BMJ Open

Downstream activities after laboratory testing in primary care: an exploratory outcome of the ELMO cluster randomised trial (Electronic Laboratory Medicine Ordering with evidence-based order sets in primary care)

Veerle Piessens ,[1] Nicolas Delvaux ,[2] Stefan Heytens ,[1] Bert Aertgeerts,[2] An De Sutter[1]

To cite: Piessens V, Delvaux N, Heytens S, *et al*. Downstream activities after laboratory testing in primary care: an exploratory outcome of the ELMO cluster randomised trial (Electronic Laboratory Medicine Ordering with evidence-based order sets in primary care). *BMJ Open* 2022;**12**:e059261. doi:10.1136/bmjopen-2021-059261

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059261).

Received 12 November 2021
Accepted 01 March 2022

[1]Public Health and Primary Care, Ghent University Faculty of Medicine and Health Sciences, Gent, Belgium
[2]Public Health and Primary Care, KU Leuven, Leuven, Belgium

Correspondence to
Dr Veerle Piessens;
veerle.piessens@ugent.be

ABSTRACT

Objective To estimate the rate and type of downstream activities (DAs) after laboratory testing in primary care, with a specific focus on check-up laboratory panels, and to explore the effect of a clinical decision support system (CDSS) for laboratory ordering on these DAs.

Design Cluster randomised clinical trial.

Setting 72 primary care practices in Belgium, with 272 general practitioners (GPs), randomly assigned to the intervention arm or the control arm.

Participants The study included 10 270 lab panels from 9683 primary care patients (women 55.1%, mean age 56.5). All adult patients who consulted one of the participating GPs during the trial period and needed a laboratory exam were eligible for participation.

Interventions GPs in the intervention group used a CDSS integrated into their online laboratory ordering system, while GPs in the control arm used their lab ordering system as usual. The trial duration was 6 months, with another 6 months follow-up.

Main outcome measures This publication reports on the exploratory outcome of DAs after an initial laboratory exam and the effect of the CDSS on these DAs.

Results 19.7% of all laboratory panels resulted in further diagnostic procedures (95% CI 18.9% to 20.5%) and 19% (95% CI 18.2% to 19.7%) in treatment changes. Check-up laboratory exams showed similar rates of DAs, with 17.5% (95% CI 13.8% to 21.2%) diagnostic DAs and 18.9% (95% CI 13.9% to 23.9%) treatment changes. Using the CDSS resulted in a significant reduction in downstream referrals (−2.4%; 95% CI −4.2% to −0.6%; p=0008), imaging and endoscopies (−0.9%; 95% CI −1.6% to −0.1%; p=0026) and treatment changes (−5.4%; 95% CI −9.5% to −1.2%; p=0.01).

Conclusion This is the largest study so far to examine DAs after laboratory testing. It shows that almost one in three laboratory exams leads to further DAs, even in check-up panels. Using a CDSS for laboratory orders may reduce the rate of some DAs.

Trial registration number NCT02950142.

Strengths and limitations of this study

- ► A large database on downstream activities after laboratory testing in the real life setting of general practice.
- ► The strong design of an RCT to evaluate the late effects on downstream activities of a clinical decision support system for laboratory ordering.
- ► Possible recollection and attribution bias because data were collected 6 months or more after the initial inclusion.
- ► Post hoc analysis, without predefined thresholds for which effects would be clinically significant.

INTRODUCTION

Downstream activities (DAs) are those medical procedures that occur due to an initial abnormal or unexpected test result. They cover a wide range, from additional laboratory tests, imaging, endoscopies and other medical investigations, over referrals, to starting, stopping or changing treatment. In general practice, laboratory tests are, apart from physical examination, the most frequently performed tests[1] and might be an essential trigger for further DAs.

DAs are part of the diagnostic and therapeutic process and should ideally lead the general practitioner (GP) to the correct diagnosis and appropriate treatment. However, additional investigations or therapeutic interventions inherently carry some risks: they may be uncomfortable or painful, there may be a (low) risk of severe complications, and they may lead to anxiety during the diagnostic process and beyond. In addition, they require a patient's time and resources and always put a burden on healthcare expenditures. Finally,

each new investigation may result in another unexpected result or reveal abnormalities with unclear clinical significance (incidental findings), increase diagnostic uncertainty and start a cascade of further investigations and therapeutic interventions, often with unknown added value, the so-called Ulysses syndrome.[2–5]

Not all lab tests are necessary or appropriate for the indication they are ordered for, and the value of abnormal results of such tests may be questionable. Moreover, inappropriate overuse of lab tests increases the risk of false positive results considerably.[6] DAs triggered by false-positive results threaten the quality of care because they never result in health benefits, always come with a financial cost, and sometimes cause discomfort, anxiety or complications.[7–10] This is especially true in 'general' laboratory panels for 'health check-ups'. Performing health check-ups in otherwise healthy adults is widespread despite the lack of evidence on its effectiveness. A recent systematic review confirmed the findings of the 2019 Cochrane Review that it is unlikely that periodic health check-ups would be beneficial in terms of mortality or morbidity, despite improved intermediate procedural outcomes, like higher uptake of some preventive services and better management of some risk factors.[11 12]

This so-called 'low-value care' has been brought to attention since the beginning of the 21st century by initiatives like 'too much medicine', 'less is more' and 'choosing wisely'.[13 14] There is an increasing interest in primary care research on low-value testing and associated DAs.[7–9 15]

However, data are scarce on the type of follow-up activities, how frequent they occur, and whether specific patient or laboratory panel characteristics make them more plausible. Moreover, almost no research exists on interventions to reduce unnecessary DAs.[16] However, withholding further follow-up after an abnormal laboratory test goes against good medical practice and feels unethical. Once the initial tests are performed and bring abnormal results, further cascade activities are unavoidable. Therefore, it is preferable to reduce avoidable triggers of these cascades, such as redundant or inappropriate laboratory tests, which was precisely the main objective of the Electronic Laboratory Medicine Ordering (ELMO) study. This study was a cluster randomised clinical trial that introduced a clinical decision support system (CDSS) for online laboratory test ordering in primary care. Using the CDSS significantly reduced the proportion of inappropriate tests and the number of tests per lab panel during the study period. Meanwhile, the intervention did not increase the risk for diagnostic error.[17] The ELMO study included effects on subsequent DAs as an exploratory outcome and provided us with an extensive database and an opportunity to gain insight into this phenomenon.[18]

RESEARCH QUESTION

We present two exploratory research questions. First, how often and which DAs do GPs undertake after an initial laboratory exam, especially after laboratory exams for a health check-up? Second, what could be the effect of a CDSS in laboratory test ordering on DAs, for all lab panels and for a subgroup of lab panels ordered for a check-up only?

METHOD

Setting, intervention and data collection

This is a post hoc exploratory analysis of a subset of data of the ELMO study, a cluster randomised clinical trial, in which 72 primary care practices (PCPs) with 272 GPs, in Flanders (Belgium), were randomly assigned to an intervention or control arm. The methods of this study have been reported previously[17 18] and can be consulted in online supplemental appendix 1. We also briefly summarise them here.

GPs recruited adult patients who needed laboratory testing for at least 1 of the 17 study indications. In the intervention arm, GPs used a CDSS integrated into their online laboratory ordering system. First, GPs selected the indications for which they wanted to have their patient tested. Then the CDSS suggested order sets with appropriate lab tests for each selected indication. The study indications are common reasons for laboratory testing in primary care, like anaemia, fatigue or diabetes. Some of the predefined indications had sub-indications, for example, for diabetes, GPs could specify whether it was for screening, 3-monthly or annual follow-up. (We provide an overview of all study indications and terminology in online supplemental appendix 2). GPs could order tests for multiple indications in one laboratory panel and were free to add or remove laboratory tests at will from the proposed order sets. Thus, a single patient encounter results in one laboratory panel, containing all tests ordered during that encounter, for one or more indications.

In the control arm, GPs used their online laboratory ordering system as usual, without the integrated CDSS, and specified for which of the 17 indications they ordered the laboratory exam.

The trial included a 6-month intervention period and a 6-month follow-up period.

For each included laboratory panel GPs were asked 6 months later to send an electronic case report form (eCRF) through a secured data system to a trusted third party with information about DAs and new diagnoses in the 6 months following the initial laboratory panel. The eCRF automatically retrieved all new diagnoses from the patient's electronic health record (EHR), and the GPs manually added whether they ordered any further laboratory exams, other investigations or referrals due to abnormalities in the laboratory result or if they changed anything to the patient's treatment plan due to the results of the laboratory tests. We encouraged GPs to interpret treatment changes broadly, including iron or vitamin supplements, dietary advice, drug treatment.

After pseudonymising by the trusted third party, this information was linked to the data of the initial laboratory order, allowing the researchers to investigate any effect or relationship between the laboratory panel and DAs. The researchers were blinded for the allocation of each patient until all data were collected and processed.

Outcomes

We checked for all lab panels (the set of lab tests ordered during one patient encounter) whether or not they resulted in DAs.

We calculated the overall proportions of lab panels with DAs and distinguished two different categories of DAs. Diagnostic DAs (DDAs) are DAs with a diagnostic purpose (additional labs, imaging, endoscopies, functional tests and referrals) and therapeutic DAs (TDAs) are those with a therapeutic purpose (changes in the patient's treatment plan).

For the analysis of the subgroup 'check-up panels', we defined a subgroup of lab panels that had 'check-up' as the only indication and compared those to panels having one or more other indications but not 'check-up'.

Patient and public involvement

Patients or the public were not involved in the design or conduct of this study.

Statistical analysis

We estimated overall proportions of panels with DAs and proportions in both study arms, using a generalised estimating equation with the PCP as the clustering variable and allocated group as a factor. Given the known age differences between allocated groups, we also added patient age as a factor in the model. We performed these analyses on the full dataset and on a subset of lab panels with 'check-up' as the only indication.

We calculated all proportions and differences together with their 95% CIs. Statistical significance was assessed at a significance level of 5%.

Sample sizes were calculated for the primary outcomes of this randomized clincial trial (RCT).[18] Therefore, we do not provide post hoc power calculations for this exploratory outcome but will provide 95% CIs of the differences to allow estimates on the power of this study to find any significant difference.[19]

All statistical analyses were performed with SAS statistical software (V.9.4, SAS Institute).

RESULTS

General

A total of 272 GPs from 72 PCPs included 10 270 eligible laboratory panels from 9683 patients. There was only one panel for most of the participating patients (9163), and 520 patients had two or more panels included. We received information on DAs for 90.7% of the included laboratory panels, evenly distributed over the intervention and control group (figure 1). The main reasons for missing information were the non-response of GPs and technical problems that prevented sending the eCRF through the secured system to the trusted third party. Detailed information on recruitment, inclusion and characteristics of lab panels with missing follow-up data can be consulted in online supplemental appendix 3.

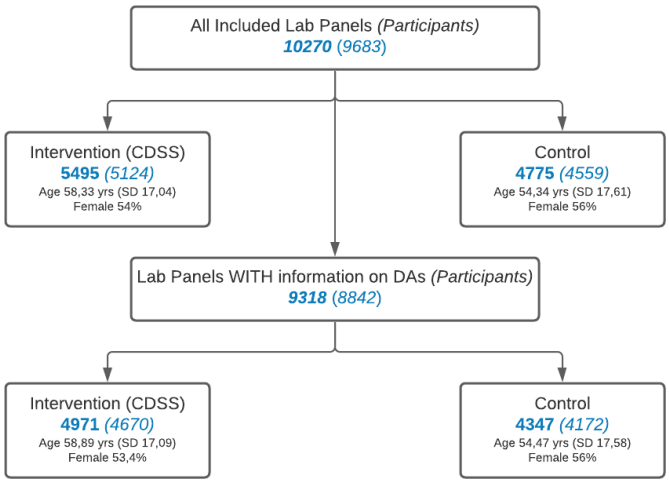

Figure 1 Included lab panels and information on downstream activities in intervention and control arm. CDSS, clinical decision support system; DA, downstream activities.

Downstream activities

Nearly 32% of the lab panels results in DAs. For 19.7% of lab panels, GPs order additional diagnostic procedures (DDAs), and for 19%, they change the patient's treatment plan (TDAs). The majority of DDAs consists of laboratory exams (14.6% of all laboratory panels), followed by referrals (6.3%), whereas TDAs mostly mean 'starting a new medication' (13.6%) (see table 1 for detailed results). Lab panels for which GPs selected 'check-up' as the only indication lead to similar rates of DAs, with 17.5% of check-up labs resulting in DDAs and 18.9% to TDAs.

Intervention versus control

Overall there is no statistically significant difference between both arms in the total number of DDAs. However, there are small but significant reductions in referrals (−2.4%) and in 'imaging and endoscopies' (−0.9%), (p values and 95% CIs are presented in table 2).

We observed a significant reduction in treatment changes (TDA) in the intervention arm. In this arm, 16.5% of laboratory panels result in modifying the patient's treatment plan, mainly the initiation of a new medication (11.7%). In the control arm, this is 21.9% and 15.7%, respectively. This means a significant absolute difference of −5.4% for any change in the treatment plan and −3.9% for starting a new medication.

Effect of the CDSS on check-up laboratory panels

There are twice as many panels for check-up only (22.7%) in the control arm compared with the intervention arm (10.1%) (table 3). GPs in the intervention arm more

Table 1 Number and proportion of laboratory panels resulting in downstream activities in all 10 270 laboratory panels and in a subgroup of 1640 panels for check-up only

	All lab panels		Lab panels for check-up only	
	N=10 270		N=1640	
	No of panels	% (CI 95%) of panels	No of panels	% (CI 95%) of panels
Diagnostic downstream activities (DDA)				
Any DDA	2022	19.7% (18.9% to 20.5%)	287	17.5% (13.8% to 21.2%)
Additional labs	1499	14.6% (13.9% to 15.3%)	213	13% (9.2% to 16.8%)
Referrals	649	6.3% (5.8% to 6.8%)	80	4.9% (3.0% to 6.7%)
Imaging & Endoscopies	248	2.4% (2.1% to 2.7%)	34	2.1% (1.4% to 2.9%)
Functional Tests*	70	0.7% (0.5% to 0.8%)	18	1.1% (0.5% to 1.7%)
Therapeutic downstream activities (TDA)				
Any TDA	1950	19% (18.2% to 19.7%)	310	18.9% (13.9% to 23.9%)
Start medication	1393	13.6% (12.9% to 14.2%)	256	15.6% (11.2% to 20.0%)
Change medication	390	3.8% (3.4% to 4.2%)	26	1.6% (1.1% to 2.2%)
Stop medication	67	0.7% (0.5% to 0.8%)	5	0.3% (0.0% to 0.6%)
Advice on healthy habits†	171	1.7% (1.4% to 1.9%)	38	2.3% (1.1% to 3.7%)

Information on downstream activities was missing for 952 panels. These panels were considered to have no downstream activities.
*Functional tests.
†Nutrition, physical activity, alcohol and tobacco.

often choose (a combination of) specific indications rather than the umbrella indication 'check-up' as the only indication.

In both study arms, GPs order more tests for check-up panels compared with panels without check-up as an indication. Check-up panels have a lower proportion of appropriate tests, result in more abnormal tests and are performed in an older population with more male patients. Although the intervention improved the appropriateness of check-up panels and reduced the number of tests, the differences with panels without check-up remain clear.

When considering laboratory panels with check-up as the only indication, the CDSS is associated with

Table 2 Proportions of lab panels resulting in downstream activities in both study arms, with the absolute differences between study arms, associated 95% CI and p values

	CDSS arm (N=5495)	Control arm (N=4775)	Difference	
	% (95% CI)	% (95% CI)	% (95% CI)	P value
Diagnostic downstream activities (DDA)				
Any DDA	18.4% (12.9% to 23.9%)	21.1% (17.6% to 24.6%)	−2.7% (−9.0% to +3.7%)	0.40
Additional labs	14.3% (8.6% to 20.1%)	14.9% (11.8% to 18.0%)	−0.5% (−6.8% to +5.6%)	0.85
Referrals	5.2% (4.0% to 6.3%)	7.6% (6.2% to 9.0%)	−2.4% (−4.2% to −0.6%)	0.008
Imaging and endoscopies	2.0% (1.5% to 2.5%)	2.9% (2.3% to 3.4%)	−0.9% (−1.6% to −0.1%)	0.026
Functional tests*	0.4% (0.2% to 0.7%)	0.9% (0.5% to 1.4%)	−0.4% (−0.9% to 0.04%)	0.052
Therapeutic downstream activities (TDA)				
Any TDA	16.5% (14.2% to 18.8%)	21.9% (18.5% to 25.3%)	−5.4% (−9.5% to −1.2%)	0.01
Start medication	11.7% (9.9% to 13.6%)	15.7% (12.8% to 18.6%)	−3.9% (−7.3% to −0.6%)	0.02
Change medication	3.6% (2.7% to 4.5%)	4.0% (3.2% to 4.9%)	−0.4% (−1.7% to +0.8%)	0.50
Stop medication	0.63% (0.32% to 0.93%)	0.67% (0.45% to 0.89%)	+0.04% (−0.9% to +0.4%)	0.81
Healthy habits advice†	1.2% (0.7% to 1.7%)	2.3% (1.3% to 3.2%)	−1.1% (−2.1% to −0.05%)	0.05

Information on downstream activities was missing for 524 panels in the CDSS arm and 428 panels in the control arm. Therefore, these panels were considered to have no downstream activities.
*Functional tests.
†Nutrition, physical activity, alcohol and tobacco.
CDSS, clinical decision support system.

Table 3 Lab panel and patient characteristics in laboratory panels for 'check-up' only compared with mixed panels and panels without check-up as an indication

	CDSS arm (N=5495)	Control arm (N=4775)
Laboratory panel characteristics		
Panels (N, %)		
No check-up	3773 (68.7%)	2839 (59.5%)
Check-up only	554 (10.1%)	1086 (22.7%)
Check-up +other indications	1168 (21.3%)	850 (17.8%)
Mean # tests/panel (mean, CI 95%)		
No check-up	19.99 (15.57 to 22.41)	24.33 (21.96 to 26.70)
Check-up only	32.51 (29.37 to 35.66)	41.75 (39.27 to 44.22)
Check-up +other indications	32.99 (31.61 to 34.37)	40.48 (37.89 to 43.08)
Mean # abnormal tests/panel (mean, CI 95%)		
No check-up	3.98 (3.58 to 4.37)	4.38 (3.92 to 4.84)
Check-up only	4.98 (4.39 to 5.57)	5.82 (5.32 to 6.33)
Check-up +other indications	5.50 (5.09 to 5.90)	5.96 (5.42 to 6.49)
Proportion of appropriate tests per panel (mean, CI 95%)		
No check-up	0.74 (0.69 to 0.77)	0.61 (0.59 to 0.63)
Check-up only	0.23 (0.13 to 0.32)	0.16 (0.14 to 0.17)
Check-up +other indications	0.67 (0.64 to 0.71)	0.42 (0.39 to 0.45)
Patient characteristics		
Patients (N)		
No check-up	3447	2660
Check-up only	530	1075
Check-up +other indications	1147	824
Patient age (years, SD)		
No check-up	55.94 (18.25)	49.58 (18.47)
Check-up only	60.75 (13.54)	60.37 (13.44)
Check-up +other indications	62.19 (13.3)	59.03 (15.46)
% Female		
No check-up	55.3	60
Check-up only	47.2	49.8
Check-up +other indications	53.4	53

CDSS, clinical decision support system.

fewer TDAs and referrals and no effect on other DDAs (table 4).

DISCUSSION

Main findings

Nearly 20% of the laboratory panels in the ELMO trial led to DDAs and 19% to TDAs, mainly starting a new medication. A subgroup analysis of check-up laboratory panels showed similar results. The intervention with a CDSS for lab test ordering was associated with a significant overall reduction of downstream treatment changes, referrals and imaging, and referrals and treatment changes in the subgroup of laboratory exams for 'check-up only'.

We believe that the direct effect of the intervention did not extend beyond the moment that GPs ordered the lab tests, so we hypothesise that any effect on further DAs was mediated by the initial reduction in low-value lab tests through the CDSS.

We have no details on what GPs understood by a 'check-up' lab. We assume that there will be a range from real check-up labs (ie, laboratory panels in people who are otherwise healthy and have no complaints or symptoms) over targeted screening tests (eg, screening for diabetes) to broad lab panels for patients who present with multiple, vague complaints. In the intervention arm, there were also fewer panels with 'check-up' as the only indication and more panels with one or more specific

Table 4 Proportions of lab panels for a check-up only resulting in downstream activities in both study arms, with the absolute differences between study arms, associated 95% CI and p values

	CDSS (N=554)	Control (N=1086)	Difference	
	% (CI 95%)	% (CI 95%)	% (CI 95%)	P value
Diagnostic downstream activities (DDA)				
Any DDA	18.6% (12.6% to 24.7%)	16.9% (12.5% to 21.3%)	+1.7% (–5.8% to +9.2%)	0.65
Additional labs	16.6% (9.2% to 24.0%)	11.2% (8.0% to 14.4%)	+5.4% (–2.7% to +13.5%)	0.19
Referrals	2.9% (1.0% to 4.7%)	5.9% (3.6% to 8.2%)	–3.0% (–6.0% to –0.04%)	0.047
Imaging and endoscopies	1.6% (0.2% to 3.0%)	2.4% (1.7% to 3.2%)	–0.9% (–2.4% to +0.7%)	0.28
Therapeutic downstream activities (TDA)				
Any TDA	12.3% (8.5% to 16.0%)	22.3% (16.7% to 27.9%)	–10.1% (–16.7% to –3.4%)	0.003
Start medication	9.9% (6.1% to 13.8%)	18.5% (13.7% to 23.3%)	–8.6% (–14.7% to –2.5%)	0.006

Proportions for other types of downstream activities could not be calculated due to the low number of events.
CDSS, clinical decision support system.

indications. When GPs in the intervention arm selected 'check-up' as an indication, the CDSS only suggested a minimalist set of tests (glucose and cholesterol), probably considerably fewer tests than GPs usually order for a check-up lab. We assume that this might have prompted GPs to reconsider the indications for which they wanted to have the patient tested, which probably led to a shift from lab panels for 'check-up only' to panels with several specific indications. Nevertheless, GPs in both the CDSS and the control group ordered remarkably more tests for check-ups than for other indications, and the CDSS reduced the number of tests and improved the appropriateness of check-up laboratory panels.

The CDSS had no effect on further laboratory testing, which was the largest subcategory of DDAs. We have no further details on the content of these downstream lab tests and whether they were reflex tests on the same blood sample (stepwise ordering of additional tests based on the results of the previous tests, for instance only ordering free thyroxine when thyroid-stimulating hormone levels are abnormal), repeated laboratory panels, or scheduled controls. The CDSS encouraged reflex testing, with a limited set of appropriate, mostly first-line tests. If reflex testing explained the observed difference in downstream laboratory tests, it would represent a shift of certain lab tests from the initial lab panel to follow-up tests rather than actual additional tests.

We only investigated the initial DAs after laboratory exams. Therefore, we have no information on further cascade investigations or treatments resulting from abnormalities that may have been detected in these first-line DAs. The term cascades refers to 'a chain of events initiated by an unnecessary test, an unexpected result, or patient or physician anxiety, which results in ill-advised tests or treatments that may cause avoidable adverse effects and morbidity'.[5] This study shows that a CDSS can mitigate the first two stages of a potential cascade (the number of inappropriate lab tests and subsequent DAs), and a further downstream effect can be assumed, but has yet to be confirmed.

Strengths and weaknesses

The major strength of this study is the strong design of an RCT to examine the late effects of a CDSS for laboratory ordering on DAs beyond its immediate effect on appropriateness and test volume of the lab panels. In addition, the pragmatic real-life setting and the magnitude of the dataset contribute to the reliability of the results. However, this study has some limitations.

First, our data may not be entirely complete. We had to rely on what GPs registered in their EHR, which is sometimes scarce, and on what they actively remembered 6 months later, which could have introduced a recollection bias. However, as health records are digitised, most information is automatically available in the EHR (electronic drug prescriptions, lab reports or specialist referrals). Second, the quality of the data might be suboptimal. At times it was unclear whether the mentioned DAs were due to the laboratory test results or instead related to the complaints the laboratory panel was performed for in the first place. This implies that the decision to initiate a DA was already taken before the lab tests were ordered. This risk of 'assignment bias' is confirmed by the observation that almost 10% of laboratory panels with no abnormal results led to further investigations or referrals. These biases may result in both over and under-reporting of DAs. However, we can assume that they occurred evenly and randomly in all subcategories and that these biases did not affect observed differences between subgroups. Third, one might fear that fewer DAs could mean that necessary DAs for quality patient care are no longer performed, which could lead to missed diagnoses and undertreatment. Unfortunately, we do not have detailed information on the exact contents of the DAs, such as which lab tests were performed or which treatments were started. Therefore, we are unable to distinguish justified DAs from unnecessary ones. However, the risk

of diagnostic error was a crucial secondary endpoint in the ELMO trial, for which it was adequately powered.[18] It was primarily assessed through a systematic chart review of all included patients and completed with data from telephone interviews with a random subset of patients.[18] Results show that the CDSS reduced test volume and inappropriate tests and did not lead to more missed diagnoses or other diagnostic errors.[17] Given this equal health outcome, we could state that the additional reduction in DAs saves healthcare costs and protects patients against unnecessary medical interventions. Fourth, as mentioned before, this is a post hoc analysis without prespecified statistical thresholds. Therefore, the calculated differences between the intervention and control groups should be interpreted with caution. No threshold was set for which effect would be clinically significant. This would have been impossible, as we had no information on the baseline rate of DAs after laboratory exams. Furthermore, it is only after we have established that using a CDSS is safe and does not increase the risk of diagnostic error that we can assume that fewer DAs are not associated with missed diagnoses. Given the now established safety of the intervention, we believe that even a minor decrease in DAs can be clinically significant. For instance, there is an absolute reduction of 0.9% in imaging and endoscopies. One can doubt the clinical significance of such a slight reduction. However, even this tiny reduction would mean 82 000 fewer imaging procedures per year for the small Belgian population (9 million adult inhabitants) if we assume that an adult patient has on average one blood test every year.[1] The net impact of such an intervention will depend on the a priori risk of low value laboratory testing, which may vary between healthcare settings. Belgian GPs lab testing practices are situated mid-range of several European countries.[20]

Comparison with existing literature

There is only limited research on DAs in primary care, and to our knowledge, this is the first study that examines the effect of an intervention for laboratory test ordering on further DAs. Watson *et al* studied British GPs' DA practices after ordering inflammatory marker tests.[9] They found that patients who had their inflammatory markers checked, compared with untested control patients, were 2–3 times more likely to have a referral in the 6 months following the lab test and 1.5–3.5 times more likely to have a new blood test. Overall, 2.4% of patients with an inflammatory marker test were referred, and 23% were scheduled for a new blood test. Houben *et al* observed Dutch GP's DDAs in routine practice and found that GPs ordered further investigations or referrals for 17% of patients with labs ordered for diagnostic reasons and with a low pretest probability. When the pretest probability was high, and the lab results came back abnormal, GPs took further action in up to 77% of patients.[15 21] This is partly in line with our findings, despite our substantially higher number of tests per panel (27 vs 9.9) and a higher proportion of lab panels with at least one abnormal result (90.6% vs 64%).

Other research on TDAs is scarce, so we could not compare our findings with other research on this topic. Almost 14% of all lab panels in this study resulted in the initiation of a new medication, which seems high. However, we believe that this is a reliable reflection of current prescribing behaviour in Belgium. In general, the prescription rate in Belgium is high. Matthys *et al* observed 613 GP consultations, and in 69.8% of all contacts, medication was prescribed.[22] Moreover, most lab panels in this study were not for screening but for specific indications, which probably resulted in a preselection of patients with a higher need to start drug treatment. Finally, the category 'starting medication' was broadly defined and also included iron or vitamin supplementation or adding another diabetes medication to an existing treatment.

A subgroup analysis of check-up laboratory panels showed that only 16% of the tests ordered in these panels was appropriate. This is probably not without consequence. A large retrospective cohort study in patients who underwent an annual check-up exam found that inappropriate, low-value screening tests (ECG, chest radiograph, …) were associated with more, sometimes invasive, downstream procedures, without evidence of health benefits.[7] We observed important rates of treatment changes and DDAs after check-up laboratory exams. This is surprising, given that, in theory, check-up labs should only be performed in healthy people. This could be a confirmation of what other researchers have warned about, that screening healthy people generates multiple DAs with no tangible health benefits.[11] On the other hand, as already mentioned before, this finding might also be due to documentation bias: patients may present with multiple complaints, and the GP decides to do a 'lab for a general check-up' rather than ticking all the relevant indications.

What do these findings mean

Further diagnostic and therapeutic procedures after laboratory exams are standard in the clinical process in primary care. Using a CDSS, which affects lab test ordering behaviour at the beginning of this process, may also impact DAs. This could be an encouragement for GPs who strive to provide a high quality of care and avoid unnecessary medical interventions, to use such CDSS, and likewise for policy-makers to support the implementation of CDSS in lab test ordering systems.

Need for further research

This was the first trial to study the effect of a CDSS on DAs. However, it was only an exploratory outcome with a post hoc statistical analysis. Further research is needed to confirm and elaborate on these results, with a specific focus on gaining insight into what prompts further (low value) DAs: specific lab abnormalities, the indications the tests were ordered for, or rather patient or GP characteristics? Since research indicates that patients appreciate general check-ups and improve their well-being,[12]

we recommend integrating nested qualitative research to capture both the patient's perspective and GP's views on observed differences in DAs.

CONCLUSION

Our findings suggest that one-third of laboratory exams in primary care lead to further diagnostic procedures or changes in the patient's treatment plan. Lab panels for a general check-up in otherwise healthy patients have similar rates of DAs. Using a CDSS for laboratory test ordering in primary care decreased downstream referrals and treatment changes but did not affect additional laboratory testing.

Acknowledgements Special thanks for their contribution to concept, design and obtaining funding: Dirk Ramaekers, data collection monitoring: Tine De Burghgraeve, guidance and support in the statistical analyses: Pavlos Mamouris, professor Dr Els Clays, professor Dr Steffen Fieuws, and the Ghent University Biostatistics Unit for their guidance and support in the statistical analysis. We thank all the participating patients and their GPs, as well as Mario Berth, Eric De Schouwer, An De Vleeschauwer, and all other clinical laboratory personnel involved in the technical support of the ELMO Study.

Contributors VP, ND, BA and ADS are guarantors of this publication, they had full access to all data and take responsibility for the integrity of the data and the accuracy of the analyses. Concept, design and obtaining funding: ND, BA and ADS. Development of the data collection tool: ND. Data collection monitoring: ND and VP. Data cleaning, processing and analysis: VP, ND, ADS and SH. Statistical analyses: VP and ND. Drafting of the manuscript: VP. Critical revision of the manuscript: all authors. All authors read and approved the manuscript.

Funding The ELMO Study was funded through the Belgian Health Care Knowledge Centre (KCE) Trials, Programme agreement KCE16011.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Research Ethics Committee UZ/KU LeuvenB322201733217. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data can be obtained by a motivated request to the first author.

ORCID iDs
Veerle Piessens http://orcid.org/0000-0002-2305-1762
Nicolas Delvaux http://orcid.org/0000-0002-7335-4075
Stefan Heytens http://orcid.org/0000-0003-1097-4987

REFERENCES

1 Hickner J, Thompson PJ, Wilkinson T, *et al*. Primary care physicians' challenges in ordering clinical laboratory tests and interpreting results. *J Am Board Fam Med* 2014;27:268–74.
2 Nguyen LT, Sullivan CT, Makam AN. The diagnostic cascade of incidental findings: a Teachable moment. *JAMA Intern Med* 2015;175:1089–90.
3 Rang M. The Ulysses syndrome. *Can Med Assoc J* 1972;106:122–3.
4 Reznik OI. Ulysses Syndrome and the Case of the Endless Search for Reassurance. In: *The secrets of medical decision making, how to avoid becoming a victim of the health care machine*. Loving Healing Press, 2006.
5 Deyo RA. Cascade effects of medical technology. *Annu Rev Public Health* 2002;23:23–44.
6 Naugler C, Ma I. More than half of abnormal results from laboratory tests ordered by family physicians could be false-positive. *Can Fam Physician* 2018;64:202–3.
7 Bouck Z, Calzavara AJ, Ivers NM, *et al*. Association of low-value testing with subsequent health care use and clinical outcomes among low-risk primary care outpatients undergoing an annual health examination. *JAMA Intern Med* 2020;180:973.
8 Bhatia RS, Bouck Z, Ivers NM, *et al*. Electrocardiograms in low-risk patients undergoing an annual health examination. *JAMA Intern Med* 2017;177:1326–33.
9 Watson J, Salisbury C, Whiting P, *et al*. Added value and cascade effects of inflammatory marker tests in UK primary care: a cohort study from the clinical practice research Datalink. *Br J Gen Pract* 2019;69:e470–8.
10 Whiting D, Croker R, Watson J, *et al*. Optimising laboratory monitoring of chronic conditions in primary care: a quality improvement framework. *BMJ Open Qual* 2019;8:e000349.
11 Krogsbøll LT, Jørgensen KJ, Gøtzsche PC. General health checks in adults for reducing morbidity and mortality from disease. *Cochrane Database Syst Rev* 2019;1:CD009009.
12 Liss DT, Uchida T, Wilkes CL, *et al*. General health checks in adult primary care: a review. *JAMA* 2021;325:2294–306.
13 Moynihan R, Smith R. Too much medicine? *BMJ* 2002;324:859–60.
14 Born KB, Levinson W. Choosing wisely campaigns globally: a shared approach to tackling the problem of overuse in healthcare. *J Gen Fam Med* 2019;20:9–12.
15 Houben PHH, van der Weijden T, Winkens RAG, *et al*. Cascade effects of laboratory testing are found to be rare in low disease probability situations: prospective cohort study. *J Clin Epidemiol* 2010;63:452–8.
16 Fried JG, Andrew AS, Ring NY, *et al*. Changes in primary care health care utilization after inclusion of epidemiologic data in lumbar spine MR imaging reports for uncomplicated low back pain. *Radiology* 2018;287:563–9.
17 Delvaux N, Piessens V, Burghgraeve TD, *et al*. Clinical decision support improves the appropriateness of laboratory test ordering in primary care without increasing diagnostic error: the ELMO cluster randomized trial. *Implement Sci* 2020;15:100.
18 Delvaux N, De Sutter A, Van de Velde S, *et al*. Electronic laboratory medicine ordering with evidence-based order sets in primary care (ELMO study): protocol for a cluster randomised trial. *Implement Sci* 2017;12:147.
19 Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy* 2001;21:405–9.
20 Leurquin P, Van Casteren V, De Maeseneer J. Use of blood tests in general practice: a collaborative study in eight European countries. Eurosentinel Study Group. *Br J Gen Pract* 1995;45:21–5.
21 Houben PHH, van der Weijden T, Winkens B, *et al*. Pretest expectations strongly influence interpretation of abnormal laboratory results and further management. *BMC Fam Pract* 2010;11:13.
22 Matthys J, Elwyn G, Van Nuland M, *et al*. Patients' ideas, concerns, and expectations (ICE) in general practice: impact on prescribing. *Br J Gen Pract* 2009;59:29–36.