Horizon Scan Report 0029 **Date: 23 May 2013**

Diagnostic Technology: Point-of-care testing for thyroid stimulating hormone

Clinical Question:

In patients who are being tested for hypothyroidism, does a point-of-care (POC) thyroid stimulating hormone (TSH) test accurately detect those biochemically hypothyroid compared to laboratory-based immunoassays, and is this cost-effective?
Does a POC TSH test have any utility in monitoring of patients at high risk of thyroid dysfunction?

Background, Current Practice and Advantages over Existing Technology:

Hypothyroidism is associated with a number of classical symptoms and signs but these are non-specific and may not be present in milder disease, especially in the elderly. Hypothyroidism is therefore diagnosed biochemically, with TSH used as a marker of thyroid function. A TSH level above the reference range (~5 mU/L, population-dependent) usually indicates hypothyroid function. An associated rise in free T4 (fT4) is usually present in symptomatic disease, whereas a high TSH and normal fT4 is usually asymptomatic and thus defined as subclinical hypothyroidism.

Since hypothyroidism cannot be reliably diagnosed clinically, current practice involves sending a blood sample for laboratory testing. Thyroid function tests are among the most requested biochemical tests in the UK[1], and disproportionate to the prevalence of the disease in the tested population[2]. A point-of-care test used as a simple screen would allow laboratory testing to be reserved for further evaluation of patients with identified hypothyroidism. This may prove to be cost-effective, due to a saving in venesection time, laboratory time, and the transportation of blood samples. There may also be increased patient satisfaction from the avoidance of unnecessary venesection, and the reassurance of an immediate negative result. A negative result may also allow a clinician to more quickly consider other explanations for a patient's symptoms.

Details of Technology:

1. Thyrotest Rapid TSH Testing Kits (Wampole Laboratories, LLC) (FDA regulated and CE marked). Requires one drop of blood. Result available in 10 minutes. [3,4]
2. ThyroChek Thyroid Testing (Screening Devices Canada, Inc.) (CLIA waived). Requires one drop of blood. Result available in 10 minutes.[5]
3. HomeTest Thyroid – TSH test (Prima). (CE marked) Requires one drop of blood. Result available in 10 minutes.[6]
4. Rapid Response Thyroid TSH Test Kit (BTNX Inc.) Requires one drop of blood. Result available in 10 minutes. [7]
5. ThyroScreen (Personal Diagnostics). Requires one drop of blood. Result available in 10 minutes. [8]
6. *In development: Vivacta Point of Care thyroid test (Vivacta Limited, Kent)* Requires 1 drop of blood. Result (quantitative) available in under 10 minutes. [9]

All test kits currently available use a lateral flow chromatographic immunoassay designed to identify TSH at concentrations >5mU/L. Each requires a small finger-prick sample of blood to be added to buffer solution (provided) in a single use test cassette. The result is read after 10 minutes in the results window of the cassette. A positive result is indicated by the presence of a line in both the control and test areas. The intensity of the line is unrelated to the TSH level in the sample.

The Vivacta product (in development) is a quantitative test using a signal transduction method to measure rate of binding of antibody and analyte. The system comprises a low cost system and disposable cartridge. An LED light source pulses light into the system; this causes micro-heating effects generated by carbon particles bound to the surface of a piezoelectric polymer film. The signal generated can be measured and displayed as a quantitative result. [9,10]

Patient Group and Use:
The British Thyroid Foundation guidelines[11] recommend a TSH test in a number of patient groups.

Firstly, a TSH test is recommended as a diagnostic tool in those patients in whom hypothyroidism may explain their presenting complaint:

- Patients with clinical symptoms of hypothyroidism; this may include acute psychiatric disturbance or apparent depression
- Patients presenting with a suspected goitre *
- Patients presenting with dyslipidaemia *

There is now a large body of evidence to suggest that there is no clinical benefit in screening a healthy elderly population to diagnose subclinical hypothyroidism [12,13].

Secondly, it is recommended as part of the surveillance for thyroid dysfunction in the following patient groups:

- Women with a history of postpartum thyroiditis (annually and prior to and at 6 to 8 weeks after future pregnancies)
- Patients with Type I diabetes (annually) *
- Patients with Down's syndrome or Turner's syndrome (annually) *
- Patients on amiodarone therapy (before commencing treatment, every 6 months on treatment, up to 12 months after cessation of therapy) *
- Patients on lithium therapy (before commencing treatment, every 6 months on treatment) *
- Patients who have had external neck irradiation (annually)
- Patients who have had radioiodine or thyroidectomy (4-8 weeks post-treatment, 3 monthly up to = one year, annually thereafter)

Finally, to monitor thyroid function in patients taking medication with direct effects on the thyroid, a TSH test is recommended in:

- Patients on antithyroid drug therapy (every 3 months until stable, or annually if used as a long-term treatment option) *
- Patients on thyroxine therapy (annually) *

Especially for those who require regular monitoring or surveillance, a rapid POC TSH test might be both time and cost effective and more acceptable to patients than regular venepuncture. A caveat to this, however, is that for many of the groups listed above, a TSH test is not the only blood test required in the diagnostic work up and therefore the time, cost and venepuncture would not be avoided [14-17] . Furthermore, for a number of patient groups (marked *) the thyroid dysfunction may occur in either direction. Adequate monitoring would therefore require a quantitative result; something which none of the currently available tests provide (pending approval of the Vivacta device).

Importance:
The UK prevalence of overt hypothyroidism is 1.1% [18], and women are 5 to 10 times more likely to develop the condition than men [19]. Many present with mild, non-specific symptoms and a TSH test is required to make the diagnosis. Consequently, thyroid function tests are among the most requested biochemical tests encountered in the UK[1]. Primary hypothyroidism is usually diagnosed and managed by a GP [20]. In 2011 a total of 25 million prescriptions for levothyroxine (25 -100 mcg tablets) were dispensed from primary care[21].

Untreated, overt hypothyroidism has known important health implications. It is associated with increased cardiovascular morbidity due to coagulopathies and dyslipidaemia [22-24] but there is conflicting evidence in demonstrating increased mortality in this group [13].
Subclinical hypothyroidism; asymptomatic raised TSH with a normal fT4, has been shown to be more prevalent than overt disease; up to 15% in elderly populations[25-27]. There is increasing evidence to show that this condition is similarly associated with adverse cardiovascular outcomes, particularly when serum TSH is grossly elevated (greater than 10mU/L)[28]. It is unclear whether treatment of such cases results in an improvement in morbidity and mortality [12,29].

Symptoms of hypothyroidism can mimic many other serious diagnoses including anaemia, chronic fatigue syndrome, malignancy [30], cognitive dysfunction [32], affective disorders [33] and acute psychosis[32]. Rapid recognition of the true problem facilitates timely treatment and can prevent further unnecessary testing.

Previous Research:

Accuracy compared to existing technology

The 2006 UK Guidelines for the Use of Thyroid Function Tests recommend that a sensitive immunometric assay provides the single most sensitive, specific and reliable test of thyroid status in both overt and subclinical primary thyroid disorders and dictates that laboratories should use a TSH method with a functional sensitivity of <0.02mU/L [11]. It is therefore important that POC TSH tests should reach a similar standard.

The manufacturer of each product has compared their test to a standard laboratory immunoassay for TSH [3,5-8] . From these studies a sensitivity and specificity for detecting a TSH concentration of 5mU/L or above has been calculated, compared to the standard laboratory immunoassay. However, there appears to be no gold standard for laboratory TSH immunoassays and thus studies comparing these devices to several immunoassays may be required. Some of the tests also underwent waiver testing to determine accuracy between expected results and those obtained by lay users. In these tests lay users were required to perform the test on laboratory sample using only the written instructions.

The results for each product are summarised in the table below:

Product	Trial details	Compared to	Number of samples	Sensitivity	Specificity	Functional sensitivity	Waiver performance
Thyrotest Rapid TSH Testing Kits	3 centre clinical trial - trained laboratory technicians took blood samples for laboratory analysis from patients with known hypothyroidism	Abbott AxSYM	289	81.3%	97.3%	Not available	60 users → 93.3% - 100% accuracy
ThyroChek Thyroid Testing	3 centre clinical trial	Second/third generation TSH assay	131	98.5%	96.9%	5.0 mU/L	60 users → 90 – 100% accuracy
Home Test Thyroid – TSH test	Not described	Abbott AxSYM	Not described	81.3	97.3%	10.0 mU/L	Not available
Rapid Response Thyroid TSH Test Kit	Not described	Second/third generation TSH assay	131	98.5-99.9%	96.9-98.5%		60 users → 90-100% accuracy
ThyroScreen	Correlation study with pre-tested whole blood samples	Abbott AxSYM	289	81.3%	97.3%	Not available	Not available

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The details of a number of these studies, such as the thyroid status of the volunteers used and the conditions under which the study was carried out, were not provided by the manufacturer. It is therefore difficult to extrapolate true relevance to primary care.

Thyrochek is the subject of further published study, independent of the manufacturer, to assess its use as a screening tool for hypothyroidism [34]. Serum samples from patients with untreated hypothyroidism and euthryoid patients with a normal TSH were analysed by both Thyrochek and an immunoadiometric assay. It found that Thyrochek was a highly sensitive and specific test for identifying patients with a TSH >6 mU/L, but was less accurate when the TSH concentration was closer to the 5 mU/L cut off (4-6 mU/L).

The Vivacta product is still in development, and we could not identify any published data on its performance. However, an in-house evaluation reports good correlation between the Vivacta system and the Siemens Centaur laboratory analyser[10].

Impact compared to existing technology
No studies were found assessing the impact of point-of-care TSH testing when compared to laboratory testing. The tests currently available can be used in screening to rule out hypothyroidism, but due to the qualitative results, can neither be used to make the diagnosis nor to monitor thyroid function. The potential effect on the patient experience, through a reduction in medical contact and a shorter turnover time, has not been assessed. Personal Diagnostics, the UK company which manufactures Thyroscreen is now collaborating with the British Thyroid Foundation (BTF). This partnership may lead to a more formal assessment of patient-centred aspects of POC testing.

Guidelines and Recommendations
The National Institute for Clinical Excellence (NICE) has not released guidelines for the testing of thyroid function. In response to this, the Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF) published guidelines in July 2006 [11]. Although the guidelines do not discuss the potential for point-of-care TSH testing, they do suggest that a rapid TSH would only be necessary in patients who have been hospitalised with thyroid disease as a cause of their presenting symptoms. This may indicate a use for point-of-care testing in the accident and emergency setting, but TSH alone is unlikely to be sufficient for emergencies such as myxoedema coma and thyrotoxic crisis. The guidelines repeat the assertion that a normal TSH is likely to rule out thyroid dysfunction, indicating that there may be a role for assessment of TSH in primary care to prevent unnecessary thyroid function testing.

Cost-effectiveness and economic impact:
No cost-effectiveness studies were identified.

Research Questions:
The currently available point-of-care TSH tests are unlikely to be useful in providing a method of immediate diagnosis, as current guidelines require that diagnosis of thyroid dysfunction requires measurement of free T_3 and T_4 [11], meaning that any abnormal tests found using point-of-care testing would need to be further investigated. The use of the current technology is therefore limited to the rapid ruling out of hypothyroidism from a longer list of differentials in a patient who presents with non-specific symptoms. Working within this remit:

1. What is the accuracy of a POC TSH test in primary care settings?
2. Is a POC TSH test time and cost-effective in primary care settings, given that other blood tests may also be required depending on history and presentation?
3. What is the impact of a POC test on the patient experience? Is the method preferable to venesection? Does having an immediate result make a difference to patients?

A POC test which can give a quantative result would have much broader application to primary care, in the monitoring and surveillance of a number of different patient groups. In addition a POC test that includes fT4 as well as TSH would provide additional diagnostic value and replace the need for most thyroid function testing in primary care.

Suggested next step:
Assessment of the accuracy of the currently available POC TSH tests in primary care settings.
Evaluation of the number of laboratory TSH tests that can be avoided in primary care by using a POC TSH test as first-line screening of thyroid function.
Cost-benefit analysis of the currently available POC tests within primary care settings.

Expected outcomes:
Currently available point-of-care TSH tests may be useful in a subset of patients in whom hypothyroidism is unlikely and needs to be excluded. However, the majority of patients will require simultaneous measurement of free T_3 and T_4 and therefore a POC TSH will not reduce the need for venesection and laboratory testing. It is therefore unlikely that they will prove to be cost- and time-efficient within primary care settings.

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