Frequencies and patterns of laboratory test requests from general practice: a service evaluation to inform point of care testing

Running head: Laboratory test requests from general practice

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List of abbreviations

POC	Point of care
OUH	Oxford University Hospitals
HDL	High Density Lipoprotein
RAST	Radioallergosorbent test
CRP	C-Reactive Protein

INR	International Normalized Ratio
FBC	Full Blood Count
HbA1c	Haemoglobin A1c

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ABSTRACT

Aims: The demand for test requests from general practice to laboratory services remains high. Tests performed at the point of care could reduce turnaround time and speed up clinical decision making. Replicating laboratory testing in the community would require panels of tests to be performed simultaneously, which is now approaching technological feasibility. We assessed frequencies and combinations of test requests from community settings to inform the potential future development of multiplex point of care panels.

Methods: We assessed all laboratory test requests made from general practice in Oxfordshire, UK, January 2014-March 2017. We summarised test request frequency overall and in combination, using heat maps and hierarchical cluster analysis. Results are also presented by age/sex subgroups. We further assessed patterns of tests requested within 7 and 14 days after an initial test request.

Results: 11,763,473 test requests were made for 413,073 individuals (28% age>65). Of more than 500 test types, 62 were requested at least 5,000 times, most commonly Renal Function Tests (approximately 296,000/year), Full Blood Count (278,000/year) and Liver Function Tests (237,000/year). Cluster analysis additionally identified a clear grouping of tests commonly used to investigate anaemia. Follow-up test frequency was much lower than the frequency of multiple tests ordered at initial presentation.

Conclusions: The current high volume of single and combination test requests highlights an opportunity for reliable multiplex point of care panels to cover a core set of frequently requested tests. The impact on test use of introducing such panels to general practice requires additional research.

INTRODUCTION

In the diagnosis of acute disease and the management of chronic disease, the availability of, and demand for, point of care (POC) tests in community settings has been gradually increasing [1]. Immediate access to test results allows clinicians to incorporate results into their decision making and to share decision making with the patient [2], and may also improve patient outcomes, patient satisfaction and cost-effectiveness [3]. In some cases, such as when measuring serum potassium, POC results have the potential to be more physiologically relevant than those from samples that have developed a shift in electrolyte balance during a long uncontrolled journey to a laboratory [4, 5].

The introduction of automation has increased efficiency and reduced per-sample costs and error rates in laboratory processes [6], but general practitioners remain keen to incorporate POC tests directly into their practice [7]. A survey in the UK in 2012 suggested a range of conditions where diagnosis in general practice might benefit from improved or new POC testing [8]. Recent high-profile reports into methods to address rising antimicrobial resistance highlighted the importance of prescribing guided by POC tests as one strategy for stewardship of antimicrobials [9, 10]. A systematic review, although highlighting the potential for shorter turnaround time, found a lack of definitive trials evaluating the use of POC tests in relation to clinical benefit in primary care [11].

Many POC blood testing technologies are currently available, but these are not necessarily fit for purpose in community settings, with evidence regarding clinical and cost-effectiveness often limited [12]. Most tests assess a single biomarker at a time. In practice, multiple testing in a patient is often required to achieve diagnostic confidence or to monitor chronic disease, which requires serial processing and multiple machines. Currently, POC testing in primary care is largely limited to blood glucose and blood ketones. Some practices additionally offer C-Reactive Protein (CRP), International Normalized Ratio (INR) and D-dimer, but these are not in widespread use. Therefore, there appears to be a conflict between the desire of clinicians to make greater use of POC testing and the limitations of many of the single-biomarker tests that are available.

One solution is to develop multiplex testing platforms capable of offering a panel of different biochemical and haematological tests from a single blood sample in a short time [13]. Methodology integration in POC testing is commonly addressed through a single-platform, multiple-cartridge model. This employs a single platform device that integrates power provision; data collection, storage and processing; result presentation; and audit trail information, while sample processing takes place on disposable single-use cartridges. Examples include the Abbott i-STAT® with CG4+ and CHEM8+ cartridges and the Alere Afinion™ Lipid Panel [14, 15].

Multiplex testing is potentially desirable in general practice, which deals with patients presenting with a large variety of conditions. Especially in older adults, non-specific complaints such as dyspnoea or cough could indicate several lung or heart conditions, including pneumonia, heart failure and pulmonary embolism [16]. A substantial proportion of patients have more than one chronic condition, which may worsen acute problems [17]. Tests conducted at POC could also support decision-making in acute situations when results from laboratory-based testing become available too late or are delayed, for example for acute coronary syndrome or sepsis.

However, it remains unclear which tests should be included in future multiplex panels. There is an absence of reliable, up-to-date information about frequency and patterns of specific test requests from general practice. Test frequency cannot necessarily be predicted by disease prevalence or clinical outcomes [18, 19], because reasons for blood testing may include reassurance or ‘uncertainty’ as well as diagnostic purposes and monitoring [20, 21].

To inform the development of multiplex POC tests, a more detailed understanding of laboratory tests currently requested from primary care is required. This comprises information about overall test frequencies, tests that are frequently requested in combination, and those that are requested in follow-up after an initial test result. This paper focuses primarily on the frequency of test requests. It is not an objective of this study to link the results of those tests to the test ordering behaviour of the practitioner. We describe the frequency of blood tests requested from general practice in Oxfordshire between 2014-2017, and the frequency of retesting within 7 and 14 days.

METHODS

In a service evaluation project agreed with the Oxford University Hospitals (OUH) NHS trust (CSS-BIO-2 4729), we obtained data from the OUH Clinical Pathology service on all laboratory blood tests requested from general practices in Oxfordshire, January 2014-March 2017. No subsampling was performed. Data files were indexed by anonymised patient identification numbers, allowing linkage of records of patients for whom multiple tests were requested.

Data were cleaned by removing entries that had clear formatting errors, such as an erroneous date stamp (less than 0.1% of all entries). Test requests were recoded from free text names into identification numbers to remove minor spelling and formatting variations. Urine tests and tests relating to dose-finding were excluded. Nucleated Red Blood Cell was also omitted as this was frequently performed as a routine laboratory test rather than as a specific request from the practitioner. No additional exclusion criteria were applied.

We initially summarised test request frequencies across the whole cohort. Separately, we used a subsample that excluded individuals who appeared to be presenting with chronic conditions, defined as individuals with at least one test request on at least 18 different dates across the study period (an average of more than one test per two months for three years).

We created tables and heat-maps to show the frequency of pairs of test request made contemporaneously (for the same individual, on the same date), restricting this to the most commonly requested tests overall (more than 5,000 occurrences in total) for presentational clarity. We also analysed these patterns with hierarchical cluster analysis, using the Jaccard metric for defining the similarity of vectors of test requests [22], and complete linkage [23]. This metric highlights patterns of test requests occurring together relative to the frequency with which each test is used. Results are presented as dendrograms: tests appearing close proximity are attached by a common ancestral branch and can be considered part of a cluster of given size, with tests occurring proportionally more often in combination appearing lower down the figure.

The above analysis was repeated to investigate groups of tests requested on different days within 7 days and on different days within 14 days, to check whether patterns varied in relation to repeat consultations. In secondary analyses we also considered subgroups defined by the sex and age of the patient (<18, 65+ and 85+ years). The lowest age group was further subdivided into ages <13 and 13-17 years for descriptive purposes.

We used the results of all analyses to identify the most common groupings of test request overall and in the subgroups defined above. To simplify presentation, we grouped together certain tests commonly performed together in biochemistry according to local laboratory protocol even if requested individually: Renal Function Tests (Plasma Creatinine, Plasma Potassium, Plasma Sodium), Liver Function Tests (Plasma Albumin, Plasma Alkaline Phosphatase, Plasma Alanine Transaminase, Plasma Total Bilirubin) and Lipid Profile Tests (Plasma Total Cholesterol, Plasma HDL-Cholesterol, Plasma Triglycerides).

As the objectives of this study included complete quantification of the frequency of test requests, no sampling was necessary and the sample size was defined by the size of the data file. Statistical analysis was performed using R version 3.2.3 [24], with figures plotted using the 'circlize' and 'ComplexHeatmap' packages [25, 26].

RESULTS

The NHS Oxfordshire Clinical Commissioning Group contains 71 practices that have a list size of more than 800 patients each, with an average population size of 10,283 patients per practice [27]. After data cleaning, the full cohort contained 11,763,473 test requests made on 1,779,238 occasions for 413,073 individuals (Figure 1). The majority of patients were female (236,281/411,983 of those with sex recorded, 57%). The age distribution of individuals (at time of first test request in the data file) was 16,668 (4%) aged <18 years; 280,745 (68%) aged 18-64 years; 97,785 (24%) aged 65-84 years; 17,875 (4%) aged 85+ years.

More than 500 different tests were requested at least once, but most of these, such as specific radioallergosorbent tests (RAST), were infrequent and for clarity are not presented. Table 1 contains information about the 17 tests requested at least

200,000 times and Supplementary Table 1 contains information about tests requested at least 5,000 times.

Table 1

	Patients	Tests	Age < 13		Age 13-17		Age 18-64		Age 65-84		Age 85+	
	N	N	N	%	N	%	N	%	N	%	N	%
Total of all tests	**413,073**	**1,779,238**	**9,570**	**0.53**	**17,085**	**0.96**	**852,010**	**47.89**	**716,714**	**40.28**	**183,859**	**10.33**
Plasma Creatinine (Cr)	334,480	959,664	6,081	0.63	10,870	1.13	477,491	49.76	380,646	39.66	84,576	8.81
Plasma Potassium (K)	332,604	952,336	6,087	0.64	10,870	1.14	473,682	49.74	377,367	39.63	84,330	8.86
Plasma Sodium (Na)	332,525	951,078	6,084	0.64	10,864	1.14	473,324	49.77	376,705	39.61	84,101	8.84
Full Blood Count (FBC)	338,376	903,661	8,257	0.91	14,230	1.57	528,354	58.47	285,767	31.62	67,053	7.42
Plasma Albumin (ALB)	307,610	768,862	5,661	0.74	10,581	1.38	414,387	53.90	281,309	36.59	56,924	7.40
Plasma Alkaline Phosphatase (ALP)	305,409	757,423	5,596	0.74	10,466	1.38	409,019	54.00	277,324	36.61	55,018	7.26
Plasma Alanine Transaminase (ALT)	301,710	732,829	5,330	0.73	10,095	1.38	399,071	54.46	266,684	36.39	51,649	7.05
Plasma Total Bilirubin (BR)	300,881	730,902	5,333	0.73	10,101	1.38	397,202	54.34	266,616	36.48	51,650	7.07
Thyroid-Stimulating Hormone (TSH)	253,922	468,885	3,615	0.77	7,958	1.70	281,020	59.93	144,053	30.72	32,239	6.88
Plasma Total Cholesterol (TC)	237,920	455,377	169	0.04	1,314	0.29	237,075	52.06	190,125	41.75	26,694	5.86
Plasma HDL-Cholesterol (HDL)	237,905	455,312	168	0.04	1,314	0.29	237,049	52.06	190,097	41.75	26,684	5.86
Plasma C-Reactive Protein (CRP)	193,435	431,992	4,466	1.03	6,502	1.51	242,442	56.12	147,075	34.05	31,507	7.29
International Normalized Ratio Raid (INR Raid)	12,157	376,014	2	<0.01	47	0.01	52,740	14.03	236,386	62.87	86,839	23.09
Blood Glycated Haemoglobin (HbA1c)	188,088	372,152	718	0.19	1,912	0.51	193,003	51.86	151,031	40.58	25,488	6.85
Plasma Glucose (PG)	180,157	283,865	1,880	0.66	3,995	1.41	158,124	55.70	101,159	35.64	18,707	6.59
Plasma Triglycerides (TG)	139,170	231,049	131	0.06	1,041	0.45	124,016	53.68	93,780	40.59	12,081	5.23
Plasma Calcium (Ca)	136,583	212,876	2,091	0.98	3,988	1.87	107,986	50.73	75,435	35.44	23,376	10.98

The most commonly requested tests were Renal Function Tests (approximately 296,000 requests per year) and Full Blood Count (FBC, 278,000/year). Other commonly requested tests included Liver Function Tests (237,000/year), Thyroid-Stimulating Hormone (144,000/year), Lipid Profile Tests (140,000/year) and CRP (133,000/year). The 334,480 patients who received at least one Plasma Creatinine test over the 39 months of the study compare with a mid-2016 total population estimate for Oxfordshire of 683,169 [28], implying that, ignoring changes in population, slightly under half (49%) of the resident Oxfordshire population had at least one Plasma Creatinine test during the 3.25-year study period. The corresponding figures for FBC and CRP are 50% and 28%, respectively. The overall burden of testing is much higher when allowing for repeat testing (Table 1).

Older age groups were over-represented: the 28% of adults aged over 65 represents a higher proportion than the general population (Oxfordshire mid-2016 population estimate, 120,971/683,169 (18%) aged over 65 [28]). In different age groups, the ratio of number of tests to the Oxfordshire population size ranged between 7.4 (age 65+) and 0.2 (age under 18). Other tests showed age-specific patterns as expected, for example increased frequency of thyroid function and glandular fever tests in the lower age groups, and Brain Natriuretic Peptide and Plasma Urea in the older age groups. Plasma Magnesium testing was disproportionately high in the adolescent group compared to younger children. Overall, paediatric testing accounted for just 1.5% of total demand (Table 1).

Figure 2 and Supplementary Figure 1 show the frequency of tests made contemporaneously (for the same patient on the same day). The heat-map enables the identification of pairs of tests that are commonly requested together: for example, on 39% of occasions when a Renal Function Test was ordered, a Lipid Profile Test was also ordered, whereas on 83% of occasions when a Lipid Profile Test was ordered, a Renal Function Test was also ordered. On 96% of occasions when a CRP test was ordered, a Full Blood Count was also ordered. Absolute numbers appear in Supplementary Table 2.

The cluster analysis indicates groups of tests that tended to be ordered contemporaneously (Figure 3). When patients with test requests on at least 18 different dates over the study period were excluded, the pattern of results remained

similar, except that tests whose primary use is for monitoring (such as INR) no longer appear (Supplementary Figures 2 & 3, Supplementary Table 3).

Groupings identified by the heat-map and cluster analysis include a large group of many commonly-requested tests, which may be subdivided into one containing renal and liver function tests, FBC and an inflammatory marker (C-Reactive Protein), and another containing tests commonly used as a general health check or for monitoring (Lipid Profile Tests, HbA1c, Plasma Glucose) and as a subset of tests that might be used to investigate fatigue (Thyroid-Stimulating Hormone, HbA1c). Another group consists of a variety of tests relating to serum iron and vitamin levels (Iron, Transferrin, Ferritin, Vitamin B12, Folate), albeit that these tests were performed less frequently overall. A group of hormone tests including Follicle-Stimulating Hormone, Luteinizing Hormone and Oestradiol and a group of bone markers (Calcium, Phosphate) are also apparent (Figure 3).

Supplementary Figure 4 shows patterns of testing among individuals who received multiple tests at different consultations within seven days. Proportions are much lower than the corresponding proportions of multiple test requests on the same day (Supplementary Figure 1). For example, only 0.3% of individuals return for a Lipid Profile Test within seven days of an initial Renal Function Test, and 1.2% return for a Renal Function Test within seven days of an initial Lipid Profile Test. In comparison to other tests, a relatively large number of individuals return for additional tests in the week following an initial Plasma Magnesium test (9.4% have a Renal Function Test and 6.9% return for a second and subsequent Plasma Magnesium test). This finding is not due to this subgroup not receiving additional tests at the same time as their index test: for example, 95% of these individuals received a Renal Function Test alongside their initial Plasma Magnesium test, higher than the overall proportion of 90% (Supplementary Figure 1). The pattern of results within 14 days is similar (Supplementary Figure 5).

Results presented by sex and age are available as Supplementary Figures 6-10.In older adults Renal Function Tests are proportionally more frequent and are more likely to be co-requested alongside other tests. Thyroid-Stimulating Hormone, Free Thyroxine and Free Triiodothyronine comprise a common test combination in children.

DISCUSSION

This paper has assessed the extent and pattern of laboratory test requests from primary care in Oxfordshire between 2014-2017. Results are based on a large, high-quality dataset that provides comprehensive coverage of the primary care population in this region of the UK. These results highlight the extremely high volume of testing among the most common tests, such as those for renal function, liver function, FBC and lipids.

We have also outlined current patterns in testing practice by identifying groups of tests ordered contemporaneously. While these patterns are consistent with expected practice in diagnosis or monitoring, quantifying this information is valuable as it informs decisions about which tests might be included on multiplex POC panels. Our analysis suggests that a standard panel containing renal and liver function, full blood count and CRP is likely to be frequently used as a screening set of bloods by GPs, and that further panels addressing the requirements of the NHS Health Check [29] and as part of an assessment of fatigue [30] would be valuable for primary care settings. The level of co-testing of CRP and FBC is high, and illustrates the potential value of multiplex POC panels for investigating acute conditions. A panel investigating causes of anaemia might also be beneficial to follow abnormal FBC.

The relatively high proportion of individuals returning for additional tests following an initial magnesium test was unexpected, but is likely to reflect retesting for renal function following an initial abnormal result, which may also be associated with low calcium [31]. However, reasons why proportionally the rate of retesting of magnesium appears higher than for other tests are unclear.

The extent of paediatric testing is relatively small. As it harder to perform it is less likely to form part of GP assessment, and because most childhood illness is acute, laboratory blood tests would not be informative in the timeframe required. However, POC testing is likely to have a clear role in the management of childhood illness, because it can be acceptable and simple to perform in primary care [32], so future demand may be higher than current figures suggest. Blood testing in children in primary care is challenging due to the time needed for anaesthetic creams to work

and the specialist paediatric phlebotomy skill required. These tests are therefore amenable to fingerprick testing, and clinical targets would include cœliac disease, glandular fever, thyroid disease and anaemia.

Component tests that might be clustered to form a context-specific multiplex POC panel would be constrained by the technical potential to group the testing methodologies. No universal POC testing methodology is currently available that would cover divergent targets such as basic components of blood chemistry and more complex protein biomarkers, as approaches of detection are necessarily different. The manufacturers of some multiplex platforms (for example Alere Afinion™) also offer single marker cartridges, such as for CRP [33], which may be preferable if marker detection is incompatible with POC multiplexing, or where there is an economic disincentive or no clinical argument for multiplexing. However, the development of multiplex panels optimised for general practice for the groupings suggested is technologically feasible, within the strictures outlined here.

This study has some limitations. As it is based on laboratory test requests only, it cannot assess whether the testing behaviour of clinicians would change if a wider variety of POC tests were available. The overall impact on testing frequencies of introducing new POC devices to general practice is therefore unknown.

A further limitation is that in some cases, results may reflect request short cuts made by clinicians to request multiple tests together, such as iron, transferrin and ferritin as a group, and B12 and folate as a group, even though options to request them individually or to deselect some tests from the group are available. We are unable to distinguish between these scenarios.

Although comprehensive, the current dataset is restricted to one region and so we could not assess regional factors that may be related to test requesting patterns. Although there is no reason to suspect systematic differences from testing decisions nationally, verifying this would be challenging as currently no suitable and accessible UK-wide database is available.

Limitations may also arise from introducing multiplex panels to primary care. Cost-effectiveness is likely to depend on the conditions for which the tests are used. For example, studies have shown that INR self-monitoring [34] and POC testing for the

NHS Health Check [35] are likely to be cost-effective, but these findings should not be extrapolated to POC testing more generally, and cost-effectiveness evidence is often unavailable [12].

In some contexts POC testing will add to an established clinical pathway, such as CRP to guide prescribing in lower respiratory tract infections, which are currently managed without support from laboratory testing in most cases because the test result comes too late to affect decision making. By contrast, the changes to the pathway in a monitoring scenario may be smaller, as the POC test could act as a direct replacement for laboratory tests. Other concerns include lack of confidence in test results [36] and the potential that reimbursement for clinicians who perform tests might increase inappropriate testing. Considerations relating to quality control are described elsewhere [37].

In summary, this study has quantified the current large extent of laboratory test requests from primary care and identified combinations suitable for multiplex POC panels. Multiplex tests are likely to play a major role in moving blood testing from laboratory settings into the community, and to meet current testing needs manufacturers should focus on the test combinations outlined. Additional research will be required to understand how the behaviour of clinicians may change once suitable test panels become available.

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FIGURE AND TABLE LEGENDS

Figure 1: Study flowchart.

Figure 2: Heat map showing test combinations ordered contemporaneously in the full study sample. Each cell indicates the percentage of occasions on which the test shown in the column (numerator) was requested, given that the test shown in the row (denominator) was requested.

Figure 3: Dendrogram showing test combinations ordered contemporaneously in the full study sample. (25-OH-D: 25-hydroxyvitamin D; Amyl: Plasma Amylase; ANA: Antinuclear Antibody; ANBhS: Antenatal Haemoglobinopathy Screening; aPTT: Activated Partial Thromboplastin Time; AST: Plasma Aspartate Transaminase; B9: Serum Folate; B12: Serum Vitamin; BNP: Brain Natriuretic Peptide; BUN: Plasma Urea; Ca: Plasma Calcium; CA125: Serum Cancer Antigen 125; CK: Plasma Creatine Kinase; CRP: Plasma C-Reactive Protein; E2: Oestradiol; EMA: Anti-Endomysial Antibody; EPG-Igs: Serum Electrophoresis & Immunoglobins; ESR: Erythrocyte Sedimentation Rate; FBC: Full Blood Count; Fe: Iron; Fer: Serum Ferritin; FSH: Follicle-Stimulating Hormone; FT3: Free Triiodothyronine; FT4: Free Thyroxine; GF: Glandular Fever Test; GGT: Plasma Gamma-Glutamyl Transpeptidase; HbA1c: Blood Glycated Haemoglobin; Hb-Path: Haemoglobinopathy; IgA: Immunoglobin A; INR: International Normalized Ratio; LFT: Liver Function Tests; LH: Luteinizing Hormone; Li: Serum Lithium; LPT: Lipid Profile Tests; Mg: Plasma Magnesium; P4: Serum Progesterone; PG: Plasma Glucose; Pho: Plasma Phosphate; PRL: Prolactin; PSA: Prostate-Specific Antigen; PT: Prothrombin Time; PTH: Parathyroid Hormone; RF: Rheumatoid Factor; RFT: Renal Function Tests; TF: Transferrin; TPO Ab: Thyroid Peroxidase Antibody; TSH:

Thyroid-timulating Hormone; TT: Total Testosterone; tTG: Tissue Transglutaminase Antibody; UA: Plasma Uric Acid; WCPC: White Cell Progenitor Count)

Table 1: Test requests, ordered by frequency and reported as the number of patients with at least one test request, number of test requests in total and by age group.

Supplementary Figure 1: Expanded version of Figure 2, including tests requested at least 5,000 times in total.

Supplementary Figure 2: Heat map, as Supplementary Figure 1, after excluding individuals who appeared to be presenting with chronic conditions (test requests on at least 18 different dates across the study period).

Supplementary Figure 3: Dendrogram, as Figure 3, after excluding individuals who appeared to be presenting with chronic conditions (test requests on at least 18 different dates across the study period).

Supplementary Figure 4: Heat map showing test combinations ordered within 7 days in the full study sample. Each cell indicates the percentage of occasions on which the test shown in the column (numerator) was requested within 7 days of the test shown in the row (denominator). For clarity, INR and INR-RAID, which are almost exclusively used in routine monitoring, are excluded.

Supplementary Figure 5: Heat map, as Supplementary Figure 4, but showing test combinations ordered within 14 days.

Supplementary Figure 6: Heat map, as Supplementary Figure 1, males only. Percentages are presented as the calculated percentage for males minus the percentage for the full sample, given in Supplementary Figure 1.

Supplementary Figure 7: Heat map, as Supplementary Figure 1, females only. Percentages are presented as the calculated percentage for females minus the percentage for the full sample, given in Supplementary Figure 1.

Supplementary Figure 8: Heat map, as Supplementary Figure 1, age <18 only.

Supplementary Figure 9: Heat map, as Supplementary Figure 1, age 65+ only.

Supplementary Figure 10: Heat map, as Supplementary Figure 1, age 85+ only.

Supplementary Table 1: Expanded version of Table 1, including tests requested at least 5,000 times in total.

Supplementary Table 2: Spreadsheet of test frequencies overall. These data are presented in Figure 2.

Supplementary Table 3: Spreadsheet of test frequencies, after excluding individuals who appeared to be presenting with chronic conditions. These data are presented in Supplementary Figure 2.

KEY MESSAGES

- This study quantifies the extremely high demand for laboratory blood tests from community settings in the UK.
- Current demand suggests an important role for multiplex devices offering panels of tests at the point of care.
- Test combinations suitable for use on multiplex point of care devices include those for a general health check and those to investigate anaemia.

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