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Background Paper

Point-of-care tests in general practice: Hope or hype?

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KEY MESSAGE:

- Point-of-care tests must be valid, reliable and rapid, and its consequences on patient management must have been established in a general practice population.
- Using point-of-care tests for other indications or in other patient groups than those in which evidence of added value exists can reduce the diagnostic performance.

ABSTRACT

Point-of-care tests are biomedical tests on patients' specimens like blood, saliva, urine or faeces, which can be used near the patient, without interference of a laboratory. The use of these tests, many of which have been recently developed, is increasing in general practice, where they add to the GP's set of diagnostic instruments. The question is, however, whether they always contribute to an effective and high-quality diagnostic process by GPs. We present a set of criteria that can be used by guideline developers, regional primary care organizations and individual GPs to evaluate a new point-of-care test in a practice setting. These criteria do not relate only to their use and quality. A point-of-care test needs to be evaluated in the right population and for the right indications, and GPs then need to use them for the indications for which they were evaluated. Expanding the range of indications can lead to an increase in false-positive and false-negative test results.

Keywords: point-of care tests, general practice setting, implementation criteria

INTRODUCTION

Only a few decades ago, a microscope was a commonly used instrument in routine general practice. GPs used haemoglobin meters, as well as strips to test faeces for occult blood loss, and an erythrocyte sedimentation rate tube was ready for use. While some point-of-care tests (also known as near-patient tests) has stood the test of time and has survived evidence-based evaluations, many of the above tests have now been replaced by standardized laboratory diagnostics. A recent study among 115 Dutch GPs showed that 95% of them used the nitrite test, while most of them also had a glucose meter (91%) or a haemoglobin meter (54%). Other point-of-care tests were used only occasionally ($<10\%$) (1).

The current paper defines point-of-care tests as additional diagnostic biomedical tests on patient materials like blood, saliva, urine or faeces that are used near the patient, without interference of a laboratory. We realize that other diagnostic tests that can be performed near the patient, such as pulse-oximetry or paper-based diagnostic questionnaires are available. However, these are outside the scope of this paper. Point-of-care tests also have to be distinguished from self-tests. In self-tests, it is the consumer or patient who decides to carry out a test, whereas in point-of-care tests, it is the GP who decides whether a test is indicated or useful. Self-tests will not be discussed in this paper (2–4).

While ten years ago, few point-of-care tests appeared to have the potential to become a success in primary care, and few high-quality studies evaluating point-of-care tests had been done (5–7), the situation seems to have changed for several tests. Currently available point-of-care tests include those for cardiovascular diseases (cholesterol, NT-pro-BNP), diabetes mellitus (HbA1c and

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glucose), kidney disease (microalbuminuria), blood coagulation (INR and D-dimers for deep vein thrombosis (DVT) and pulmonary embolism), myocardial damage (heart-type fatty acid binding protein (H-FABP), troponin, CK-MB) and infections (leukocyte count, C-reactive protein (CRP)), group A beta-haemolytic streptococci for pharyngitis and a point-of-care test for mononuleosis infectiosa).

The advantages of point-of-care tests would appear self-evident, especially when dealing with acute problems, which might require rapid intervention. The availability of these tests in the GP's own practice means that GP and patient can act almost instantly, without having to wait for the result. Recent research showed that patients were more satisfied about the care they received when point-of-care testing was performed (8). Nevertheless, the use of point-of-care tests in general practice has its disadvantages. Such tests need to be introduced with great care, and only after their added value in a practice setting has been established. When a GP or health centre is considering the introduction of a specific point-of-care test, it should be checked for quality and efficacy, and the same should be done when guideline developers are considering whether to include such a test in a new set of guidelines.

While studies looking at prioritization criteria for the assessment of new diagnostic technologies are available in general (9), this paper presents a set of criteria that can be used to evaluate specific point-of-care tests for use in general practice.

CONDITIONS FOR SENSIBLE TESTING

What aspects need to be evaluated when considering using a particular point-of-care test? We propose multiple conditions that a new point-of-care test should satisfy before large-scale introduction into general practice can be recommended (Box 1). These criteria are based on the current literature, as well as extensive experience of the clinical research teams of the authors (5–10). The ten criteria are explained in Box 1.

Box 1. Criteria for the introduction of new point-of care tests into general practice.

Use and quality control *in a general practice setting*:

1 **Test accuracy:**
Is the test valid, reliable and robust?
2 **Quality control:**
Can feasible long-term quality control be assured?
3 **Time to decision:**
Is the test result available quickly enough?
4 **Usability:**
Is the test easy to use?
5 **Frequency of use:**
Will the test be used frequently enough?

Indication and efficacy *in a general practice setting*:

6 **Indication for testing:**
Is the indication for using the test sufficiently clear and defined?
7 **Test interpretation:**
Is enough information available for a correct interpretation of the various potential test results?
8 **Immediate effect on GP's decision:**
Will the test result have direct consequences for the GP's decision-making?
9 **Effect on patient outcomes:**
Does the test produce results that under normal practice conditions will benefit patients with the relevant indication?
10 **Cost-effectiveness:**
Has the use of the test been proved to be cost-effective?

USE AND QUALITY CONTROL

Test accuracy and quality control

Although the authorization and introduction of point-of-care tests is not regulated by strict criteria like those that apply to medication, point-of-care tests, which are sold to professionals do have to meet the European CE labelling criteria. By labelling their product CE, the producers declare that the product satisfies all relevant European regulations. However, this does not prove the validity of a test. While the US Food & Drug Administration (FDA) demands costly validation studies before a point-of-care test is allowed to be marketed, European end-users have to check the validity and quality of these tests for themselves. In hospitals, such checks are often carried out by the laboratories, and general practice laboratories sometimes do the same for GPs (10).

It is essential that the results of point-of-care tests are in agreement with those of the reference standard (usually standardized laboratory values) for the same specimens (validity) and that repetition of a test will produce the same result (reliability). Regular quality control procedures involve testing the validity and reliability of a test. An internal quality assessment often takes the form of a measurement to check whether the instrument is still producing reliable values, while external quality assessment involves not only testing the instrument itself, but also comparing the test result with a reference standard, usually a test at a hospital laboratory. Since hospital laboratory equipment is subject to such external testing, it would seem obvious that this should also be done for diagnostic equipment used in GP practices.

New tests are usually evaluated in a laboratory setting under ideal circumstances. It is crucial, however, that point-of-care tests are robust, which means that they should also produce the right results in the bustle of a routine practice setting, under perhaps less than ideal circumstances. The use of the more laborious tests may involve several moments where the test can be incorrectly carried out or read. If a test is applied in an acute situation at a patient's home, reading a colour chart or assessing agglutination can be difficult in a dimly lit bedroom, which was a problem, for instance, with the first point-of-care

D-dimer test (SimpliRED). Also assessing an albuminuria test strip is prone to error if it is not read in daylight.

In addition to this requirement of robustness, there may be issues of quality control and the feasibility of test use. An instrument that needs to be calibrated every morning and is used only occasionally may not be used at all or be used incorrectly. Also, certain reagents or tests have to be kept refrigerated. This precludes their use in house calls and may threaten the quality of the tests if they are accidentally left out of the refrigerator at certain moments. This means that complicated use and quality control procedures may threaten the reliability and robustness of some tests, reducing their suitability for use in general practice.

Usability, time to decision and frequency of use

Point-of-care tests may range from a simple strip of paper, which requires only a drop of blood, to fully automated systems in which a cartridge containing specimens is processed, and a test result is produced after a few minutes. The test results may be nominal (positive or negative), ordinal (multiple categories, e.g. <20, 20–40 and >40 mmol/l) or ratio (in precise units, e.g. 3 or 28 mg/l). There are different opinions on the usefulness of various types of interpretation, with some preferring a dichotomous result, and others preferring a continuous scale. The advantage of a continuous scale is that the degree of abnormality can be used in the interpretation, but this in itself may cause certain problems, and the most practical cut-off value is not always clear.

How fast a test needs to be, depends on the disorder for which it is used. The minimum requirement is that the result must be available within the timeframe in which a decision has to be made. Ideally, a test should only take a few minutes, so the result can be used during the same consultation. Similarly, the meaning of 'ease of use' is not precisely defined: a test that uses whole blood is obviously easier and more patient-friendly than one that requires venous blood or even plasma.

The final criterion relating to use and quality control concerns the incidence of the disorders for which a test is used. The fact that most tests have a limited shelf-life means that if the prevalence (of suspecting a disorder, not that of the disorder itself) is too low, GPs may have to discard unused tests. In addition, it means that a GP may not acquire the necessary dexterity in carrying out a rarely used test, or the necessary experience in interpreting its results.

INDICATIONS AND EFFICACY

Indication for testing and test interpretation

Point-of-care tests only offer added value when the doctor is unsure about the diagnosis. In the context of general practice, their most important function is to exclude quickly serious pathology. It might, therefore, seem ideal if a test has maximum sensitivity, but things are not that simple. Doctors need to know the characteristics of a particular test for patients for whom they want to use it.

For instance, the D-dimer tests used in hospitals to exclude thrombosis of the leg or pulmonary embolism have a high sensitivity. This minimizes the risk of missing serious disease, but increases the risk of false-positive results, due to the lower specificity of the tests. The point-of-care thrombosis test has a lower sensitivity, but a higher specificity. GPs will only carry out this test after stratification based on a decision rule and will, therefore, not test high-risk patients, whom they will immediately refer for specialist work-up. This implies that the GP reduces the prior probability in those patients whom they do test to such an extent that the rate of false-negative results becomes comparable to that of the reference standard, i.e. the ultrasonography or CT-scanning. The higher specificity of the point-of-care test (in combination with the low prevalence that results from applying the decision rule) means that more of the GPs' patients are spared an unnecessary trip to the hospital than if a laboratory test had been used (see also Box 2). What matters is, therefore, a careful balancing of test characteristics and prior probabilities (11).

This balance is not merely a matter of calculations. Characteristics and the positive and negative predictive value of a test are also partly determined by characteristics of patients and their specific disorders (i.e. the case-mix) (12). Test characteristics based on different populations are necessarily subject to spectrum bias: because of prior selection, patients in a secondary care setting are often in much more advanced stages of the disorder. Besides a lower prevalence of disease in general practice (which implies a lower positive predictive value and a higher negative predictive value), disorders will often be at a less advanced stage. Incipient disorders are more difficult to detect, which implies a lower sensitivity and hence a greater risk of missing a disorder. This implies that patients in which the test characteristics were determined have to be comparable to patients who consult their GP, and who are eligible for the test.

After the implementation of a point-of-care test in routine practice, there is the risk for expanding indications to do the test. GPs may be tempted to do a CRP test for a patient with abdominal pain, or have the practice assistant do a preliminary D-dimer test, without applying the decision rule first. However, the exact predictive value of the test is unknown for these indications. In these cases, a large probability of false-positive findings exists, which may result in unnecessary anxiety and unnecessary additional diagnostics and/or treatment (13).

Box 2a. Example: checking heart-type fatty acid-binding protein for acute coronary syndrome against the Box 1 criteria.

Heart-type Fatty-Acid Binding Protein (H-FABP) is a cardiac marker used to detect acute coronary syndrome (ACS). The H-FABP point of care test measures the protein that is released upon cardiac damage. A finger prick is used to obtain four drops of blood, which are applied to a test card. The results are obtained within 15 minutes. Studies have proved the validity, reliability and robustness of the test (in a hospital setting) (24,25). GPs frequently see patients with chest pain and should, therefore, be in a position to use the test on a regular basis. This means that all of the above criteria for use and quality control appear to be met. The indication for its use (suspected ACS) is clearly defined, and information is available about the interpretation of the test result (the FABP test produces a dichotomous result, with a cut-off value of 7 ng/ml). The test may have direct consequences for patient management decisions. Patients can be referred to a cardiologist (or referral may be avoided if the result is negative). A study in the Dutch city of Utrecht involved GPs applying the test to 298 patients with suspected ACS. In the end, 22% of them were found to have the condition. Sixty-five per cent of those with a positive test result had the syndrome (positive predictive value), while 84% of those with a negative test result did not have the syndrome (negative predictive value). This means that the test cannot be sufficiently relied upon to exclude an acute coronary syndrome; its negative predictive value is insufficient for this life-threatening condition. This implies that the cost-effectiveness of the test in primary care cannot be determined (as the test characteristics are insufficient to allow this to be assessed in a randomised study). Based on the current available evidence, the H-FABP point of care test with this cut-off point is, therefore, not appropriate for excluding acute coronary syndrome in a general practice setting.

Box 2b. Example: checking the D-dimer test for deep vein thrombosis against the Box 1 criteria.

D-dimers are breakdown products released by fibrinolysis of a blood clot. Levels of D-dimers in the blood are only elevated in situations of increased coagulation activity. The D-dimer test is thus used to identify increased blood coagulation activity, which may occur in deep vein thrombosis (DVT) or pulmonary embolism. The point of care test is easy to carry out and involves applying a drop of capillary blood and a buffer onto a test strip, similar to a pregnancy test. The test does not need to be kept refrigerated and can easily be carried in the doctor's bag for home visits. The test result is dichotomous and is read as a blue line on the test strip. The result is available within 10 minutes and can thus be used to base a decision on, even at the patient's own home. A prospective study in Dutch general practice assessed the value of the D-dimer Simplify test in terms of excluding thrombosis of the leg (11). Using a clinical decision rule and the point of care test proved to enable GPs to exclude thrombosis of the leg with sufficient certainty in 50% of the patients ($n = 1\ 028$), without any further examinations. A diagnostic meta-analysis showed that the test had satisfactory validity and reliability (26). A GP with a standardised practice size of 2 350 patients can be expected to include thrombosis of the leg in a differential diagnosis five-to-eight times a year, and about 80% of these patients will have a negative outcome of the decision rule, which means that the GP will use the test 4–6 times a year (27). The indication for the use of this test is clearly defined (patients with a painful, swollen and/or red leg, with the GP suspecting thrombosis without there being a positive outcome of the decision rule). The cost-effectiveness of the diagnostic strategy for excluding thrombosis of the leg using a decision rule and the D-dimer test has been convincingly established (28). This means that the D-dimer point of care test for DVT meets all criteria and is suitable for routine use in the general practice setting. Hence, the test has been included in the Dutch College of General Practitioners' guidelines on DVT (27).

Box 2c. Example: checking the D-dimer test for pulmonary embolism against the Box 1 criteria.

It appeared attractive to use the same strategy to exclude pulmonary embolism and GPs, participating in the research programme for DVT asked repeatedly if it would be possible to use the Simplify test to exclude PE. The test could be used in the same way as described above. Decision rules were available for pulmonary embolism, and a scenario study based on ambulatory patients participating in a large Dutch secondary care study showed that such a strategy to exclude PE might be safe and efficacious in general practice as well (29). However, the frequency of pulmonary embolism among patients in general practice is unknown, as are the test characteristics of the point of care test among general practice patients suspected of having pulmonary embolism. Furthermore, clinical decision rules often perform differently in different populations (12). For that reason a primary care prospective observational diagnostic study in 598 patients suspected of pulmonary embolism was conducted and it showed that a Wells score of ≤ 4 combined with a negative qualitative D-dimer test result can safely (safety not different from a multi-detector CT-scan) and efficiently (45.5% of patients scored negative on the decision rule and had a negative D-dimer test) exclude pulmonary embolism (23). One full-time GP could be expected to use the D-dimer test for this particular diagnosis two-to-four times a year. Added to the frequency of its use for the indication of thrombosis of the leg, this would appear to be sufficient to recommend its future use, also in a diagnostic strategy to exclude PE. The exact yield, however, has to be determined in a management study.

Immediate effect on GP's decision and patient outcomes

A point-of-care test should preferably be evaluated for the intended indication in a randomized intervention study. This is the only way to determine whether the use of the test will lead to improved care (e.g. more specific medication or fewer unnecessary referrals to secondary care). The results of a point-of-care test should preferably have direct consequences for the management at that particular moment, although there may be differences of opinion about the exact nature of these consequences. For instance, the introduction of point-of-care tests for patients with hyperlipidaemia (cholesterol test), diabetes (HbA1c) and coagulation disorders (INR) in

general practice was not successful in terms of quality and satisfaction among professionals (14).

Although cost-effectiveness remains to be shown, the same researchers did show that the use of point-of-care tests resulted in improved adherence to therapy among these patient groups compared to the use of standard laboratory tests (15). Similarly, patients undergoing a point-of-care test for infections also showed greater adherence (16,17).

Cost-effectiveness

Additional diagnostic tests cost money. Although cost-effectiveness is a complex concept, costs and reimbursement are known to play a major role in decisions to use point-of-care tests. Health insurance companies and national governments may also use the criteria presented here to decide upon reimbursement. Larger diagnostic centres or general practice laboratories, which are present in some European countries, may facilitate this process by coordinating the implementation and dissemination of those new point-of-care tests meeting the criteria. In any case, much attention should be given to training courses for GPs on the use and interpretation of these tests and quality control.

WHAT POINT-OF-CARE TESTS WILL BECOME PART OF ROUTINE PRACTICE AND GUIDELINES?

Point-of-care tests for chronic disorders (like cholesterol or HbA1c) seem less suitable for regular use in routine general practice. For most chronic diseases, monitoring requires multiple tests, for which one finger prick does not provide enough blood. Although a finger prick might seem more patient-friendly than a venapuncture, multiple simultaneous finger pricks are not. In addition, costs rise rapidly when multiple point-of-care tests have to be applied.

Acute disorders are an excellent area for point-of-care testing (18), and the greatest progress has been made for these disorders in recent years, with immediate effects on routine care. For instance, CRP tests have enabled GPs to distinguish between serious and self-limiting lower respiratory tract infections (19). In a randomized intervention study, the use of the CRP point-of-care test led to a significant reduction in the number of prescriptions for antibiotics, without compromising patients' recovery (20–22). Similarly, the D-dimer test has produced favourable results in deep vein thrombosis and pulmonary embolism. Box 2 checks this test against the criteria presented here, showing that the D-dimer test meets all of them, which is why it was included in the Dutch College of General Practitioners' guidelines on deep vein thrombosis. Recent research showed the usefulness of the same test in cases of suspected pulmonary embolism (23) The heart-type fatty-acid binding protein (H-FABP) point-of-care test for cardiac ischaemia fails to meet the criteria and is not expected to be included in national guidelines on acute coronary syndrome.

This paper mainly focuses on examples of currently available point-of-care tests. It is to be expected that more tests will be developed to be run on point-of-care devices in the future. Whether general practice expresses a need for these tests, will largely depend on criteria as described. Preferably, GPs themselves should prioritize which tests could benefit their patients and their practice most.

SUPPLEMENTARY IS THE OPERATIVE WORD

We should like to emphasize in this background paper that no single point-of-care test will ever be able to replace thorough history-taking and physical examination as any test is part of a diagnostic procedure and can never be a stand-alone option. Point-of-care tests can be helpful in the grey area of diagnostic uncertainty. GPs may add a point-of-care test to the diagnostic procedure to increase the likelihood of a particular disease, but in far more cases it will reduce this likelihood, thereby enabling GPs to rule out a specific disease. Since diagnostic point-of-care tests will never produce a clear-cut definitive answer, GPs crucially need to be trained in the use and interpretation of the values they produce. It is also essential that such training courses are developed on the basis of evidence obtained in primary care. This means that point-of-care tests are not a simple shortcut to diagnosis or treatment. They are part of a balanced process in which the test result is an integral part of the way GPs decide on diagnosis and prognosis and communicate with their patients.

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