Use of laboratory tests in Belgium

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ABSTRACT

Objectives – The use of laboratory tests is rising internationally, which can have multiple negative effects. Therefore, we wanted timely and accurate information on test use. This study aims to identify trends in the use of all and specific laboratory tests.

Design – Retrospective cohort study analysing data from 2002 to 2021.

Setting – The Belgian Intego database containing primary, secondary, and tertiary health care information through general practitioner data collection. During the time frame 107 distinct GP practices evenly distributed in Flanders contributed to the data.

Participants – 601 341 patients of all ages and sexes that visited a participating GP at least once during the time frame.

Main outcome measures – Proportion of patients that get tested, number of orders per patient, number of tests per order, number of tests per patient, ranking number of most ordered tests, percentage of all tests.

Results – We analysed 90 121 176 tests. Proportion tested, number of orders per patient, number of tests per order and number of tests per patient all seemed to increase over the years. Age and test use seemed correlated. No clear link was found between test use and sex. Test use appeared distributed differently regarding number of orders per year (twofold for those getting just one order a year, and single centred in those with multiple orders). We found limited evidence in ranking number analysis of most used tests; however, the sudden apparition of PCR sequencing of Sars-CoV-19 is noteworthy. Furthermore, we are cautious in drawing conclusions when analysing percentage use of specific tests, but observed an important increase in the use of vitamin D.

Conclusions – Our data confirms international findings in increase in test use. Older people seem to get more tests (fewer tests per order, multiple orders). Younger people get less tests in less orders. Apparent aberrations in test use may be explained by the introduction of PCR sequencing of Sars-CoV-19.

NEDERLANDSE SAMENVATTING

Het gebruik van laboratoriumtesten neemt internationaal toe. Dit kan verschillende negatieve gevolgen hebben. Daarom is tijdige en accurate informatie over het testgebruik gewenst. Deze studie heeft tot doel trends in het gebruik van alle en specifieke laboratoriumtesten te identificeren.

We ontwikkelende een retrospectieve cohortstudie met een analyse van data van 2002 tot 2021 uit de Belgische Intego-databank met informatie uit de eerste, tweede en derde lijn. Gedurende de studieperiode hebben 107 verschillende huisartsenpraktijken, gelijkmatig verdeeld over Vlaanderen, bijgedragen aan de gegevens van 601 341 patiënten van alle leeftijden en geslacht, die ten minste eenmaal een deelnemende huisarts bezochten gedurende deze periode.

We analyseerden de data naar proportie patiënten die zich laat testen, aantal orders per patiënt, aantal testen per order, aantal testen per patiënt, rangnummer van de meest gebruikte testen, percentage van alle testen.

Er waren 90 121 176 tests opgenomen in de analyse. Het percentage tests, het aantal orders per patiënt, het aantal tests per order en het aantal tests per patiënt leken allemaal toe te nemen in de tijd. Leeftijd en testgebruik schijnen gecorreleerd te zijn. Er werd geen duidelijk verband gevonden tussen testgebruik en geslacht. Testgebruik leek verschillend verdeeld in functie van het aantal orders per jaar (tweevoudig bij één order en enkelvoudig bij meerdere orders). We vonden beperkt aanwijzingen in de rangnummeranalyse van de meest gebruikte testen, maar de plotselinge introductie van PCR-sequencing van Sars-CoV-19 viel wel op. Verder zijn we voorzichtig met het trekken van conclusies uit het analyseren het gebruik van specifieke tests, maar we merkten wel een belangrijke toename op in het gebruik van vitamine D.

Onze gegevens bevestigen de internationale bevindingen wat betreft de toename van het testgebruik. Oudere mensen lijken meer tests te krijgen (minder tests per order, meerdere orders). Jongere mensen krijgen minder tests in minder orders. Schijnbare afwijkingen in de data zouden kunnen worden verklaard door de invoering van PCR-sequencing van Sars-CoV-19.

USE OF LABORATORY TESTS IN BELGIUM

INTRODUCTION

The use of laboratory tests is a fundamental part of medical care. Laboratory tests contribute to up to 70% of all critical decisions in health care.(1) A national survey among primary care physicians in the United States conducted in 2012, showed that diagnostic laboratory tests were ordered for an average of 31.4% of their patients on a weekly basis.(2)

The number of laboratory tests used in primary care settings has considerably increased over the last decades, which has been described worldwide.(3–7) A retrospective analysis of 250 million tests used in United Kingdom primary care, revealed a 3.3-fold increase from on average 1.5 tests in 2000 to 5 tests in 2015 and 2016 per patient annually.(3) In Belgium, a similar study in primary care was conducted by the Belgian Health Care Knowledge Centre (KCE) for the period 1995 to 2005.(4) The use of laboratory tests on average per year increased in all test categories. The smallest increase was found for hormonology tests (50%), while coagulation test use increased with 300%. Smaller intervals between the same tests were found to be related with taking chronic medication (on average 4 months compared to 7 months), having had (longer) hospitalization, staying in nursing homes, and receiving home nursing.(4)

Several studies have indicated an inappropriate use of laboratory tests.(8–10) A 15-year meta-analysis revealed an overall mean rate of 20.6% overutilization, and 44.8% underutilization.(9) An example of overutilization is vitamin D testing, which showed an exponential increase as high as a twofold growth in ordering rate in Switzerland and comparable results in the UK.(3,11) All the while the clinical significance of screening by measuring vitamin D remains ambiguous.(3,8,12–15) Research related to underlying mechanisms of inefficient use of laboratory tests, has primarily focused on overuse. Factors influencing overutilization of laboratory tests include the increased availability of tests, the ease of use, high workloads, limited time for decision making, and willingness to meet the patients' needs to gain reassurance through testing.(16–18) One study found a decrease in laboratory test when

availability increased, though the used test were not necessarily more appropriate.(19) Another factor closely linked to appropriate testing is the familiarity of the physician with the test.(9) Furthermore, physician characteristics have been described related to higher tendency to use tests, e.g. female sex, working environment, and tolerance to error and uncertainty.(18,20)

The increasing use of laboratory tests in primary care has several consequences affecting society, physician, and patient. First, the increased use of tests adds to the growing financial costs of healthcare. In the UK, up to £ 3 billion of the total of £ 106 billion of the National Health Service budget has been used for laboratory tests, of which 45% were requests from primary care.(21) Not only the cost of the tests themselves, but also all health care expenses because of ordering the test must be considered.(9)

Second, the growing use of diagnostic tests has a direct impact on the workload of the physicians ordering them. With the growing availability of tests, the uncertainty when deciding which test to order increases correspondingly.(2,19) The next hurdle is interpreting the result. One study found that physicians designate up to 70 minutes per day on analysing test results.(22) Communicating the result is the final task flowing from the initial test order, which is a complicated process in itself, and prone to error.(22,23)

Third, overuse of testing may also have negative consequences for the patient. For example, incidental findings may lead to a series of follow up testing, this has since long been described as the cascade effect.(5,24–26) A recent study has found that almost all physicians reported consequences of incidental findings after diagnostic testing. This ranged from potentially anxiety inducing follow up to harmful interventions in up to 86.7% of the cases.(24) An example of the latter is the invasive diagnostic procedures following an elevated Prostate-specific antigen (PSA) blood test.(27,28) Updated guidelines have already proven to be successful in reducing inappropriate PSA screening and subsequently lowering intervention rates.(27)

Timely and accurate information on laboratory test use in health care is important to identify trends. Insights may inform interventions supporting appropriate use of laboratory tests which may optimize healthcare quality and resource utilization. To our knowledge, no recent study has analysed laboratory test use in Belgium, since the KCE study for the period 1995 to

2005. Therefore, this study aimed to gain information about the use of these tests in the last decade. We analysed the use of all laboratory tests and specific laboratory tests for the study period from 2002 to 2021.

ABBREVIATIONS

ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase (Dutch: AF, Alkalische Fosfatase)
ASAT	Aspartate Aminotransferase
CBC	Complete Blood Count
CRP	C reactive protein
eGFR	Estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
Gamma GT	Gamma Glutamyl Transferase
GP	General Practitioner
IMA	Agency of the seven health insurance funds in Belgium (Dutch: Intermutualistisch Agentschap)
KCE	Belgian Health Care Knowledge centre (Dutch – French: Kenniscentrum – Centre d'Expertise)
LOINC	Logical Observation Identifiers Names and Codes
PSA	Prostate-specific antigen
YCG	Yearly Contact Group

METHODS

Study design

A retrospective cohort study design was used to gain information about laboratory test use and identify changes of overall and specific laboratory test use in Belgium. Data were obtained from the Intego database, a Belgian family practice morbidity registration network managed at the Department of General Practice of the University of Leuven.(29) The data analysed for this research was anonymised for personal data referring to either patient or GP, limiting ethical concerns. Evidently, ethical approval was obtained before commencing the study.

Data collection

Registration of Intego Data began in 1994, for this study we analysed the data of the timeframe 2002 until 2021. During this 20-year period, 107 distinct GP practices were participating in the Intego project, uniformly distributed throughout Flanders, Belgium, resulting in data from 601 341 patients. Earlier studies have shown that this sample is representative for the Flemish population.(29,30) The quality of the data is guaranteed by strict selection of the registering doctors and validation of the data afterwards. Firstly, GPs must apply for inclusion in the registry and meet predetermined quality standards. Secondly, the collected data is compared to those of other GPs for internal validation and to international registries and database for external validation.(29) We included all patients that were registered in the Intego database at least once during the entire time frame.

Data cleaning

Based on the available data in the health records registered in the Intego database, all mentions of laboratory tests were extracted. This includes all laboratory results, regardless of whether these were ordered by the GP or another doctor in care of the patient. We retained those that appeared at least 1 000 times. These text labels were uniformed by converting to lower case and removal of special characters, which resulted in 2 456 unique names of tests that account for approximately 98% of all tests. Since multiple entries may refer to the same tests, for example “hemoglobine”, “haemoglobine”, and “hb” all refer to the same measurement of hemoglobin; we wanted to link all tests to a Medidoc code, in this example “13705A.B”. Medidoc codes are used to identify laboratory test results and communicate them between laboratories and physicians. Their use originated in the former Belgian electronic health record software with the same name. Doing so, we can combine their count since they refer to the same test, instead of measuring the use of each entry as a different test.

When possible, these names were automatically matched with a Medidoc code using available databases with Medidoc codes from Corilus and Intego. The remaining test names were matched through expert-based manual coding to a Medidoc code where possible, using data from Corilus and the ReTaM database of the Belgian Federal Public Service for Health, Food Chain Safety and Environment.(31,32) This manual process was done and reviewed by two experts, and reviewed by a third colleague. Some test names did in fact not refer to a

laboratory test (e.g., subheadings in test report) excluding 275 entries; or they did refer to a laboratory test, but no Medidoc code was available for this test, excluding another 13 entries. For 399 entries, the entry was unclear to be matched to a Medidoc code. For example, the type of sample was not stated, making it impossible to determine whether it should be matched to the Medidoc code referring to that of a urine sample, a blood product, a faeces sample … and so on. This process resulted in 1 769 entries matched to a Medidoc code, accounting for 72% of all entries referring to 105 661 393 tests (86% of those initially retained). The entries that were excluded accounted for about 6 million tests in the original database (1994 to 2021). This process is visualised in the first half of Figure 1.

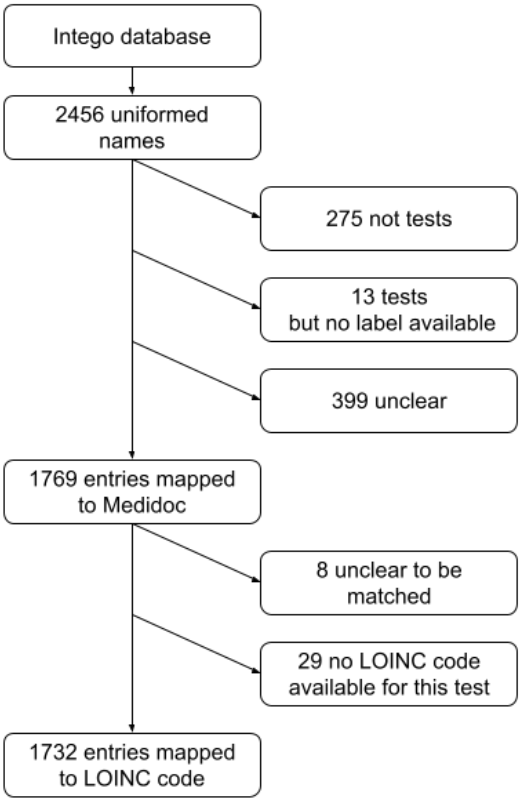


Figure 1: Flow diagram for laboratory test identification and inclusion.

Although this mapping to the Medidoc system helped the analysis, there were still important limitations. For example, when determining renal function, a laboratory would typically report creatinine, estimated glomerular filtration rate using MDRD and/or CKD-EPI, and sometimes urea. Using the Medidoc system, this results in counting up to 4 tests. We found a way to group these tests using the Logical Observation Identifiers Names and Codes (LOINC) system, which is an international project creating a database to uniformly identify clinical information,

including but not only laboratory tests.(33) Mapping each Medidoc code to a LOINC code provides in benefitting from the existing grouping in this database. The example of renal function is illustrated in Table 1.

Laboratory test	Medidoc	LOINC			
		Code	Group	Subgroup 1	Subgroup 2
Creatinine (serum/plasma) [mg/dL]	57139A.B	2160-0	Chemistry	Preferred unit	Renal function
Estimated glomerular filtration rate - MDRD	57710A.D	77147-7			
Estimated glomerular filtration rate - CKD-EPI	57710F.D	62238-1			
Urea (serum/plasma) [mg/dL]	13513A.B	3091-6			

Table 1: Illustration of the grouping of tests.

Part of the mapping of the Medidoc codes to LOINC codes was done automatically using existing databases linking the two systems, like ReTaM.(31) The remaining Medidoc codes were matched manually using the search engine provided on the LOINC website.(33) Again, this expert based manual coding was done and reviewed by two researchers and reviewed by a third. Of all Medidoc codes, 8 were unclear to be matched correctly, and 37 referred to a test for which no LOINC code is available. This resulted in 1732 entries correctly linked to a LOINC code, which identifies 105 411 449 tests or 85% of the originally retained tests. This process is visualised in the second half of Figure 1.

Due to technical and practical reasons, we were not able to use the LOINC grouping we just described for this study. We did however manually group the tests for complete blood count (CBC), because of their high volume if all different tests would be counted separately (~ 38% of all test records). Furthermore, these tests are rarely ordered individually to begin with. To complete this grouping, 61 Medidoc codes were selected, which can be found in Supplementary Table 1. If one or more of these codes were asked for a patient, they counted for one CBC test. Ungrouped these tests accounted for ~ 52.4 million tests. After grouping this number went down to ~ 3.8 million tests with on average 14 Medidoc codes for each CBC test.

For all other tests, the labelling to Medidoc codes, as mentioned earlier, was used. The test records were deduplicated based on only keeping distinct Medidoc codes for the same patient on the same date. For the analysed period 2002 until 2021, the number of test records went down from ~ 149 million to ~ 139 million. For the analysis of specific tests, we selected 25

Medidoc codes based on the 22 tests picked by O'Sullivan, two more based on their specific diagnostic use and finally the Sars-CoV-2 PCR test was added because of its unique position as new and important test.(3,34) The selected tests are available in Supplementary Table 2. If more than one Medidoc code was available, we chose the most used one. Finally, we defined a test order as all tests for one patient on one date.

Data preparation

After this data cleaning, the necessary tables were extracted from the Intego database. Based on our study objectives, we requested the following tables.

Firstly, a table with the number of patients that visited the GP for every year, which is defined as the Yearly Contact Group (YCG) in Intego; the number of patients that got a laboratory test that year; the number of orders of laboratory tests they got that year, an order as defined earlier; and finally, the number of tests they got that year, accumulated for the whole year. This data was collected for each year from 2002 until 2021 and was stratified by sex and eight age groups (0 to 4, 5 to 14, 15 to 24, 25 to 44, 45 to 64, 65 to 74, 75 to 84, 85 and older).

Secondly, a table with the number of patients for each year that got a specific number of tests in either one or more than one laboratory order. For those receiving more than one order, the total number of tests for that year was used. Between one and ten, patient numbers were reported for all ten intervals. Starting from 11 up to 50, the intervals were broadened to 5 tests. Then, for those receiving 51 to 80 test per year, numbers were given per interval of 10 tests. Finally, the number of patients receiving 81 to 100 and more than 100 tests were stated.

Lastly, a table with the top 1000 most ordered tests for each year, giving the number of patients that got that specific test for each year.

Statistical analysis

For each year we calculated the proportion of patients that got tested. Then we calculated for each patient that got a test: the average number of orders, the average number of tests per order, and the average number of tests. We did this for all patients each year, and subsequently for each age group, and for each sex.

Next, for each number of patients that got a specific number of tests per year in either one or more than one laboratory order, we calculated the percentage that these patients contributed

to the total in each subgroup (one vs. more than one order) for each year. Since the intervals for the specific number of tests changes, we corrected for the range of their interval. This renders an average percentage for each number of tests within that range.

As a control to the earlier analysis of orders per patient, we will compare the proportions of patients who got either one or more than one order, regardless of the number of tests.

Further, we explored the table of 1000 most ordered test and identified the top 15 most ordered tests for each year. Subsequently we evaluated their rank order in each year. Next, using the specific tests we selected in advance, see earlier, we made an overview of what percentage they contribute to the total number of tests for each year.

For all analyses, we couldn't make assumptions on their distribution since the analyses were based on aggregated data. Therefore, no statistical testing can be done to identify group difference. Likewise, regression analysis is not feasible either. Moreover, the application of regression on a cohort study without a fixed study population needs to be done with the necessary corrections, since this data is not the result of a longitudinal study. During the calculations, when proportions were higher than one, they were adjusted to one and properly signalled. This problem is addressed further in the discussion. All analyses were conducted with Microsoft Excel.

Patient and public involvement

We did not involve patients nor the public in the study design or in conducting the study.

RESULTS

Exploration of overall test use

In total, 90 121 176 test were ordered for all patients from 2002 until 2021. Table 2 summarises the calculated parameters for each year. When plotted on a scatterplot (Figure 2), the proportion of tests showed a marked difference before and after 2015, with four proportions greater than one leading up to what suggests a sudden drop. Looking back at the original data, we saw that this was due to an important increase in the number of patients in the YCG, in comparison to a rather moderate growth in the number of patients that got tested. This original data is illustrated in Supplementary Table and Figure 3.

Year	Proportion tested	Orders per patient**	Tests per order**	Tests per patient**
2002	0.79	1.94	11.99	23.24
2003	0.73	1.99	12.57	25.02
2004	0.81	2.03	13.08	26.57
2005	0.81	2.04	13.31	27.11
2006	0.82	2.07	13.52	27.97
2007	0.88	2.10	13.78	28.93
2008	0.91	2.17	14.14	30.63
2009	0.92	2.21	14.42	31.87
2010	0.96	2.27	14.71	33.44
2011	0.93	2.29	14.52	33.26
2012	1*	2.30	14.42	33.11
2013	1*	2.26	14.85	33.50
2014	1*	2.27	15.38	34.91
2015	1*	2.29	15.82	36.26
2016	0.71	2.28	16.40	37.45
2017	0.70	2.25	16.79	37.77
2018	0.47	2.32	17.05	39.57
2019	0.48	2.33	17.19	40.00
2020	0.57	2.37	14.15	33.50
2021	0.61	2.52	12.91	32.56

Table 2: The calculated parameters for each year for the total op patients. The 1* signifies proportions that, when calculated, were above 1. They were adjusted to 1. ** These parameters are the average based on the aggregated data.

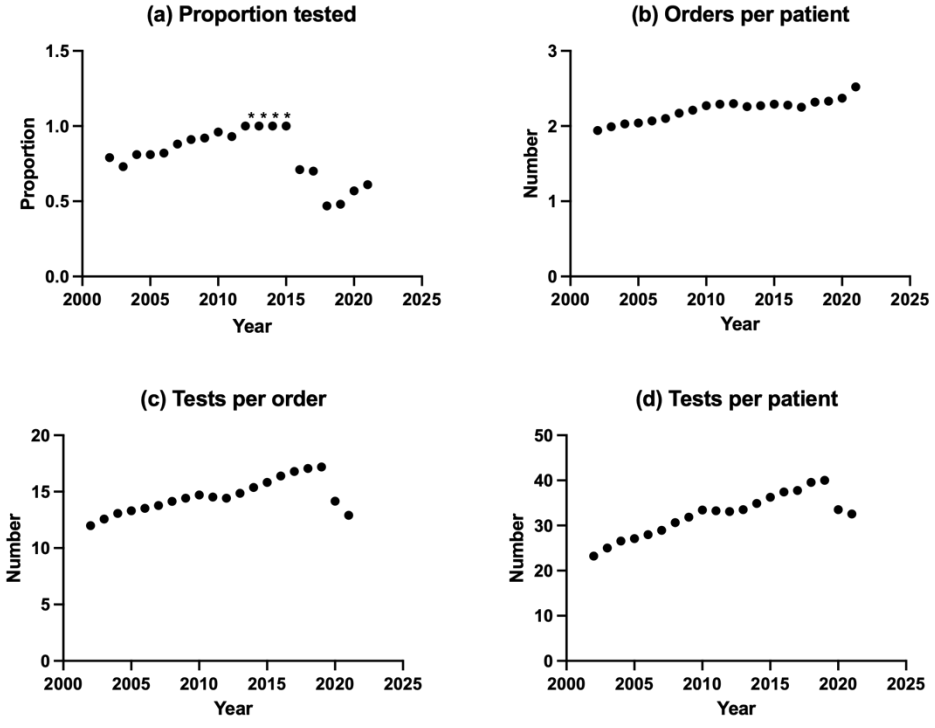


Figure 2: Scatterplots of the parameters mentioned in Table 2. The * in graph (a) signifies the proportions that, when calculated, were above 1. They were adjusted to 1.

Furthermore, the average number of orders per patient seemed to be increasing each year. Both tests per order and tests per patient appeared to be increasing as well but were suddenly and remarkably lower in the last two years of the study.

Exploration of test use by age group

When we calculated the same parameters stratified by age group, data showed that for each year proportions were the highest for age group 65 to 74 years old and those adjacent. For each year, the two lowest age groups had the lowest proportion of tests. Across the years, the proportion seemed to rise for alle age groups up until 2015. Of course, the same lower proportions were shown here after this date, as was evident for overall test use in Table 2 and Figure 2 (a). A summary comparing 2002, 2011 and 2021 is shown in Figure 3 (a).

Compared to the proportion tested, the average number of orders per patient was distributed differently across the age groups. As of 2004, the oldest age group had the highest average number of orders. In 2002 and 2003, the one but oldest age group had the highest number. For all years, the overall trend suggested more orders for higher age groups; except for the youngest age group, that had a higher number compared to the second age group in all years, but not in 2021. The seeming increase across the years as was shown for all ages in Table 2 and Figure 2 (b) is repeated in all age groups, except less apparent or even a decrease in the later years for the three oldest age groups. A summary comparing 2002, 2011 and 2021 is shown in Figure 3 (b).

For the average number of tests per order, the distribution across the age groups was more comparable to that of the proportion tested. Up until 2018, the highest number was reported in the age group 45 to 64 years old. In 2019 and 2020, this was shifted to those 65 to 74 years old and in 2021 even to the 75 to 84 years old. The lowest number was noted in the youngest age group in all years, except for the last two years, where the second age group had a lower number. There was a noteworthy lower number of tests per order for the last two years in all age groups, more noticeable in the younger once and more discrete in the older ones. The apparent drop in overall number of tests per order, as was shown in Table 2 and Figure 3 (c) was thus mostly due to changes in the younger patients in those years. A summary comparing 2002, 2011 and 2021 is shown in Figure 3 (c).

When analysing the distribution across the age groups for the number of tests per patient, we saw for all years that people of older age seemed to have received more tests. Exceptions were the two oldest age groups, where the difference was less apparent, and the last two years of the analysis, where the second age group was each time lower compared to the youngest age group. The apparent drop shown in Table 2 and Figure 3 (d) was noticeable in all age groups, but much more evident in the younger once compared to the older ones. A summary comparing 2002, 2011 and 2021 is shown in Figure 3 (d).

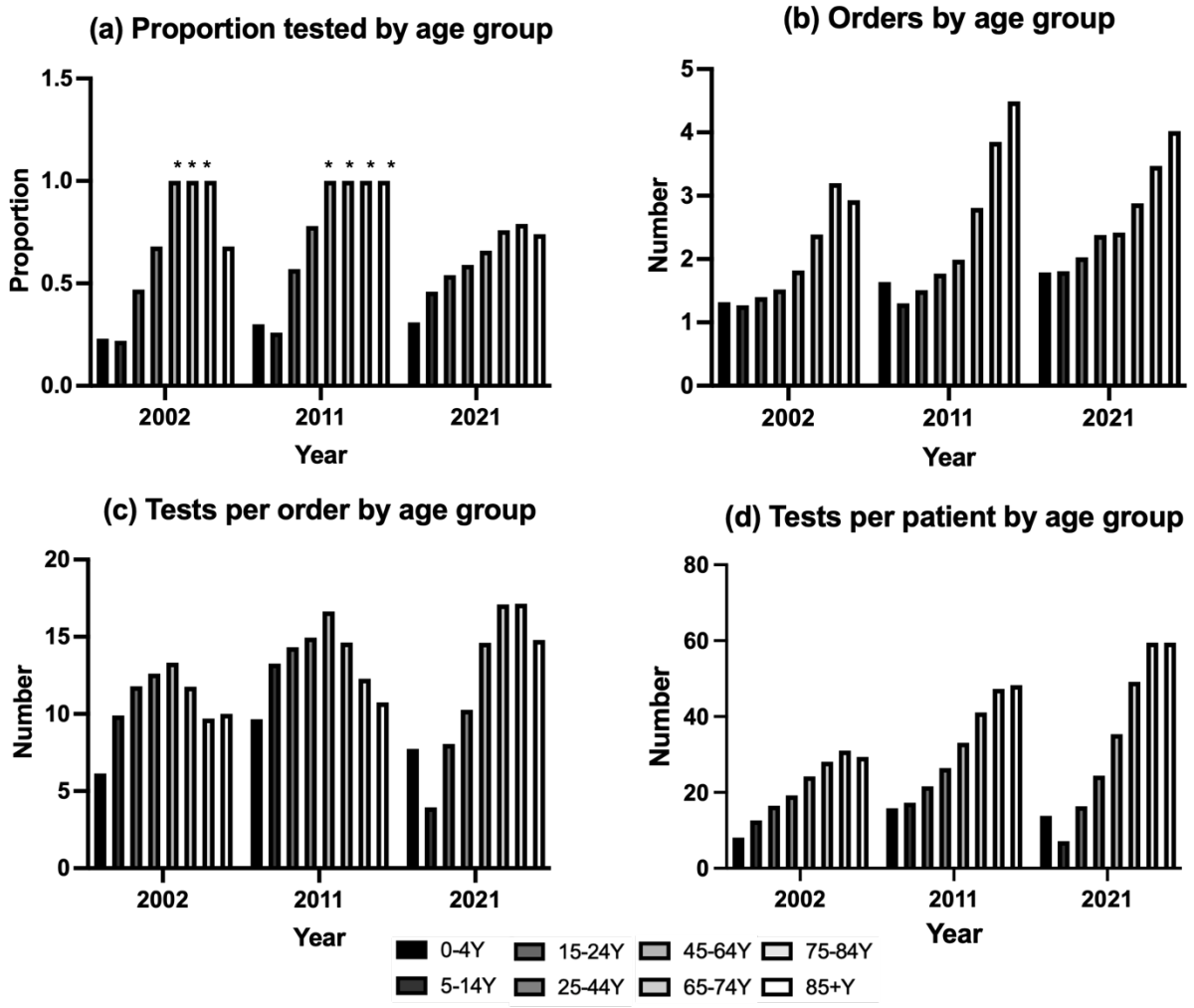


Figure 3: Summary of the analysed parameters for the years 2002, 2011, 2021. The * in graph (a) signifies the proportions that, when calculated, were above 1. They were adjusted to 1.

Exploration of test use by sex

Next, we analysed the same parameters stratified by sex. The proportion of patients tested was almost always higher in female patients compared to male patients, though it is not certain if this is a significant difference. This finding was consistent before and after the apparent drop in 2015 described earlier (Table 2, Figure 2 (a)). Furthermore, the number of orders, the average number of tests per order, and average number of tests per patient showed no major differences between the sexes The presumed drop in the last two years in these lats two parameters, as discussed earlier (Table 2, Figure 2 (c)), was as remarkable in male as in female patients. These findings are illustrated by the graphs in Figure 4.

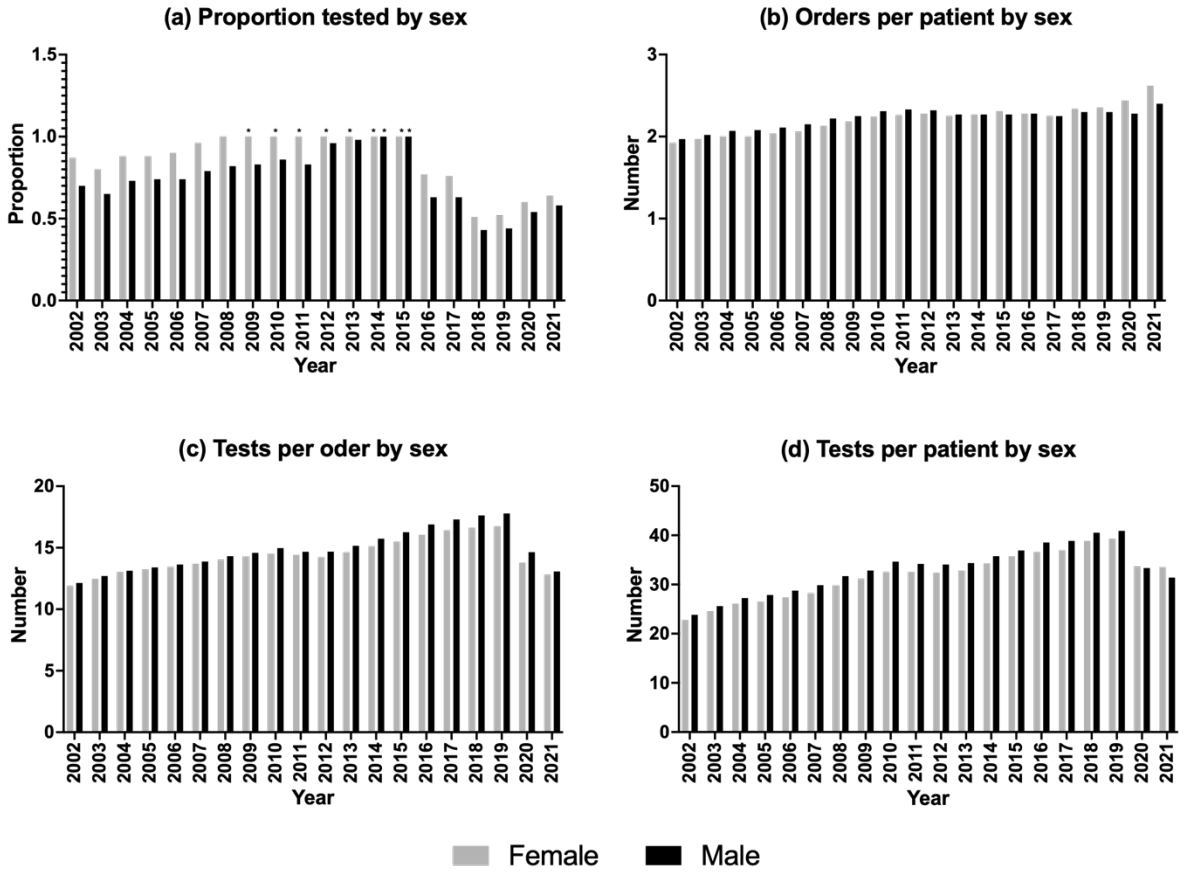


Figure 4: Graphs of the analysed parameters for all years in timeframe. The * in graph (a) signifies the proportions that, when calculated, were above 1. They were adjusted to 1.

Exploration of distribution of patients by order number and by test number

Comparing the percentages of patients that got a certain number of tests in either one or more than one order showed some important differences. The results of 2002, 2011, and 2021 are visualised in Figure 5.

In the subgroup of patients receiving one order, patients seemed to be distributed around two peaks. These being one test and, depending which year, 16 to 20 or 21 to 25 tests. Comparing the different years with each other, the data suggested a shift towards more tests per one order. For the last two years, however, those with one test were greatly outnumbering the others.

Looking at the patients with one order and up to 10 tests, we saw a slightly higher number of patients receiving only one test, with lowering percentages for increasing test numbers up to 10. Exceptions were the years 2017 to 2019, where those receiving 2 tests slightly outnumber those with one test.

For the subgroup receiving more than one order, patients were centred around one value alone which also seemed to increase over the years. Patients seemed more evenly distributed around this centre, nevertheless an important increase in the number of patients receiving 81 to 100 tests a year was suggested in this data. However, the last two years showed great exceptions to this finding. Comparable to the other subgroup, the years 2020 and 2021 showed a marked increase of those receiving 2 tests outnumbering those in the earlier described centre. Of course, there were no patients receiving one test in this subgroup as by definition they got at least 2 tests.

As a control to the analysis of proportion earlier (Figure 2 (a)), we compared the total number of patients that got one order that year compared to those identified with more than one order that year, regardless the number of tests they got. We saw an apparent increase of the number in the second group over the years. This is visualised in Figure 6.

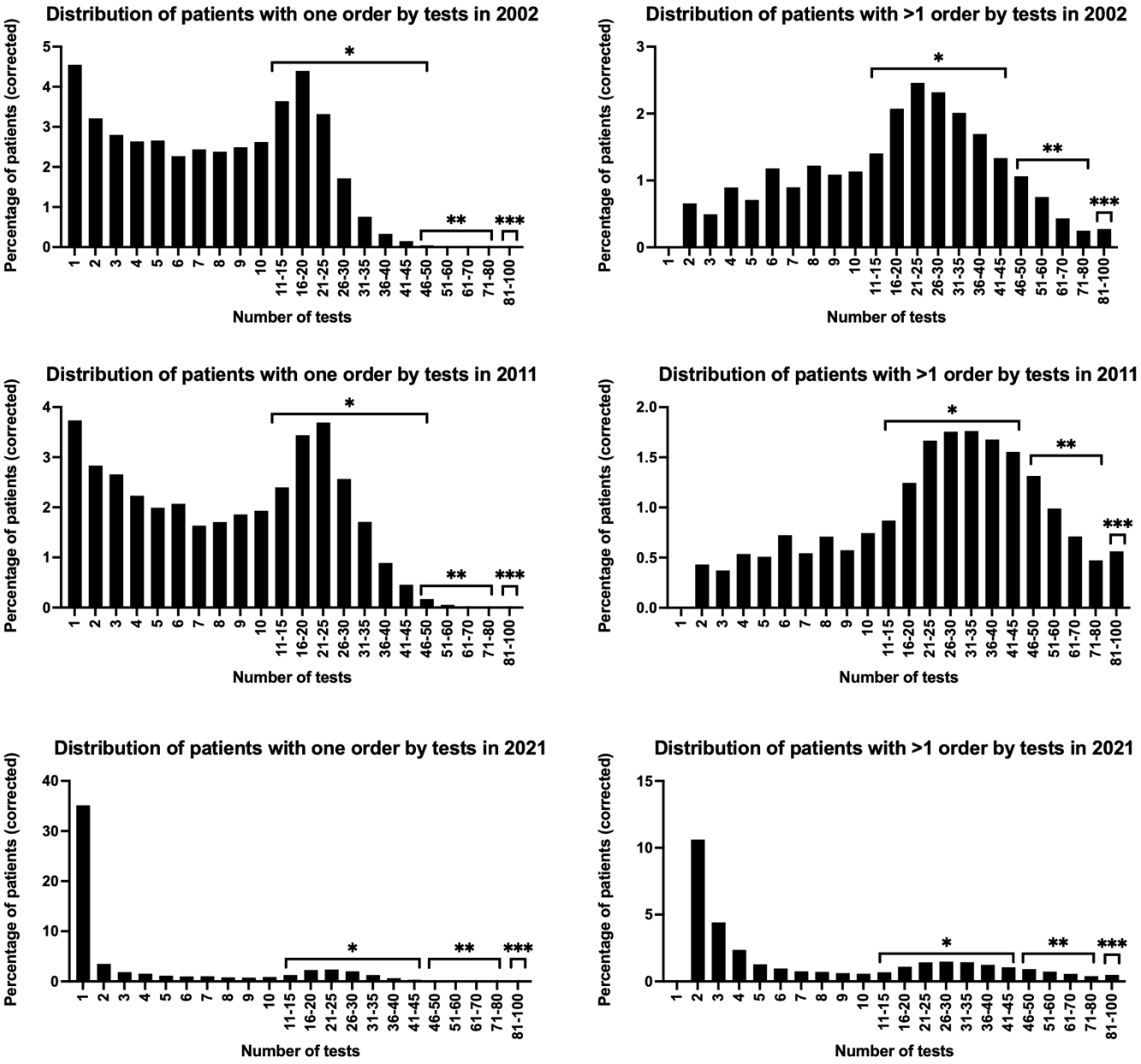


Figure 5: For each number of tests the corrected percentage of patients is given. For the intervals with more tests, the correction renders an average for each number of tests within the interval. * For the intervals of 5 tests, the overall percentage was divided by 5. ** For the intervals of 10 tests, the overall percentage was divided by 10. *** For the interval of 20 tests, the overall percentage was divided by 20.

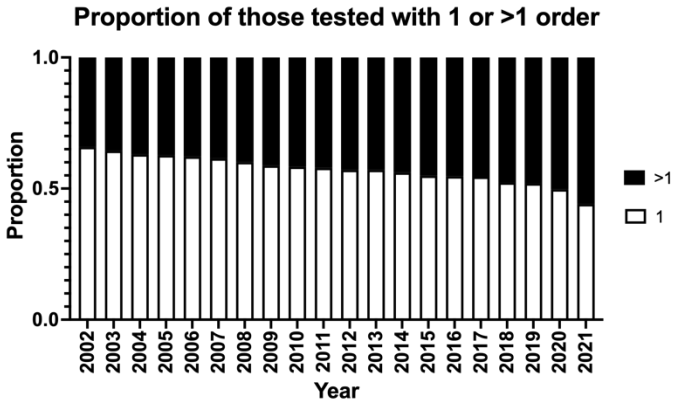


Figure 6: Of each year in the dataset, the proportion of those receiving 1 or >1 order that year is given.

Exploration of most common test use

Evaluating the ranking numbers of the selected tests, we saw some interesting changes over the years. All ranking numbers and their percentage of all tests for each year is provided in Supplementary Table 4, along with the Medidoc codes used for the analysis.

First, we noted the downfall of the erythrocyte sedimentation rate (ESR) from 3 in 2002 to 13 in 2020 and 2021. Being a parameter for inflammation, we compared this with another such parameter: C reactive protein (CRP). This test followed a marked increase in ranking over the years, only 15th in 2002, but becoming 4th in 2021.

The top two remained unchanged during the entire study period. On the first place was complete blood count (CBC), the only grouped test in this study. Creatinine came in second every year. When we looked at its derived parameters we saw the introduction, rise and stagnation of the MDRD version of eGFR starting in 2005. The CKD-EPI version of eGFR, although only introduced in 2011, overtook its counterpart to become top 12 in 2021. Urea and uric acid, also linked to renal function, showed no apparent change in ranking.

Furthermore, we remarked the decrease of total cholesterol, HDL cholesterol, total cholesterol to HDL cholesterol ratio, LDL cholesterol, and triglycerides. Also fasting glucose seemed to get lower rankings over the years. Sodium and potassium stayed close to each other in every rank, without clear rise or fall. Same goes for the liver function tests aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma glutamyl transferase (Gamma YT). Alkaline phosphatase (ALP) on the other hand came in lower every year, but did so more moderately.

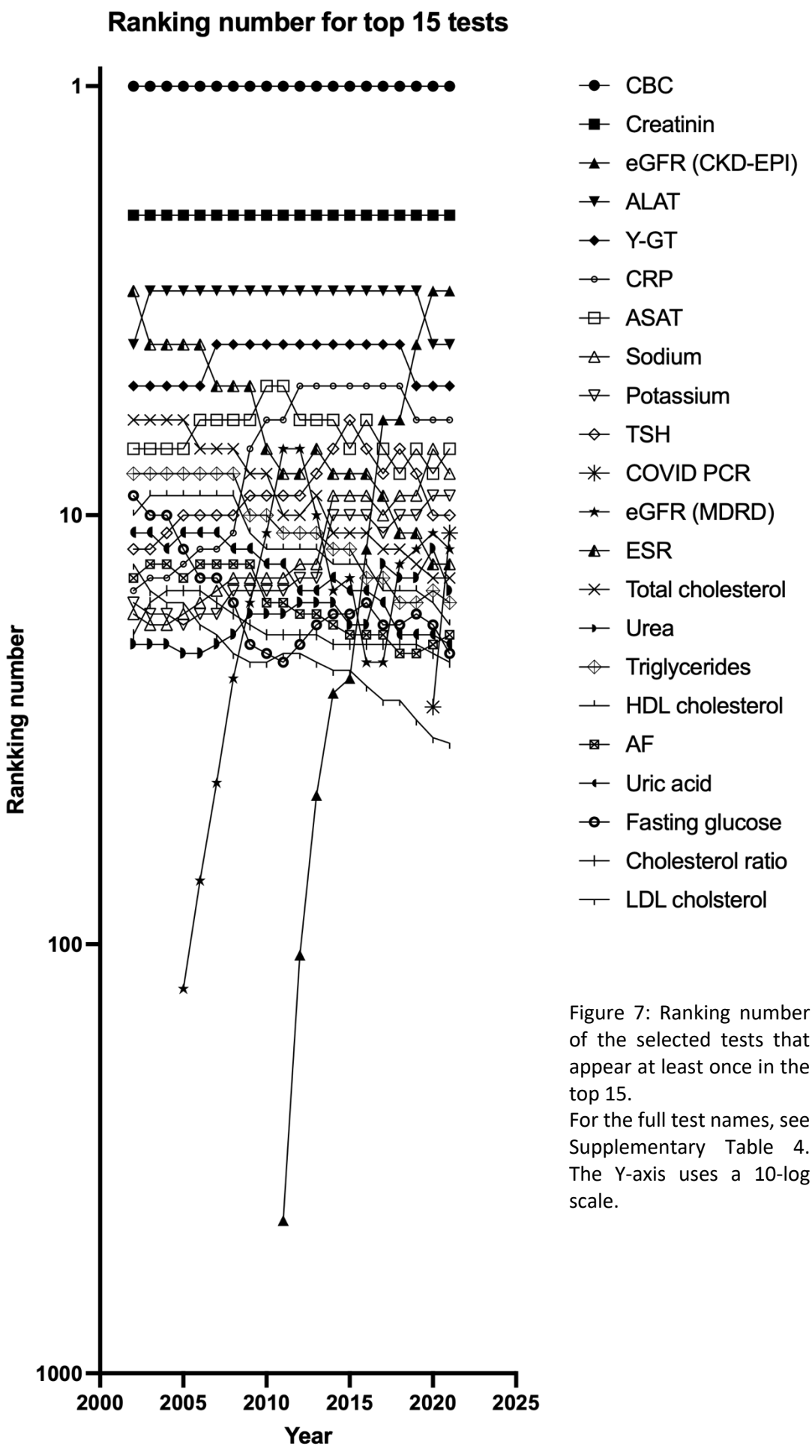


Figure 7: Ranking number of the selected tests that appear at least once in the top 15.
For the full test names, see Supplementary Table 4. The Y-axis uses a 10-log scale.

Finally, in 2020 we saw the introduction at place 28 and subsequent even higher ranking in 2021 of the Sars-CoV-2 RNA sequencing.

Exploration of specific test use

We analysed the percentages of the tests we selected in advance as described in the methods section. We must be very careful to draw conclusions lightly considering the limitations stipulated earlier. For all the selected tests, their percentage of the total number of tests for that year is given in Supplementary Table 5.

However, it was noticeable that Vitamin D was more used over the years, with initially percentages of 0.01%, to finally 1.22%. Likewise, Troponine T accounted for little more than 0% in 2002, but already 0.08% in 2021. Another noteworthy test was D-dimer, with a percentage of 0.02 in 2002, but 0.14 in 2021. On the contrary, fibrinogen seemed to be less used, where it contributed around 0.13% in the beginning of the time frame, it is limited to 0.04% in 2021.

DISCUSSION

We analysed the use of laboratory tests in Belgium for each year. Our data suggested, but did not statistically prove, a rise in the proportion of patients that got a laboratory test. Furthermore, our data hinted at a rise in the number of orders that a patient gets each year, as both the average number of orders per patient per year seemed to rise, and the proportion of patients that got only one order looked like it's decreasing. On average, the number of laboratory tests per order seemed to be increasing. As did the number of laboratory tests per patient. This data is in line with the earlier findings in Belgium, the recent investigation in the United Kingdom, and established international results.(3,4,7)

Given the current financial pressure on the healthcare system to which this apparent rise in laboratory test contributes, our findings may aid regulating organs and policy makers in making informed decisions. It should be noted that this financial burden is not only a direct result from each ordered test, but also from the consequences of these tests. As more testing, especially inappropriate "over testing" leads to even more tests, interventions, and therapies.(8–10) As to why these numbers are rising, a lot of explanations are possible, both patient and doctor centred.(3,16–18,35,36)

When analysing these parameters stratified by age group, we saw that all four of them seemed to be correlated with age, though not all distributions for each parameter were alike. Combing these findings suggests that the middle age groups were most likely to get a test. However, when patients got tested, those in the oldest age groups still got the most tests overall. While both younger and older age groups tended to have less tests per order, the younger had less tests in those fewer orders, resulting in less tests overall. In contrast, the older age groups compensated the smaller number of tests per order with more frequent orders, thus resulting in more tests overall per patient.

The most likely explanation for these findings is that age is linked to morbidity, resulting in a higher need for laboratory tests. These are necessary for diagnosis in the first place, but also the follow up care is likely to contribute to the described figures. Especially chronic illnesses, like diabetes, chronic kidney disease and hypertension, call for regular blood tests, though less tests per order may suffice. Moreover, the use of chronic medication and residency in nursing homes, which are more common in elderly people, have been linked to higher test use.(4)

The data showed no remarkable difference based on sex. Only the proportion was systematically higher in the female patient population. This could be of no statistical significance. However, if it was, this may be explained by more laboratory tests linked to female health. Pre-conception bloodwork, follow up during pregnancy, menstruation linked iron deficiency anaemia, female sex hormone surveillance, perimenopausal tests … can all effectively contribute to these higher proportions of tested patients.

When we looked at the number of patients per specific number of tests, we must note that the most useful data could be found analysing only those receiving one order. This is because for those patients receiving more than one order, no data was available about their distribution over these different orders. For those receiving one order, we saw a division between on the one hand those leaning towards one and on the other hand those centred around 16 to 25 tests. Over the years, there was a suggestion of more patients getting more tests. When we explored the second part of the data, being the patients receiving more than one order, we still recognised the rise in patients receiving more tests over the years. It is important to keep in mind that we’re looking at pooled data for all orders here. Both groups thus confirmed the earlier described findings.

An important exception was the extreme high percentage of patients that got one test in the years 2020 and 2021 in the group receiving one order. This extreme rise in use of one test in one order was most likely the effect of the use of PCR sequencing of Sars-CoV-19. This test was introduced in 2020 and once its availability was upscaled in Belgium, requesting the test was compulsory for all symptomatic patients and intermittently even for all high-risk contacts of Covid-19 patients.(34) Furthermore, the test was offered in testing centres without the need of an actual medical doctor prescribing it. Likewise, a higher number of patients receiving a low number of tests (2 to 10) in 2020 and 2021 was evident in the second group receiving multiple orders. This probably reflects the same mechanism.

Moreover, these findings are likely to be illustrated by the marked drop in the number of tests per order or per patient for the last two years in the data set. Indeed, this drop could be explained by a sudden increase in the use of a test that is typically ordered alone, consequently suggesting the impact of the use of PCR sequencing of Sars-CoV-19 on our dataset.

When we calculated the proportion of patients tested, we got a proportion greater than 1 for some stratifications ranging from 2002 to 2017, combined with a marked drop in proportion size after 2015. Stratified by age groups, this was more common in the middle to higher age groups, from 2002 to 2017. Stratified by sex, this appeared more in the female patient group (2009 to 2015 vs. 2014 to 2015). This anomaly is due to mismatching between both databases of the YCG and the laboratory tests, which should be targeted in the Intego team for future research. Furthermore, the YCG was calculated in the older Intego database using only patients who had a diagnosis recorded in the visit. After 2018 however, all patients who have contacted the GPs contributed to the YCG, regardless of the recording of a diagnosis. This makes comparing these proportions before and after 2018 difficult. Correcting for these distortions will be of great importance for upcoming analyses of the Intego data.

We were able to deduct some interesting findings evaluating the ranking of the most used test. However, we must be very cautious when drawing conclusions. Most of all because this analysis did only look at the first Medidoc code for each kind of test, thus not correcting for the fact that some tests have multiple codes or changing codes over the years and should in fact be combined. This might explain why CBC, the only combined test in the analysis, was the most used test for all years in the study. All the while metabolic parameters, such as cholesterol, seemed to decline, even though their use is well integrated in evidence based

medical practice up to this day. After grouping the codes referring to laboratory tests, these results may differ greatly. This goes in fact for all parts of our analysis. The methods we described using the LOINC system seem promising for this effect. Secondly, no data was available to correct ranking for age and sex. Still, the apparition of PCR sequencing of Sars-CoV-19 that is proposed as an explanation of the earlier findings is very clear.

The same limitations go for the results of the last part, detailing the percentages of specific tests. However, the apparent rise in use of vitamin D shown in our data confirms international findings, although the use and value of this test is still ambiguous.(3,8,11–15) Considering these findings, it would be interesting to assess the appropriateness of the used tests, as efforts arise to increase this factor.(37)

Given that no recent study had analysed this kind of data for Belgium, we can say that our research adds to the knowledge on laboratory test use throughout the years. Using the Intego data, we examined a representative population for Flanders. Upcoming research should aim at including data from the entire country, for example using the data from the agency of the seven health insurance funds in Belgium (Intermutualistisch Agentschap, IMA). As laboratories nationwide report to this agency which tests have been executed to get refunding settled with patients, the use of their data has powerful potential.

For future analysis, more detailed statistical tests should be conducted. For example, group comparison using a Z-test may confirm the findings in our analysis. Additionally, a Poisson regression could be fitted to model the expected number of tests. Alternatively, JoinPoint regression could be used, as was done by O'Sullivan for the UK analysis.(3) Jointpoint regression identifies the locations of significant changes in slope while correcting for age and gender. Furthermore, it calculates the annual percentage change, making comparison between years evident. However, for valid use of these kind of statistical tests, more detailed data is necessary. For example, the sample size and the distribution of the number of tests within each group. Also, as always correlation and causality must not be confused, and thorough research of the findings remains fundamental.

Finally, it would be beneficial to analyse the characteristics of the physicians ordering the tests, thus broadening the scope of this kind of research, as physician characteristics have been linked to appropriateness of test use.(18,20) Identifying the differences in laboratory test use between different kind of physicians may help guideline development and policy

makers. For example, analysing the typical laboratory test panels ordered by a GP or by a specialist doctor, may identify test use characteristics useful for targeted information campaigns promoting appropriate test use, such as Choosing Wisely in the UK.(38)

FINAL STATEMENTS

Contributors

Maxim Hellyn, Nicolas Delvaux, and Jonas Crèvecoeur designed the study. Maxim Hellyn, Nicolas Delvaux and Ahmed Zayed did the data clean up. Ahmed Zayed provided the data tables. Jonas Crèvecoeur, Pavlos Mamouris, and Febe Brackx provided statistical expertise. Maxim Hellyn analysed the data and wrote the manuscript.

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Competing interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/ disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Ethical approval for this study was granted by the ethical review board of the Medical School of the Catholic University of Leuven (file number MP018029).

Data access

Jonas Crèvecoeur, Nicolas Delvaux, Pavlos Mamouris, and Ahmed Zayed had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data clean up. Maxim Hellyn had access to the necessary, anonymous files to complete the labeling and the data clean up; and to the provided data tables based on the original database.

Data sharing

Besides the provided supplementary data hereafter, there is no additional data available.

Transparency

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPLEMENTARY DATA

Hereafter the following supplementary data is added:

- STROBE-statement
- Ethical approval
- Supplementary tables and figures

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	7
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	7
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	9
Objectives	#3	State specific objectives, including any prespecified hypotheses	10
Methods			

Study design	#4	Present key elements of study design early in the paper	11
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	12
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	11
Bias	#9	Describe any efforts to address potential sources of bias	12
Study size	#10	Explain how the study size was arrived at	14
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	14
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
15			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	15
Statistical methods	#12c	Explain how missing data were addressed	15
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical	#12e	Describe any sensitivity analyses	

methods			
n/a			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	13
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	
13			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	n/a
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
13			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
n/a			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
16			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
Main results	#16b	Report category boundaries when continuous variables were categorized	15

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	22
Discussion			
Key results	#18	Summarise key results with reference to study objectives	25
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	27
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	25
Generalisability	#21	Discuss the generalisability (external validity) of the study results	27
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

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Analyse van het gebruik van laboratoriumonderzoeken in België.

Dossiernr.:	MP018029
Masterproef:	Masterproef I HAIO, 2019-2022
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2020-2021
Korte omschrijving / abstract:	**Importance**: Timely and accurate information on laboratory test use in primary care is important to identify trends. Insights may inform interventions supporting appropriate use of laboratory tests which may optimize healthcare quality and resource utilization. **Objective**: Since the KCE study for the period 1995-2005, no more recent study has analysed laboratory test use in Belgium in primary care. Therefore, this study aims to gain information about the use of these tests in the last decade. **Design**: This observational retrospective cohort study investigates the use of laboratory tests by physicians in Belgium. Data from the last 15 years is collected from the Intego network. Via joinpoint regression analysis trends in laboratory use is determined. **Setting**: The Intego network is a network of primary care physicians in Flanders, the Dutch speaking part of Belgium. **Participants**: All patients presenting in primary care.
Toegepaste technieken:	Statistische analyse van database

Key publication:	1. de Sutter A, Van den Bruel A, Devriese S, Mambourg F, Van Gaever V, Verstraete A HM, Sutter DA, den Bruel VA, Gaever V v. Laboratoriumtesten in de huisartsgeneeskunde. Good Clinical Practice (GCP) [Internet]. 2007 [cited 2020 Jan 28];KCE report(59A). Available from: http://www.kce.fgov.be 2. O'Sullivan JW, Stevens S, Hobbs FDR, Salisbury C, Little P, Goldacre B, et al. Temporal trends in use of tests in UK primary care, 2000-15: Retrospective analysis of 250 million tests. BMJ (Online). 2018;363. 3. Delvaux N, Sutter A de, Velde S van de, Ramaekers D, Fieuws S, Aertgeerts B. Electronic Laboratory Medicine ordering with evidence-based Order sets in primary care (ELMO study): protocol for a cluster randomised trial. 2017;1–8. 4. Delvaux N, Piessens V, Burghgraeve T de, Mamouris P, Vaes B, Stichele R vander, et al. Clinical decision support improves the appropriateness of laboratory test ordering in primary care without increasing diagnostic error: the ELMO cluster randomized trial. Implementation Science [Internet]. 2020 Dec 1;15(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33148311/ 5. Hickner J, Thompson PJ, Wilkinson T, Epner P, Sheehan M, Pollock AM, et al. Primary care physicians' challenges in ordering clinical laboratory tests and interpreting results. Journal of the American Board of Family Medicine. 2014 Mar;27(2):268–74. 6. O'Sullivan JW, Albasri A, Nicholson BD, Perera R, Aronson JK, Roberts N, et al. Overtesting and undertesting in primary care: A systematic review and meta-analysis. BMJ Open. 2018 Feb 1;8(2). 7. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The landscape of inappropriate laboratory testing: A 15-year meta-analysis. PLoS ONE [Internet]. 2013 Nov 15;8(11). Available from: https://pubmed.ncbi.nlm.nih.gov/24260139/ 8. Chami N, Simons JE, Sweetman A, Don-Wauchope AC. Rates of inappropriate laboratory test utilization in Ontario. Clinical Biochemistry [Internet]. 2017;50(15):822–7. Available from: http://dx.doi.org/10.1016/j.clinbiochem.2017.05.004 9. Mrazek C, Simundic AM, Salinas M, von Meyer A, Cornes M, Bauçà JM, et al. Inappropriate use of laboratory tests: How availability triggers demand – Examples across Europe. Clinica Chimica Acta [Internet]. 2020 Jun 1;505:100–7. Available from: https://pubmed.ncbi.nlm.nih.gov/32084382/ 10. Duddy C, Wong G. Efficiency over thoroughness in laboratory testing decision making in primary care: findings from a realist review. BJGP Open. 2020;bjgpopen20X101146. 11. Ganguli I, Simpkin AL, Lupo C, Weissman A, Mainor AJ, Orav EJ, et al. Cascades of Care after Incidental Findings in a US National Survey of Physicians. JAMA Network Open [Internet]. 2019 Oct 16 [cited 2021 May 10];2(10). Available from: https://pubmed.ncbi.nlm.nih.gov/31617925/ 12. Deyo RA. Cascade Effects of Medical Technology. Annu Rev Public Health [Internet]. 2002;23:23–44. Available from: www.annualreviews.org 13. Mold JW, Stein HF. The Cascade Effect in the Clinical Care of Patients. New England Journal of Medicine [Internet]. 1986 Feb 20;314(8):512–4. Available from: https://pubmed.ncbi.nlm.nih.gov/3945278/ 14. Brodersen J, Schwartz LM, Heneghan C, O'Sullivan JW, Aronson JK, Woloshin S. Overdiagnosis: what it is and what it isn't [Internet]. Vol. 23, BMJ evidence-based medicine. NLM (Medline); 2018. p. 1–3. Available from: http://ebm.bmj.com/ 15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Vol. 147, Annals of Internal Medicine. American College of Physicians; 2007. p. 573–7.
Trefwoorden:	diagnostic tests laboratoriumonderzoek diagnostische tests eerstelijnsgeneeskunde primary care laboratory tests
Gewenste taal van communicatie:	nl
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De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef integraal deel uitmaakt van een studie die reeds werd goedgekeurd door een erkend ethisch comité.

U hoeft bijgevolg geen nieuw dossier in te dienen in het kader van uw masterproef. Wel dient u het UZ/KU Leuven toe te voegen als nieuw deelnemend centrum aan het huidige dossier indien dit nog niet het geval was. Gelieve u bij het betreffende comité te informeren en u te conformeren aan de daar geldende procedures en hun adviezen te volgen.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij de goedkeuring om het onderzoek in het kader van de masterproef te starten.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet elke eerdere goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier bij het comité dat eerder uw dossier goedkeurde.

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Supplementary Table 1: Medidoc codes grouped for complete blood cell count

	Medidoc code	LOINC code (*)	Label (Dutch) (**)	Label (English) (***)	Number of tests (****)
1	13705A.B	718-7	Hemoglobine	Hemoglobin (blood)	3861216
2	13707A.B	789-8	Erythrocyten	Erythrocytes (blood)	3780715
3	13707B.B	787-2	MCV	Mean corpuscular volume (erythrocytes)	3707862
4	13707C.B	788-0	RDW	Erythrocyte distribution width (erythrocytes)	1205854
5	13707D.B	785-6	MCH	Mean corpuscular hemoglobin (erythrocytes)	3692171
6	13707E.B	786-4	MCHC	Mean corpuscular hemoglobin concentration (erythrocytes)	3672877
7	13707F.B		Hematocriet		3721915
8	13707G.B		Kleurindex serum		3
9	13707K.B		Nucleated Red Blood Cells		26
10	13707W_B	11158-3	Uitzicht serum	Appearance of Serum	321501
11	13707X_B	6742-1	RBC morfologie	Erythrocyte morphology finding [Identifier] in Blood	105095
12	13707Y_B		Erythrocyten normochroom		401
13	13707Z_B		Erythrocyten normocytair		32
14	13709A.B	6690-2	Leukocytentelling	Leukocytes (blood) - in #/volume - automated count	3559129
15	13709B.B		Leucoconcentratie		2907
16	13711A.B		Heinz bodies		8
17	13713..B	69738-3	Leukocyten formule	White blood cell differentiation (blood)	20906
18	13713A.B		Staafkernige granulocyten		269822
19	13713B.B		Segmentkernigen		2432543

Supplementary Table 1: Overview of the Medidoc codes used in the group for complete blood cell count. (*) Matching of Medidoc to LOINC where possible. (**) Dutch label based on Medidoc code. (***) English labeling based on LOINC code. (****) Total number of tests labeled with this Medidoc code from 2002 until 2021.

20	13713C.B	26449-9	Eosinofielen	White blood cell differentiation: Eosinophils (blood) - in #/volume	3924898
21	13713D.B	26444-0	Basofielen	White blood cell differentiation: Basophils (blood) - in #/volume	3794209
22	13713E.B	26474-7	Lymfocyten	White blood cell differentiation: Lymphocytes (blood) - in #/volume	3917204
23	13713F.B	26484-6	Monocyten	White blood cell differentiation: Monocytes (blood) - in #/volume	3860441
24	13713H.B		Neutrofielen		1511986
25	13714..B	69738-3	Leukocyten formule (%)	White blood cell differentiation (blood)	14870
26	13714A.B	26508-2	Staafkernigen (%)	White blood cell differentiation: Neutrophils band form (blood) - in %	29656
27	13714B.B	26505-8	Segmentkernigen (%)	White blood cell differentiation: Neutrophils segmented (blood) - in %	1021569
28	13714C.B	26450-7	Eosinofielen (%)	White blood cell differentiation: Eosinophils (blood) - in %	1315419
29	13714D.B	30180-4	Basofielen (%)	White blood cell differentiation: Basophils (blood) - in %	1296169
30	13714E.B	26478-8	Lymfocyten (%)	White blood cell differentiation: Lymphocytes (blood) - in %	1313537
31	13714F.B	26485-3	Monocyten (%)	White blood cell differentiation: Monocytes (blood) - in %	1301282
32	13714H.B	26511-6	Neutrofielen (%)	White blood cell differentiation: Neutrophils (blood) - in %	333138
33	13717A.B	777-3	Trombocyten	Platelets (blood) - automated count	3320874
34	13717B.B		Trombocriet		488
35	13717C.B	28542-9	MPV	Platelet mean volume (blood)	267754
36	13717D.B	51631-0	PDW	Platelet distribution width [Ratio] in Blood	13767
37	13717E.B	11125-2	Morfologie trombocyten	Platelet morphology finding [Identifier] in Blood	16246
38	13717F.B		Bloedplaatjes klein		1293
39	13717G.B		Bloedplaatjes groot		126

Supplementary Table 1: Continued

40	13721A.B	4679-7	Reticulocyten	Reticulocytes (blood) - in %	555378
41	13721C.B	33516-6	Reticulocyten immatuur	Immature reticulocytes (blood) - in %	27373
42	13721D.B		Reticulocyten-hemoglobine concentratie		24003
43	13721E.B		Reticulocyten maturiteit-index		600
44	13721F.B		Reticulocyten (low fractie)		911
45	13721G.B		Reticulocyten (medium fractie)		910
46	13721H.B		Reticulocyten (high fractie)		911
47	63011S.B		Commentaar RBC: anisocytose		18674
48	63011T.B		Commentaar RBC: poikilocytose		4215
49	63011U.B		Commentaar RBC: macrocytose		5228
50	63011V.B		Commentaar RBC: microcytose		2729
51	63011W.B		Commentaar RBC: traancellen		762
52	63011X.B		Commentaar RBC: acanthocytose		363
53	63011Y.B		Commentaar RBC: echinocytose		456
54	63011Z.B		Commentaar RBC: doelcellen		186
55	63012A.B		Commentaar RBC: ovalocytose		1901
56	63012B.B		Commentaar RBC: basofiele stippeling		50
57	63012C.B		Commentaar RBC: hypochromie		2686
58	63012D.B	14196-0	Reticulocyten (absoluut)	Reticulocytes (blood) - in #/volume	188293
59	63012E.B	771-6	Erythroblasten (absoluut)	Erythrocytes nucleated (blood) - in #/volume - automated count	87096
60	63012G.B	26508-2	Neutrofielen niet-gesegmenteerd (relatief)	White blood cell differentiation: Neutrophils band form (blood) – in %	8
61	63012J.B	26462-2	Large Unidentified Cells (absoluut)	White blood cell differentiation: Large unstained cells (blood) - in #/volume	107
				Total:	**58532749**

Supplementary Table 1: Continued.

Supplementary Table 2: Medidoc codes used for the specific test analysis

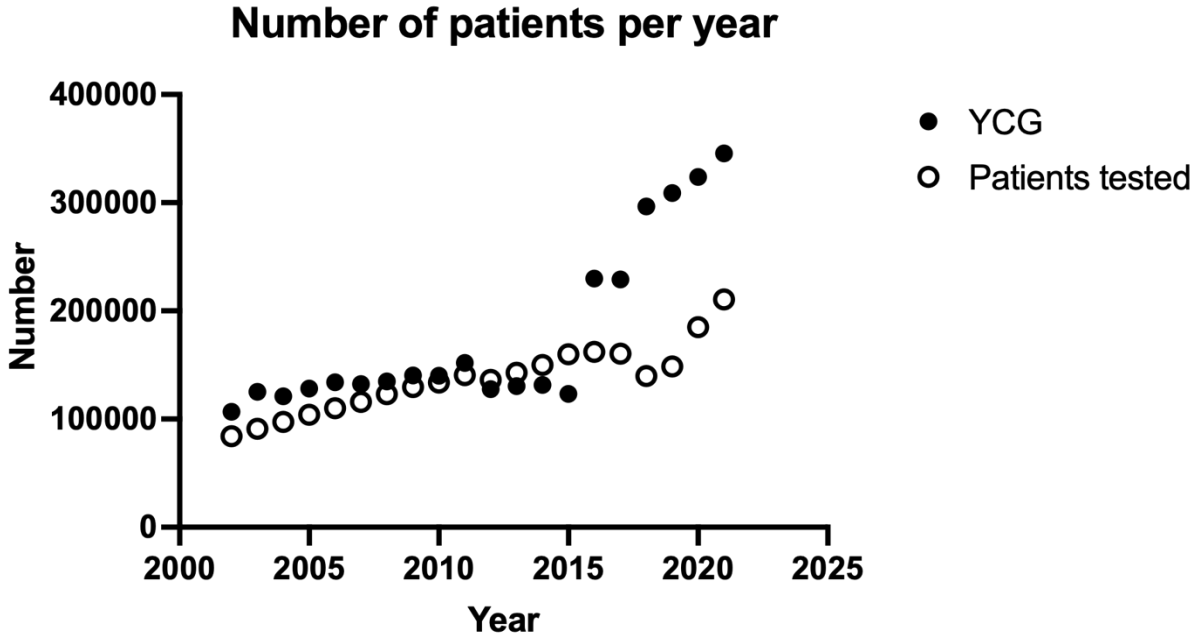
Medidoc code	Laboratory test	Selection criterium
135110.B	Glucose - fasted (serum/plasma)	O'Sullivan
13553A.B	Alanine aminotransferase (serum/plasma) - Liver function	O'Sullivan
13723A.B	Erythrocyte sedimentation rate (blood)	O'Sullivan
15362B.R	SARS-CoV-2 (COVID-19) RNA by Sequencing	Unique introduction
44303A.B	Folate (serum/plasma)	O'Sullivan
44311A.B	Ferritin (serum/plasma)	O'Sullivan
44313A.B	Cobalamins (serum/plasma) - Vitamin B12	O'Sullivan
44396A.B	Prostate specific Ag (serum/plasma)	O'Sullivan
447130.B	Thyroid Stimulating Hormone (serum/plasma)	O'Sullivan
44845A.B	25-hydroxyvitamin D3 (serum/plasma) - Vitamin D	O'Sullivan
44861A.B	Estradiol (serum/plasma)	O'Sullivan
44867A.B	Progesterone (serum/plasma)	O'Sullivan
44933A.B	Testosteron (serum/plasma)	O'Sullivan
57131A.B	Cholesterol (serum/plasma)	O'Sullivan
57139A.B	Creatinine (serum/plasma)	O'Sullivan
57163A.B	Iron (serum/plasma)	O'Sullivan
57183A.B	Hemoglobin A1c (blood)	O'Sullivan
57217I.B	C reactive protein (serum/plasma)	O'Sullivan
57259A.B	Creatine kinase (serum/plasma)	O'Sullivan
57273A.B	Lipase (serum/plasma)	Diagnostic relevance
57277A.B	Gamma glutamyl transferase (serum/plasma) - Liver function	O'Sullivan
58148A.B	D-dimer (platelet poor plasma)	Diagnostic relevance
58165A.B	Fibrinogen (blood)	O'Sullivan
63102C.B	Troponin T (serum/plasma)	O'Sullivan
N/A	Complete Blood Count	O'Sullivan

Supplementary Table 2: Overview of the used Medidoc codes for the 25 selected specific tests for analysis and the reason why they got selected. O'Sullivan: test selected in the 2018 paper by O'Sullivan. Diagnostic relevance: test often used for specific diagnosis. Unique introduction: PCR test for Sars-CoV-2 which was a new test that was used very frequently very fast. N/A: Not applicable.

Supplementary Table and Figure 3: Number of patients per year

Year	YCG	Patients tested
2002	106664	84047
2003	125202	91038
2004	120962	97425
2005	128251	103861
2006	133931	109937
2007	132322	115926
2008	134733	123110
2009	140259	129537
2010	140126	133846
2011	151971	140763
2012	127717	136322
2013	130398	142953
2014	131651	149898
2015	123261	159956
2016	229830	162244
2017	228955	160436
2018	296575	139714
2019	309027	148571
2020	323882	185037
2021	345547	210645

Supplementary Table 3: For each year the number of patients in the YCG and the number of patients who got tested are given.



Supplementary Figure 3: For each year the number of patients in the YCG and the number of patients who got tested are plotted.

Supplementary Table 4: Tests used in the analysis of the top 15 tests

		2002		2003		2004		2005		2006		2007	
Laboratory test	**Medidoc code**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**
CBC	N/A	1	5.18	1	5.02	1	4.82	1	4.77	1	4.65	1	4.55
Creatinine	57139A.B	2	4.28	2	4.13	2	4.07	2	4.04	2	3.98	2	3.91
eGFR (CKD-EPI)	57710F.D	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00
ALAT	13553A.B	4	3.96	3	3.88	3	3.81	3	3.79	3	3.72	3	3.63
Gamma GT	57277A.B	5	3.73	5	3.69	5	3.59	5	3.56	5	3.48	4	3.36
C reactive protein	57217I.B	15	2.42	14	2.50	14	2.52	13	2.59	12	2.57	12	2.56
ASAT	13551A.B	7	3.50	7	3.45	7	3.34	7	3.31	6	3.22	6	3.10
Sodium	57225A.B	17	2.01	18	2.10	18	2.09	17	2.15	16	2.18	15	2.21
Potassium	57213A.B	16	2.03	17	2.12	17	2.10	18	2.15	17	2.16	17	2.17
TSH	447130.B	12	2.97	12	2.94	11	2.92	10	2.92	10	2.87	10	2.81
SARS-CoV-2 PCR	15362B.R	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00
eGFR (MDRD)	57710A.D	N/A	0.00	N/A	0.00	N/A	0.00	127	0.06	71	0.16	42	0.59
ESR	13723A.B	3	4.15	4	3.81	4	3.68	4	3.60	4	3.53	5	3.38
Total cholesterol	57131A.B	6	3.63	6	3.48	6	3.43	6	3.37	7	3.27	7	3.19
Urea	13513A.B	20	1.89	20	1.96	20	1.95	21	1.89	21	1.91	20	1.94
Triglyceriden	57227A.B	8	3.48	8	3.32	8	3.28	8	3.24	8	3.11	8	2.99
HDL-cholesterol	57133A.B	10	3.16	9	3.07	9	3.11	9	3.11	9	3.00	9	2.90
Alkalische fosfatase	57283A.B	14	2.56	13	2.54	13	2.54	14	2.56	13	2.51	13	2.37
Urinzeuur	13501A.B	11	3.13	11	3.00	12	2.85	11	2.82	11	2.76	11	2.68
Glucose - fasted	135110.B	9	3.22	10	3.02	10	2.96	12	2.74	14	2.46	14	2.32
Tot-CHOL:HDL-CHOL	57133D.B	19	2.00	16	2.19	15	2.37	15	2.38	15	2.27	16	2.18
LDL-cholesterol	57133B.B	13	2.67	15	2.49	16	2.18	16	2.23	18	2.13	19	1.95

Supplementary Table 4: Tests used in the analysis of the top 15 tests, all tests appeared at least in one year in the top 15. Reported here: their Medidoc code, their ranking number and percentage of all tests for each year. CBC: complete blood count; ESR: erythrocyte sedimentation rate; N/A: not applicable; Rank: ranking number; %: percentage of all tests of that year.

	2008		2009		2010		2011		2012		2013		2014	
Laboratory test	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**
CBC	1	4.45	1	4.39	1	4.31	1	4.30	1	4.31	1	4.28	1	4.24
Creatinine	2	3.81	2	3.78	2	3.76	2	3.74	2	3.72	2	3.69	2	3.66
eGFR (CKD-EPI)	N/A	0.00	N/A	0.00	N/A	0.00	440	0.01	106	0.09	45.00	0.53	26	1.24
ALAT	3	3.48	3	3.44	3	3.39	3	3.35	3	3.35	3	3.33	3	3.23
Gamma GT	4	3.18	4	3.20	4	3.11	4	3.08	4	3.09	4	3.13	4	3.07
C reactive protein	11	2.65	7	2.79	6	2.82	6	2.87	5	2.90	5	2.84	5	2.86
ASAT	6	2.90	6	3.04	5	2.83	5	2.89	6	2.78	6	2.73	6	2.63
Sodium	14	2.22	14	2.27	14	2.37	14	2.38	13	2.36	13	2.37	9	2.41
Potassium	15	2.15	15	2.23	15	2.33	15	2.37	14	2.33	14	2.34	10	2.39
TSH	10	2.72	9	2.68	9	2.62	9	2.59	9	2.57	8	2.61	7	2.57
SARS-CoV-2 PCR	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00
eGFR (MDRD)	24	1.44	16	2.15	11	2.54	7	2.70	7	2.71	10	2.49	15	2.19
ESR	5	3.26	5	3.05	7	2.97	8	2.64	8	2.61	7	2.67	8	2.55
Total cholesterol	7	3.07	8	2.79	8	2.67	10	2.59	10	2.56	9	2.53	11	2.38
Urea	19	1.99	17	2.03	17	2.05	17	2.14	16	2.12	16	2.08	16	2.06
Triglyceriden	8	2.80	10	2.68	10	2.57	11	2.50	11	2.45	11	2.42	12	2.27
HDL-cholesterol	9	2.72	11	2.62	12	2.52	12	2.45	12	2.41	12	2.40	13	2.26
Alkalische fosfatase	13	2.33	13	2.30	16	2.25	16	2.20	17	2.12	17	2.08	18	2.04
Urinzeuur	12	2.56	12	2.53	13	2.49	13	2.40	15	2.32	15	2.31	14	2.22
Glucose - fasted	16	2.07	20	1.89	21	1.82	22	1.68	20	1.79	18	2.04	17	2.05
Tot-CHOL:HDL-CHOL	17	2.04	18	1.98	19	1.94	19	1.91	19	1.87	19	2.00	20	1.92
LDL-cholesterol	21	1.85	22	1.79	22	1.76	21	1.69	21	1.78	22	1.71	23	1.61

Supplementary Table 4: Continued.

	2015		2016		2017		2018		2019		2020		2021	
Laboratory test	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**	**Rank**	**%**
CBC	1	4.16	1	4.10	1	4.07	1	4.01	1	4.00	1	3.91	1	3.87
Creatinine	2	3.65	2	3.59	2	3.61	2	3.55	2	3.59	2	3.55	2	3.53
eGFR (CKD-EPI)	24	1.53	12	2.15	6	2.58	6	2.73	4	2.93	3	2.99	3	3.01
ALAT	3	3.16	3	3.09	3	3.08	3	2.96	3	2.94	4	2.96	4	2.96
Gamma GT	4	3.04	4	2.99	4	2.96	4	2.89	5	2.87	5	2.88	5	2.88
C reactive protein	5	2.86	5	2.84	5	2.84	5	2.82	6	2.75	6	2.85	6	2.88
ASAT	7	2.58	6	2.53	7	2.50	8	2.42	7	2.43	8	2.42	7	2.46
Sodium	9	2.30	9	2.31	10	2.33	9	2.33	9	2.34	7	2.43	8	2.44
Potassium	10	2.29	10	2.27	11	2.30	10	2.30	10	2.32	9	2.39	9	2.41
TSH	6	2.59	7	2.51	8	2.47	7	2.44	8	2.40	10	2.33	10	2.35
SARS-CoV-2 PCR	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	N/A	0.00	28	1.19	11	2.19
eGFR (MDRD)	14	2.17	22	1.66	22	1.58	13	2.03	12	2.16	11	2.18	12	2.15
ESR	8	2.52	8	2.46	9	2.38	11	2.19	11	2.17	13	2.07	13	2.03
Total cholesterol	11	2.29	11	2.18	12	2.13	12	2.04	13	2.01	14	1.94	14	1.97
Urea	18	2.03	18	2.00	13	2.04	14	1.98	14	1.96	12	2.08	15	1.94
Triglyceriden	12	2.19	14	2.10	14	2.04	16	1.96	16	1.94	15	1.88	16	1.91
HDL-cholesterol	13	2.18	13	2.10	15	2.01	15	1.97	15	1.94	16	1.88	18	1.90
Alkalische fosfatase	19	1.98	19	1.95	19	1.91	21	1.82	21	1.77	20	1.80	19	1.82
Urinzeuur	15	2.17	15	2.05	16	1.99	19	1.88	19	1.87	19	1.82	20	1.81
Glucose - fasted	17	2.03	16	2.01	18	1.95	18	1.91	17	1.91	18	1.82	21	1.80
Tot-CHOL:HDL-CHOL	20	1.94	20	1.92	20	1.88	20	1.83	20	1.81	21	1.77	22	1.78
LDL-cholsterol	23	1.54	25	1.35	27	1.25	27	1.19	30	1.07	33	0.99	34	0.92

Supplementary Table 4: Continued.

Supplementary Table 5: Percentages of total tests for used in the specific tests analysis

Laboratory test	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Testosterone	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.02	0.03	0.04	0.04	0.03	0.04	0.04	0.04
Troponin T	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.03	0.05	0.05	0.06	0.06	0.08	0.09	0.09	0.07	0.07	0.10	0.08
Progesterone	0.07	0.08	0.07	0.07	0.07	0.07	0.08	0.08	0.08	0.08	0.08	0.08	0.09	0.09	0.08	0.08	0.09	0.09	0.09	0.09
D-dimer	0.02	0.03	0.04	0.05	0.05	0.06	0.07	0.09	0.09	0.09	0.08	0.09	0.10	0.10	0.11	0.11	0.11	0.11	0.14	0.14
Fibrinogen	0.13	0.13	0.12	0.14	0.12	0.12	0.12	0.13	0.12	0.10	0.09	0.09	0.08	0.05	0.05	0.05	0.04	0.04	0.04	0.04
Estradiol	0.09	0.10	0.09	0.09	0.09	0.09	0.10	0.09	0.10	0.09	0.10	0.10	0.10	0.10	0.09	0.09	0.10	0.10	0.09	0.10
Vitamin D	0.01	0.01	0.02	0.01	0.02	0.02	0.04	0.07	0.18	0.28	0.48	0.67	0.78	0.90	0.98	1.05	1.14	1.16	1.20	1.22
PSA	0.80	0.85	0.86	0.84	0.84	0.81	0.78	0.75	0.73	0.59	0.48	0.43	0.40	0.39	0.38	0.39	0.39	0.39	0.40	0.40
Lipase	0.55	0.60	0.68	0.66	0.67	0.65	0.72	0.75	0.75	0.45	0.42	0.48	0.54	0.53	0.49	0.45	0.47	0.50	0.56	0.56
CK	0.62	0.60	0.63	0.66	0.60	0.63	0.64	0.63	0.65	0.68	0.67	0.66	0.64	0.64	0.63	0.58	0.55	0.54	0.56	0.52
Folate	0.49	0.59	0.64	0.67	0.74	0.74	0.78	0.77	0.82	0.80	0.85	0.94	0.93	0.96	1.03	1.10	1.10	1.04	1.00	1.03
Hb A1c	0.77	0.76	0.84	0.85	0.86	0.85	0.85	0.86	0.88	0.88	0.89	0.90	0.86	0.83	0.80	0.78	0.76	0.78	0.78	0.75
Vitamine B12	0.61	0.71	0.78	0.83	0.98	1.04	1.08	1.10	1.17	1.19	1.22	1.28	1.30	1.35	1.40	1.44	1.44	1.33	1.21	1.23
COVID PCR																			1.19	2.19
Iron	2.01	1.98	1.96	1.92	1.91	1.91	1.88	1.86	1.82	1.83	1.77	1.74	1.71	1.65	1.55	1.47	1.39	1.33	1.26	1.31
Ferritin	1.76	1.77	1.85	1.92	1.95	1.98	2.00	1.98	1.98	1.99	1.98	2.00	1.97	2.04	2.00	1.98	1.94	1.87	1.85	1.90
Fasting glucose	3.22	3.02	2.96	2.74	2.46	2.32	2.07	1.89	1.82	1.68	1.79	2.04	2.05	2.03	2.01	1.95	1.91	1.91	1.82	1.80
Totale cholesterol	3.63	3.48	3.43	3.37	3.22	3.10	2.90	2.79	2.67	2.59	2.56	2.53	2.38	2.29	2.18	2.13	2.04	2.01	1.94	1.97
TSH	2.97	2.94	2.92	2.92	2.87	2.81	2.72	2.68	2.62	2.59	2.57	2.61	2.57	2.59	2.51	2.47	2.44	2.40	2.33	2.35
ESR	4.15	3.81	3.68	3.60	3.53	3.36	3.18	3.05	2.82	2.64	2.61	2.67	2.55	2.52	2.46	2.38	2.19	2.17	2.07	2.03
CRP	2.42	2.50	2.52	2.59	2.57	2.56	2.65	2.79	2.83	2.87	2.90	2.84	2.86	2.86	2.84	2.84	2.82	2.75	2.85	2.88
Y-GT	3.73	3.69	3.59	3.56	3.48	3.38	3.26	3.20	3.11	3.08	3.09	3.13	3.07	3.04	2.99	2.96	2.89	2.87	2.88	2.88
ALAT	3.96	3.88	3.81	3.79	3.72	3.63	3.48	3.44	3.39	3.35	3.35	3.33	3.23	3.16	3.09	3.08	2.96	2.94	2.96	2.96
Creatinine	4.28	4.13	4.07	4.04	3.98	3.91	3.81	3.78	3.76	3.74	3.72	3.69	3.66	3.65	3.59	3.61	3.55	3.59	3.55	3.53
CBC	5.18	5.02	4.82	4.77	4.65	4.55	4.45	4.39	4.31	4.30	4.31	4.28	4.24	4.16	4.10	4.07	4.01	4.00	3.91	3.87

Supplementary Table 5: For all the selected tests used in the specific tests analysis, their percentage of the total number of tests for that year is given. For full test names and their Medidoc codes, see Supplementary Table 2.