is a lateral flow immunoassay (LFIA) test strip. Qualitative and quantitative assays are possible.	Choi *et al*., 2017[46]
Sandwich immunoassay	Chemiluminescence	0.4 mIU/mL	Employed a radio-frequency-identification (RFID) sensor	Yazawa *et al*. 2014[47]
Sandwich immunoassay	Chemiluminescence	0.03 mIU/mL	Platform is a multiplex POCT, being able to measure GH, FSH, TSH, Prolactin, and LH simultaneously	Yang *et al*., 2018[48]
Sandwich immunoassay	†MPQ	0.017 mIU/mL	Superparamagnetic nanolabels incorporated into immunochromatographic lateral flow test strips.	Znoyko *et al*. 2020[49]
Sandwich immunoassay	Fluorescence	0.4 mIU/L	Proof of concept of the KinExA technology for use in POCTs	Wani *et al*. 2016[50]
Sandwich (Competitive) immunoassay	Fluorescence	0.24 ng/mL	In vivo TSH measurement	Alves *et al*. 2017[51]
Sandwich immunoassay	Fluorescence	60 nU/L	Sample matrix interference was significantly reduced by pre-processing the samples using affinity purification. Nanoparticle label was also explored	Näreoja *et al*. 2017[36]
Unlabelled Immunoassay				
Non-competitive immunoassay	Extended-Gate ‡FET	5×10^{-13} M	Direct immunodetection of TSH in whole serum; temperature modulation improved the analytical performance of the device	Gutiérrez-Sanz *et al*. 2017[52]
Non-competitive immunoassay	Electrochemical Impedance Spectroscopy	0.026 mIU/L	Novel alternative to the classic competitive immunoassay methods. Method showed no interference from glucose, salts. And proteins. TAT of about 3 min	Ozcan and Aydin 2021[53]

*LOD: Limit of Detection; †MPQ: Magnetic particle quantification; ‡FET: Field-effect transistor; §SPR: Surface plasmon resonance

in their clinics rather than their analytical performance.[56] In another survey, Jones and colleagues showed that primary care physicians may be reluctant to accept POCTs due to concerns about their accuracy, and the added burden of running needless tests which may not necessarily improve patient outcomes.[19]

While identical surveys in Africa are few and far between in the scientific literature, a working committee of QA leaders from East Africa (Ethiopia, Kenya, Mozambique, Uganda, and Zambia) tasked with improving the use of POCTs in the African sub-region sought ways to advance the technical performance of POCTs rather than addressing the unique needs of the attending clinicians.[57] This position was further reiterated by 98.5% of the respondents who believed that access to more POCTs would improve clinical outcomes significantly.[58] Although this position aptly addresses the exclusive challenges of low- and middle-income countries where the diagnostic capacity of most health centers is often stretched beyond its limit mainly due to insufficient budgetary allocation for the purchase of state-of-the-art diagnostic equipment, brain drain, lack of basic amenities and infrastructure, and inadequately trained professionals[59-63]; it, however, ignores other challenges unique to the African society. For example, in rural areas in developing countries, health care delivery is frequently a one-man affair; therefore, including POC testing in the list of tasks will overburden the attending clinician and increase patient waiting times substantially.

Beyond purchasing more POC testing devices, one reasonable way of addressing this problem is to survey clinicians in resource-limited settings to understand what their specific diagnostic needs are. To put this in perspective, a study evaluating the usefulness and overall cost: benefit ratio of POCTs in primary health centers in Sweden revealed that POCT usage may not necessarily improve patient management since some POC tests are batched and physicians are not always immediately informed of the test results; thus, delaying clinical decisions. Furthermore, physicians only opt to discuss their patients' results when they are abnormal[64]; thereby, raising concerns about the ethics of testing in the first instance. Given

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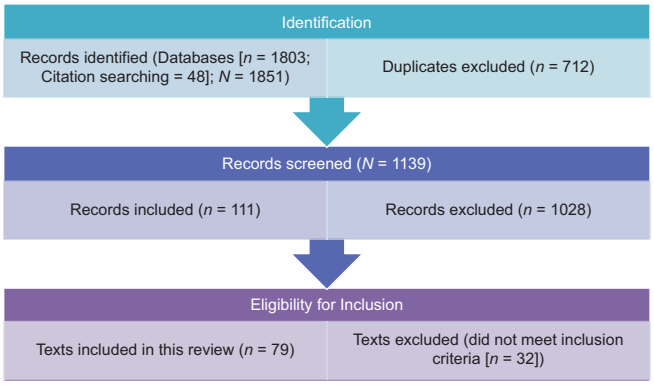

Figure 1: Flowchart showing the article selection process

that in-laboratory methods are generally faster, cheaper and more accurate than POCTs[65]; it, therefore, holds that merely improving the technical performance of POCTs while flooding the diagnostic space with these devices may not necessarily improve clinical outcomes; rather, productive conversations with attending clinicians, and the prudent use of POCTs[66] are more likely to yield the desired results.

Another issue with the use of POCTs is data insecurity. In many centers, the results generated from POCTs are not electronically linked to the patients' records. This means that entering test results manually will significantly increase the margin for post-analytical errors. To forestall these events and create a more coordinated patient management plan, there is the need to automate all updates made to the medical records of patients[67]; however, not much has been done regarding the cybersecurity of data submitted from POCTs.[68] To guarantee the safety of data transmission, different POCT manufacturers working independently, designed their exclusive data management and sharing platforms. While this approach may have addressed the data (in)security problem, it comes at an additional cost to the end-users as they have to change their computers and entire connectivity interface whenever they change POCTs.[69] This led to the creation of the POCT1 standards of connectivity developed by the CLSI.[70] These standards defined the protocol for interfacing POCTs with Laboratory Information Management Systems (LIMS) and other relevant data management platforms.[71]

Johannis and colleagues have identified five critical needs that must be addressed to improve the IT requirements of POCTs.[72] These concerns include user management, data management, update management, network friendliness and user-friendliness. To address these issues, the authors have suggested the use of no less than a 4-digit password, with a window for emergency access in case the patient is incapacitated. In cases where the POCT is connected to a central network, it is essential that these connections are encrypted, thereby, restricting access to unauthorized users. These recommendations also put the General Data Protection Regulation requirements regarding POCTs into consideration where the type and duration of data storage must be clearly defined and adhered to.[73]

Maintaining the precision and accuracy of POCTs is another crucial factor affecting their use in clinical settings. Since POCTs are mainly used by clinical staff who have very little or no technical training in maintaining the reliability of the results generated from these instruments, inaccuracies arising from instrument malfunction are likely to go unnoticed. Furthermore, clinicians are primarily focused on caring for their patients and may not notice subtle changes in the functionality of POCTS, which over time, may result in significant deviations from accuracy and precision. This challenge can readily be overcome by organizing regular training programs for POCT operators, or where possible, restricting the operation of POCTs to competent laboratory professionals as is done in STAT laboratories.[74]

Instruments and processes adopted in central laboratories are monitored using stringent protocols such as the Westgard rules and the lean six sigma process. This, however, is not the case for POCTs as their manufacturers exclusively design their devices for emergency and small volume testing, and as such, they are likely to fail quality checks done using conventional control materials and interpretation guidelines. Another reason for this is the incompatibility of the sample matrices used on these instruments. For example, while clinical chemistry laboratory instruments are designed to test serum/plasma samples, POCTs often use whole blood. Furthermore, these discrepancies make direct comparisons of results challenging.[75] While some POCTs have a self-check function to monitor the operationality of the device at start-up, this function only guarantees the functionality of the instrument and not necessarily the accuracy of the results generated.

One reasonable way of ensuring the technical performance of POCTs is by designing QC programs in-house to suit the exclusivity of these POCTs. For example, QC programs developed for benchtop blood gas analyzers may not function properly on cartridge- and strip-based instruments.[76] It is, however, critical that these QA processes test the entire analytical process(es) and not just the technical performance of the POCT. The use of internal quality control (IQC) is another way of ensuring the accuracy of test results obtained from POCTs. While it is desirable to use third-party IQC materials to allow for an independent check of the entire testing system,[77] it is expected that these control materials be provided by the POCT manufacturers with well-defined acceptance ranges.[78] In addition to these interventions, it is also essential that, in line with the ISO 22870 requirements,[79] POCT operators be trained on the theory and practice of IQC to ensure the optimal performance of their instruments.

Conclusion

The thyroid hormones are important for metabolism in nearly all tissues of the human body and as such, an abnormal thyroid function will have far-reaching effects on the overall health of the individual. TSH measurement has been established as an important baseline test in diagnosing thyroid dysfunction

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because subtle changes in the circulating levels of thyroxine and triiodothyronine lead to remarkable changes in blood TSH levels. The analytical approaches to TSH measurement have evolved over four generations; the distinction among these generations is marked by their functional sensitivity. These improvements eliminated the need for TRH stimulation tests and permitted the diagnosis of sub-clinical hyperthyroidism.

Since the development of the first POCT for clinical use in 1962, these devices have found their way into nearly every facet of laboratory diagnostics due to their rapid turn-around-times, testing convenience, ease of use, and relatively lower costs. However, the main factors limiting the wide acceptance of POCTs are concerns over their clinical usefulness, accuracy, and data(in) security. While exploring more ways to improve the diagnostic sensitivity and specificity of novel POCT technologies for TSH assays, it is also important to monitor the technical competence of POCT operators and carry out regular quality checks of the performance of these devices in order to maintain the clinical usefulness of POCTs. Finally, further research is required to understand the dynamic expectations of clinicians regarding POCT use in diagnosing thyroid dysfunction especially in low- and middle-income countries where data on this subject is worryingly lacking.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Iervasi G, Clerico A. Harmonization of free thyroid hormone tests: A mission impossible? Clin Chem Lab Med 2011;49:43–8.
2. Dittadi R, Rizzardi S, Masotti S, Prontera C, Ripoli A, Fortunato A, *et al*. Multicenter evaluation of the new immunoassay method for TSH measurement using the automated DxI platform. Clin Chim Acta 2017;468:105-10.
3. Sheehan MT. Biochemical testing of the thyroid: TSH is the best and, oftentimes, only test needed - A review for primary care. Clin Med Res 2016;14:83–92.
4. Kuyl JM. The evolution of thyroid function tests. J Endocrinol Metab Diabetes South Africa 2015;20:11–6.
5. Spencer CA. Assay of Thyroid Hormones and Related Substances. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, *et al*., editors. Thyroid Disease Manager. South Dartmouth (MA), USA: MDText.com Inc.; 2000.
6. Çalcı E, Dogan H, Saglam F, Turhan T, Berker D. Comparison of the performance of a second (Fast TSH) and third (HYPERsensitive TSH) generation autometed TSH immunassays in healthy euthyroid subjects. Erciyes Med J 2019;41:46-9.
7. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 1994;78:1368–71.
8. Nicoloff JT, Spencer CA. The use and misuse of the sensitive thyrotropin assays. Clin Endocrinol Metab 1994;71:553–8.
9. Spencer CA, Takeuchi M, Kazarosyan M. Interlaboratory/intermethod differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. Clin Chem 1995;41:367–74.
10. Grotzke M. The Thyroid Gland. In: Bishop ML, Fody EP, Schoeff LE, editors. Clinical Chemistry: Techniques, Principles, Correlations. 6th ed. China: Lippincott Williams & Wilkins; 2010.
11. Kost GJ. Guidelines for point-of-care testing. Improving patient outcomes. Am J Clin Pathol 1995;104(Suppl 1):S111-27.
12. Howick J, Cals J, Jones C. Current and future use of point-of-care tests in primary care: An international survey in Australia, Belgium, the Netherlands, the UK and the USA. BMJ 2014;4:e005611.
13. Metzar J. ADVIA Centaur® XP. Immunoass Handb 2013;567–70.
14. Kost G. Goals, guidelines and principles for point-of-care testing. In: Hagerstown M, editor. Principles & Practice of Point-of-Care Testing. Lippincott Williams & Wilkins; 2002. p. 3–12.
15. Wang J. Electrochemical glucose biosensors. Chem Rev 2007;108:814–25.
16. Tolan N, Karon B. The evolution of point-of-care testing: Can we improve our future knowing our past? Point Care 2015;14:146–50.
17. Louie RF, Tang Z, Shelby DG, Kost GJ. Point-of-care testing: Millennium technology for critical care. Lab Med 2000;31:402–8.
18. Lingervelder D, Koffijberg H, Kusters R, IJzerman MJ. Point-of-care testing in primary care: A systematic review on implementation aspects addressed in test evaluations. Int J Clin Pract 2019;73:e13392.
19. Jones CHD, Howick J, Roberts NW, Price CP, Heneghan C, Plüddemann A, *et al*. Primary care clinicians' attitudes towards point-of-care blood testing: A systematic review of qualitative studies. BMC Fam Pract 2013;14:117.
20. Turner PJ, Van den Bruel A, Jones CHD, Plüddemann A, Heneghan C, Thompson MJ, *et al*. Point-of-care testing in UK primary care: A survey to establish clinical needs. Fam Pract 2016;33:388–94.
21. Zion Market Research. Point of Care Testing Market to be Worth around USD 78.85 Billion by 2028, growing at a CAGR of 12.3% from 2021 to 2028 - Zion Market Research [Internet]. 2021 [cited 2022 Feb 19]. Available from: https://www.prnewswire.com/news-releases/point-of-care-testing-market-to-be-worth-around-usd-78-85-billion-by-2028--growing-at-a-cagr-of-12-3-from-2021-to-2028---zion-market-research-301400336.html.
22. John A, Price C. Economic evidence and point-of-care testing. Clin Biochem Rev 2013;34:61–74.
23. Spindel S, Sapsford K. Evaluation of optical detection platforms for multiplexed detection of proteins and the need for point-of-care biosensors for clinical use. Sensors 2014;14:22313–41.
24. Rossi A, Khan D. Point of care testing: Improving paediatric outcomes. Clin Biochem 2004;37:456–61.
25. St-Louis P. Status of point-of-care testing: Promise, realities, and possibilities. Clin Biochem 2000;33:427–40.
26. Wu G, Zaman MH. Low-cost tools for diagnosing and monitoring HIV infection in low-resource settings. Bull World Health Organ 2012;90:914–20.
27. Mor M, Waisman Y. Point-of-care testing: A critical review. Paediatr Emerg Care 2000;16:45–8.
28. Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, *et al*. Diagnostic point-of-care tests in resource-limited settings. Lancet Infect Dis 2014;14:239–49.
29. Nikoleli GP, Siontorou CG, Nikolelis DP, Bratakou S, Karapetis S, Tzamtzis N. Biosensors based on microfluidic devices lab-on-a-chip and microfluidic technology. Nanotechnology and Biosensors. Elsevier Inc; 2018. p. 375–94.
30. Saggiomo V, Velders AH. Simple 3D printed scaffold-removal method for the fabrication of intricate microfluidic devices. Adv Sci 2015;2:1500125.
31. Convery N, Gadegaard N. 30 years of microfluidics. Micro Nano Eng 2019;2:76–91.
32. Ahmadi S, Rabiee N, Bagherzadeh M, Karimi M. Microfluidic devices for pathogen detection. In: Hamblin MR, Karimi MB, editors. Biomedical Applications of Microfluidic Devices. Elsevier; 2021. p. 117–51.
33. Warsinke A. Point-of-care testing of proteins. Anal Bioanal Chem 2009;393:1393–405.
34. Marks H, Schechinger M, Garza J, Locke A, Coté G. Surface enhanced Raman spectroscopy (SERS) for *in vitro* diagnostic testing at the point of care. Nanophotonics 2017;6:681–701.
35. Moskovits M. Surface-enhanced Raman spectroscopy: A brief

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retrospective. J Raman Spectrosc 2005;36:485–96.
36. Näreoja T, Rosenholm JM, Lamminmäki U, Hänninen PE. Super-sensitive time-resolved fluoroimmunoassay for thyroid-stimulating hormone utilizing europium (III) nanoparticle labels achieved by protein corona stabilization, short binding time, and serum preprocessing. Anal Bioanal Chem 2017;409:3407–16.
37. Jung W, Han J, Kai J, Lim JY, Sul D, Ahn CH. An innovative sample-to-answer polymer lab-on-a-chip with on-chip reservoirs for the POCT of thyroid stimulating hormone (TSH). Lab Chip 2013;13:4653–62.
38. Haddad RA, Giacherio D, Barkan AL. Interpretation of common endocrine laboratory tests: Technical pitfalls, their mechanisms and practical considerations. Clin Diabetes Endocrinol 2019;5:12.
39. Zhang Z, Cheng H. Recent development in sample preparation and analytical techniques for determination of quinolone residues in food products. Crit Rev Anal Chem 2017;47:223–50.
40. Favresse J, Burlacu MC, Maiter D, Gruson D. Interferences with thyroid function immunoassays: Clinical implications and detection algorithm. Endocr Rev 2018;39:830–50.
41. Orton S. Immunoassays. In: Bishop M, Fody E, Schoeff L, editors. Clinical Chemistry: Techniques, Principles, Correlations. 6th ed. China: Lippincott Williams & Wilkins; 2010. p. 185–201.
42. Treviño J, Calle A, Rodríguez-Frade JM, Mellado M, Lechuga LM. Surface plasmon resonance immunoassay analysis of pituitary hormones in urine and serum samples. Clin Chim Acta 2009;403:56–62.
43. Wang D, Skinner JP, Ruan Q, Tetin SY, Collier GB. Affinity assisted selection of antibodies for point of care TSH immunoassay with limited wash. Clin Chim Acta 2015;438:55–61.
44. Beitollahi H, Ivari SG, Torkzadeh-Mahani M. Application of antibody–nanogold–ionic liquid–carbon paste electrode for sensitive electrochemical immunoassay of thyroid-stimulating hormone. Biosens Bioelectron 2018;110:97–102.
45. Bolodeoku J, Bains S, Pinkney S, Coker O, Tk K, Anyaeche C. iMedPub journals an evaluation of the Boditech i-CHROMA TM thyroid-stimulating hormone (TSH) method: Precision and accuracy. Ann Clin Lab Res 2019;7:1–6.
46. Choi S, Hwang J, Lee S, Lim DW, Joo H, Choo J. Quantitative analysis of thyroid-stimulating hormone (TSH) using SERS-based lateral flow immunoassay. Sensors Actuators B Chem 2017;240:358–64.
47. Yazawa Y, Oonishi T, Watanabe K, Shiratori A, Funaoka S, Fukushima M. System-on-fluidics immunoassay device integrating wireless radio-frequency-identification sensor chips. J Biosci Bioeng 2014;118:344–9.
48. Yang C, Sun Z, Zhang G, Wang L, Zhang J, Zhang X. Development of a novel parallel determination platform: A feasibility study tested on a chemiluminescence device. Anal Methods 2018;10:298–307.
49. Znoyko SL, Orlov AV, Bragina VA, Nikitin MP, Nikitin PI. Nanomagnetic lateral flow assay for high-precision quantification of diagnostically relevant concentrations of serum TSH. Talanta 2020;216:120961.
50. Wani TA, Zargar S, Wakil SM, Darwish IA. New analytical application of antibody-based biosensor in estimation of thyroid-stimulating hormone in serum. Bioanalysis 2016;8:625–32.
51. Alves TG, Melo MC de C, Kasamatsu TS, Oliveira KC, de Souza JS, da Conceição RR, *et al*. Novel immunoassay for TSH measurement in rats. Arch Endocrinol Metab 2017;61:460–3.
52. Gutiérrez-Sanz Ó, Andoy NM, Filipiak MS, Haustein N, Tarasov A. Direct, label-free, and rapid transistor-based immunodetection in whole serum. ACS Sens 2017;2:1278–86.
53. Ozcan HM, Aydin UD. A simple immunosensor for thyroid stimulating hormone. Artif Cells Nanomed Biotechnol 2021;49:61–70.
54. McNerney R, Daley P. Towards a point-of-care test for active tuberculosis: Obstacles and opportunities. Nat Rev Microbiol 2011;9:204–13.
55. Bénéteau-Burnat B, Pernet P, Pilon A, Latour D, Goujon S, Feuillu A, *et al*. Evaluation of the GEM® Premier™ 4000: A compact blood gas CO-Oximeter and electrolyte analyzer for point-of-care and laboratory testing. Clin Chem Lab Med 2008;46:271–9.
56. Cals JWL, Schols AMR, Weert HCPM Van, Stevens F, Zeijen CGIP, Holtman G, *et al*. Sneltesten in de huisartspraktijk. Ned Tijdschr Geneeskd 2014;158:A8210.
57. African Society of Laboratory Medicine A. Keeping on Point: Ensuring High Quality Point-of-Care Testing in Africa. 2015. Available from: https://aslm.org/news-article/keeping-on-point-ensuring-high-quality-point-of-care-testing-in-africa/. [Last accessed on 2021 Jul 21].
58. Parkes-Ratanshi R, Kikonyogo R, Hsieh YH, Nakku-Joloba E, Manabe YC, Gaydos CA, *et al*. Point-of-care diagnostics: Needs of African health care workers and their role combating global antimicrobial resistance. Int J STD AIDS 2019;30:404–10.
59. Zimbudzi E. Stemming the impact of health professional brain drain from Africa: A systemic review of policy options. J Public Health Afr 2013;4:e4.
60. Godman B, Basu D, Pillay Y, Mwita JC, Rwegerera GM, Anand Paramadhas BD, *et al*. Review of ongoing activities and challenges to improve the care of patients with type 2 diabetes across Africa and the implications for the future. Front Pharmacol 2020;11:108.
61. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: A barrier to effective health care. Clin Infect Dis 2006;42:377–82.
62. Jalavu TP, Rensburg M, Erasmus R. Clinical staff knowledge and awareness of point-of-care-testing best practices at Tygerberg Hospital, South Africa. Afr J Lab Med 2020;9:853.
63. Ezegbogu MO, Abdulsalam K. Creatinine assay methods in reseource-limited settings: A review. Bayero J Med Lab Sci 2018;3:37–47.
64. Grodzinsky E, Wirehn AB, Fremner E, Haglund S, Larsson L, Persson LG, *et al*. Point-of-care testing has a limited effect on time to clinical decision in primary health care. Scand J Clin Lab Invest 2004;64:547–52.
65. Singh G, Savage NM, Gunsolus B, Foss KA. Requiem for the STAT Test: Automation and point of care testing. Lab Med 2020;51:E27–31.
66. Saxena S, Wong ET. Does the emergency department need a dedicated stat laboratory? Continuous quality improvement as a management tool for the clinical laboratory. Am J Clin Pathol 1993;100:606–10.
67. Richardson H. Medical laboratories — requirements for quality and competence: An ISO perspective. Vox Sang 2002;83(Suppl 1):333–5.
68. Pezzuto F, Scarano A, Marini C, Rossi G, Stocchi R, Di Cerbo A, *et al*. Assessing the reliability of commercially available point of care in various clinical fields. Open Public Health J 2019;12:342–68.
69. Nichols JH. Point-of-care testing. In: Clarke W, Marzinke MA, editors. Contemporary Practice in Clinical Chemistry. 4th ed. Academic Press; 2020. p. 323–36.
70. Dudley MN, Ambrose PG, Bhavnani SM, Craig WA, Ferraro MJ, Jones RN, *et al*. Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and Pseudomonas aeruginosa: I. Cephalosporins and Aztreonam. Clin Infect Dis 2013;56:1301–9.
71. Hakman M, Groth T. Connectivity Infrastructure and Components for POCT Environments - overall Infrastructure. J Assoc Lab Autom 2001;6:60–8.
72. Johannis W, Bietenbeck A, Malchau G, Streichert T. Point-of-care testing (POCT) and IT security concepts. J Lab Med 2020;44:107–11.
73. Lechner NH. An Overview of Global Professional Publications related to Medical Device Cybersecurity. In: Proceedings of the Central European Conference in Information and Intelligent Systems, 2020. p. 221–32.
74. Arbiol-Roca A, Dot-Bach D. Critical issues and new trends on stat tests in clinical laboratory. EJIFCC 2019;30:59–66.
75. Cameron M. Quality management in point of care. Medlab Magazine. 2017. Available from: https://www.medlabme.com/magazine/en/lab-management-articles/quality-management.html. [Last accessed on 2021 Jul 21].
76. Martin CL. Quality control issues in point of care testing. Clin Biochem Rev 2008;29(Suppl 1):S79-82.
77. Holt H, Freedman DB. Internal quality control in point-of-care testing: Where's the evidence? Ann Clin Biochem 2016;53:233–9.
78. Roche Diagnostics. ACCU-CHEK Inform II Blood Glucose Monitoring System Operator's Manual. Roche Diagnostics; 2014. p. 1–192.
79. International Organisation for Standardization (ISO). ISO 22870:2016 - Point-of-care testing (POCT) — Requirements for quality and competence. 2016.