Downstream diagnostic activities following laboratory testing in primary care: a secondary data-analysis of the ELMO study.

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Abbreviations

ACS	acute coronary syndrome
CDSS	clinical decision support system
CI	confidence interval
CKD	chronic kidney disease
CPOE	computerized physician order entry
CRP	C-reactive protein
ELMO	electronic laboratory medicine ordering with evidence-based order sets
ESR	erythrocyte sedimentation rate
GP	general practitioner
OR	odds ratio
RR	risk ratio/ relative risk
SD	standard deviation
STI	sexually transmitted infection
TSH	thyroid-stimulating hormone

Abstract

Background: Laboratory testing plays an indispensable role in primary care and is the most frequently used diagnostic tool. However, the rate of downstream diagnostic activities after laboratory testing in primary care is understudied.

Methods and research questions: In the Electronic Laboratory Medicine ordering with evidence-based Order sets in primary care (ELMO) study, patients aged ≥ 18 years with laboratory testing for at least one of 17 indications were studied across 280 general practitioners from 72 primary care practices in Belgium. In that cluster randomized controlled clinical trial, the integration of a clinical decision support system into a computerized physician order entry was studied. This study compares the occurrence of downstream diagnostic activities between the control and intervention group during a 6-month follow-up period (first research question). The control group, relating most to standard care, is used to study the association between lab panel size and the occurrence of downstream activities (second research question). Additionally, the association between the presence of a lab test in a lab panel and the occurrence of downstream activities is examined for 15 common lab tests or clusters of tests, representing approximately 80 % of the most frequently requested lab tests in the ELMO study (third research question).

Results: For the first research question, 9,683 patients were included, of which 4,559 in the control group (mean age = 54 years; 56% female), and 5,124 in intervention group (mean age = 58 years; 54% female). For the second and third research question, 4,192 patients from the control group (mean age = 54 years; 56% female) were included. In the intervention group, fewer patients underwent at least one downstream activity ($p = 0.0290$). More specifically, fewer patients underwent

downstream medical imaging ($p = 0.0047$), referrals ($p < 0.0001$) and functional testing ($p = 0.0102$) compared to the control group, but not lab testing ($p = 0.5383$). In the control group, no association between the size of the laboratory panels and the occurrence of at least one downstream activity ($p = 0.1789$) was observed, with similar results for downstream lab testing ($p= 0.0640$), referrals ($p = 0.2879$), functional testing ($p = 0.3119$) and imaging ($p = 0.1944$). The following association between lab tests or clusters in lab panels and increased downstream testing for patients in the control group was observed: liver tests and patients with downstream imaging ($p = 0.0066$), C-reactive protein and patients with downstream imaging ($p = 0.0009$), erythrocyte sedimentation rate and patients with downstream imaging ($p = 0.0061$), D-dimer and patients with downstream imaging ($p < 0.0001$), ESR and patients with downstream laboratory testing ($p = 0.0459$), troponin and patients with downstream referral ($p < 0.0001$) and troponin and patients with downstream functional testing ($p < 0.0001$).

Conclusion: A small reduction in the proportion of patients undergoing downstream imaging, referrals, and functional testing, but not lab testing, was observed in the intervention group. The size of lab panels does not seem to be associated with (more) downstream activities. The presence of certain frequently requested lab tests (inflammatory markers and liver tests) in lab panels might be associated with more downstream testing, which could be explored in future research.

Introduction and background

Laboratory testing plays an indispensable role in primary care as an accessible tool for screening and diagnosis as well as management and monitoring of diseases and treatments. This explains why a substantial proportion of health care contacts in primary care result in laboratory testing. Furthermore, of all medical activities, laboratory testing is the most frequently used diagnostic tool (1).

Many laboratory tests are inappropriate, meaning they are under-, over-, or misused in the diagnostic process. In secondary care, around a third of lab testing is considered inappropriate, with an over-and underuse of 21% and 45% respectively (2). In primary care, the rate of inappropriate testing varies substantially and is widely understudied (3). Several factors can drive inappropriate testing in primary care. The commonly held perception of laboratory testing as a relatively trivial or inconsequential intervention, often permits clinicians to prioritize efficiency over thoroughness in test-ordering (4). Decisions will therefore often be based on heuristics, routines and be subjected to external influences, such as time or patient pressures, and limited specialist capacity (4). With an increasing amount of testing and associated costs in healthcare, inappropriate testing could create an economic burden on society (5). Besides the economic impact, inadequate testing might delay diagnosis and cause harm (6). An additional challenge in primary care is the false positive paradox, encompassing the high number of false positives in a low prevalence setting, even when test specificity is high (7). For example, a British prospective cohort study has shown that inflammatory markers for ruling out infection, cancer or auto-immune disease in primary care may generate false positives and lead to increased observed rates of follow-on GP consultations, tests, and referrals (8).

A cascade in medicine is defined as a chain of events initiated by an unnecessary test, results that were unexpected or other factors such as patient or physician anxiety. It can result in more testing or treatments that may cause avoidable adverse effects or morbidity (9).

In a Dutch observational prospective study, researchers directly measured cascade activities after laboratory testing in primary care. Physicians ordered further diagnostic testing for 22 (17.3%) patients with abnormal results compared to only 2 (1.6%) patients with normal results ($p < 0.001$), they referred 12 (9.4%) patients with abnormal results to secondary care compared to 8 (6.2%) patients with normal results ($p = 0.33$) (10). For 3.1% of the patients with an abnormal result, more than one cascade activity occurred. The authors conclude that cascade activities after laboratory testing are found to be rare in low disease probability situations and they suggest that improving the interpretation of a blood test could help the appropriateness of further downstream testing (10). The rate of cascades after initial laboratory testing in primary care is an understudied phenomenon.

With clinical decision support systems (CDSS), general practitioners (GPs) can be guided towards evidence-based and value-based laboratory testing. Current evidence supports the combination of computerized physician order entry (CPOE) systems and reflex testing practices (i.e., more tests being automatically ordered based on the results of a first test) (11). The effects of other strategies such as guidelines, education, cost displays, feedback, and changes to the order forms, vary and are not well established (12).

In the ELMO study (Electronic Laboratory Medicine Ordering with evidence-based Order sets in primary care), researchers conducted a cluster randomized controlled

trial in Belgian primary practices, recruiting 280 GPs affiliated to laboratories who implemented a web-based Computerized Physician Order Entry (CPOE) for laboratory tests linked to the patient's electronic health record (13). The researchers designed evidence-based order sets for 17 indications as a CDSS, nudging the GP towards more evidence-based orders. Appropriateness in the ELMO study was defined as the relevance of the test for the indication or condition for which it was ordered. The order sets included multiple clinical presentations for specific indications like screening, diagnosis, or follow-up and were based on clinical practice guidelines developed by the Flemish College of Family Physicians (13). A test was considered inappropriate when a physician ordered tests not belonging to the above-mentioned evidence-based order sets for a given indication, or when they failed to include a crucial lab test for some indications, as described in the ELMO protocol (13). The intervention group ordered laboratory tests with a CPOE and integrated CDSS whereas the control group ordered laboratory tests as usual, through a CPOE. The primary outcome was defined as the proportion of appropriate tests over the total number of ordered tests and inappropriately not-requested tests. Results of the study have shown a reduction in quantity of requested laboratory testing with no difference in diagnostic error between groups (14). As a secondary outcome, downstream activities were measured. In this study, downstream diagnostic activities are defined as observed investigations following laboratory testing, which contribute to the diagnostic process and are therefore distinguished from therapeutic activities. They do not imply a causal relationship with the lab test per se, as opposed to cascades.

This paper elaborates on the occurrence of downstream diagnostic activities after initial laboratory testing in primary care patients by conducting a secondary data-

analysis on patients from the ELMO trial. More specifically, it aims to answer the following research questions.

Firstly, does the intervention (i.e., the use of an integrated CDSS) affect the number of patients undergoing downstream diagnostic activities (lab testing, imaging, referrals, and functional testing) within 6 months after initial blood testing?

Secondly, what is the association between the size of the laboratory panels and the occurrence of downstream diagnostic activities for patients in the control group (most relating to standard primary care)?

Thirdly, which specific laboratory tests (or clusters of related laboratory tests) are associated with patients undergoing downstream diagnostic activities in the control group (most relating to standard primary care).

Methods

In this study, a secondary analysis was conducted on data obtained in the ELMO trial, which measured downstream activities as a secondary outcome. The ELMO protocol defined downstream activities as the occurrence of at least one diagnostic activity within 6 months following the initial blood sample. They were registered as dichotomous variables (present or absent) and included four types of downstream activities: laboratory testing, imaging, referral, and functional testing (e.g., spirometry, electrocardiogram). In the ELMO study, physicians ordered laboratory tests for the following 17 indications: chronic kidney disease (CKD), type 2 diabetes mellitus, cardiovascular disease management, acute diarrhea, fatigue, hypertension, check-up, anemia, thyroid disease, liver disease, gout, rheumatoid arthritis, suspicion of

acute coronary syndrome (ACS), suspicion of lung embolism, chronic diarrhea, sexually transmitted infections (STI), and follow-up of medication (13).

The relevant data of the ELMO study, situated on the HealthData server and managed by Sciensano, was compiled into two new databases. Statistical analyses were conducted using SAS Enterprise Guide Software (Copyright © 2021 SAS Institute Inc.)

Some relevant features of the two datasets are listed below:

The first dataset regarding appropriateness of the laboratory tests in the ELMO study contained a total of 281,672 laboratory tests, 9,205 laboratory panels and 8,728 patients. During the extraction process from the HealthData server, not all patients from the ELMO study (9,683 patients; 10,270 lab panels) were included in this dataset, for reasons unknown. This dataset contained no information on downstream activities.

The second dataset, regarding downstream activities per patient in the ELMO study, contained a total of 10,270 laboratory panels and 9,683 patients, the same number of patients as in the ELMO study. The following dichotomous variables were relevant for our data-analysis: the occurrence of at least one downstream activity, laboratory testing, imaging, functional testing, and referral. The details of the data management can be found in the original ELMO protocol (13).

For the first research question, the second dataset (9,683 patients) was analyzed, using a Chi-square test to assess independence between two categorical variables: the study group (control or intervention) and the occurrence of at least one downstream activity (yes or no). Relative risk was used to estimate the effect size of the intervention, the use of an integrated CDSS, on the occurrence of downstream activities for six months after initial lab testing. Relative risks were calculated from

two-by-two tables using the formula $RR = \frac{a/(a+b)}{b/(b+d)}$, with the numerator indicating the proportion of intervention-arm patients undergoing downstream activities and the denominator indicating the proportion of control-arm patients undergoing downstream activities. This was applied to patients with at least one downstream activity as well as imaging, functional testing, referral, and downstream laboratory testing separately. The following null hypothesis was stated: there is no difference in the proportion of patients undergoing downstream activities between the intervention and control group. The significance level was set at 0.05.

To explore downstream activities in standard primary care (second and third research question), patients from the intervention group were excluded to avoid the confounding influence of a clinical decision support system.

To explore the association between lab panel size and downstream activities, the two datasets were merged to analyze lab panels for 4,192 patients from the control group of the ELMO study. In the case of multiple lab panels per patient, the first lab panel was selected during the data cleaning process. The difference in size of the lab panels was examined for control-arm patients with versus without at least one downstream activity. The same was done for imaging, referrals, functional testing, and laboratory testing separately.

Additionally, the difference was calculated between patients with at least one downstream activity and without for lab panels containing more than 10, 20 or 50 lab tests. The following null hypothesis was stated: there is no difference in the size of lab panels between patients with versus without downstream activities. The significance level was set at 0.05. As the distributions of laboratory panel size were not normally distributed, the Mann-Whitney *U* test was used for this analysis.

For the third research question, the laboratory tests were identified that accounted for 80% of the total number of tests in the ELMO study. Different laboratory clusters were formed from separate laboratory tests to bundle separate tests into clusters with a shared topic of interest. This was guided by the seventeen evidence-based laboratory panels used in the ELMO study (3). The clusters are listed in appendix A. Again, only patients from the control-arm of the ELMO study (N = 4,192 patients) were included to rule out the possible confounding influence of the CDSS in the intervention-arm. The Chi-square test was used to assess independence between two categorical variables: the presence of the lab test/cluster in the patient's lab panel (yes or no) and the occurrence of at least one downstream activity (yes or no). Downstream activities were measured during a 6-month follow-up period. The analysis for the third research question was done for laboratory testing, imaging, referrals, and functional testing separately. Relative risk was used as a measure for the effect size, with the numerator indicating the proportion of patients undergoing downstream activities for whom the lab test/cluster was included in at least one lab panel and the denominator the proportion of patients undergoing downstream activities for whom it was not included in a lab panel. The null hypothesis stated: there is no association between the presence of the lab test/cluster in at least one lab panel of a patient and downstream activities for patients in the control-arm. Again, the significance level was set at 0.05.

Results

Downstream activities in the ELMO study.

Patient demographics for all research questions are reported in appendix B.

Thousand, eight hundred thirty-five patients (19%) of the patients in the ELMO study underwent at least one downstream activity of which 13.8% a lab test, 6.3% a downstream referral, 2.4% downstream imaging and 0.7% a downstream functional test, during a 6-month follow-up period after initial lab testing. The two-by-two tables for the comparison of downstream activities (reported as at least one downstream activity, and separately for imaging, lab testing, referrals, and functional testing) between the control and intervention-arm of the ELMO study during a follow-up period of 6 months, are listed below (Tables 1-5). The Chi-square test of independence showed a statistically significant ($p < 0.05$) relationship between the two variables (study group and the occurrence of downstream activities) for the following downstream activities: at least one downstream activity ($p = 0.0290$), imaging ($p = 0.0047$), referrals ($p < 0.0001$) and functional testing ($p = 0.0102$). There was no significant relationship for downstream laboratory testing ($p = 0.5383$). The intervention group had 1.74% less patients [(95% CI {0.1759% – 3.3095%}); RR = 0.9123 (95% CI {0.8402 - 0.9906}); $p = 0.0290$] undergoing downstream activities than the control group. For downstream imaging, the difference amounted to 0.88% [(95% CI {0.2672% - 1.5105%}); RR = 0.6928 (95% CI {0.5364 – 0.8946}); $p = 0.0047$]. For referrals, the difference amounted to 2.19% [(95% CI {1.2172% - 3.1767%}); RR = 0.7066 (95% CI {0.6053 - 0.8248}); $p < 0.0001$], and for functional testing to 0.43% [(95% CI {0.0972% – 0.7880%}; RR = 0.5296 (95% CI {0.3233 - 0.8675}); $p = 0.0102$)]. For lab testing there was no significant difference observed ($p = 0.5383$).

Table 1	Downstream activities -	Downstream activities +	Total
Control group	3,653 (80.13%)	906 (19.87%)	4,559
Intervention group	4,195 (81.87%)	929 (18.13%)	5,124
Total	7,848	1,835	9,683

Columns indicate numbers (proportion) of patients without/with at least one downstream activity and total number of patients included. Rows indicate numbers (proportion) of patients of the control/intervention group and total number of patients.
(Chi-Square statistic = 4.7686; p = 0.0290)

Table 2	Downstream imaging -	Downstream imaging +	Total
Control group	4,428 (97.13%)	131 (2.87%)	4,559
Intervention group	5,022 (98.01%)	102 (1.99%)	5,124
Total	9,450	233	9,683

Columns indicate numbers (proportion) of patients without/with downstream imaging and total number of patients included. Rows indicate numbers (proportion) of patients of the control/intervention group and total number of patients.
(Chi-Square statistic = 8.0063; p = 0.0047)

Table 3	Downstream lab -	Downstream lab +	Total
Control group	3,939 (86.40%)	620 (13.60%)	4,559
Intervention group	4,405 (85.97%)	719 (14.03%)	5,124
Total	8,344	1,339	9,683

Columns indicate numbers (proportion) of patients without/with downstream laboratory testing and total number of patients included. Rows indicate numbers (proportion) of patients of the control/intervention group and total number of patients.
(Chi-Square statistic = 0.3788; p = 0.5383)

Table 4	Downstream referral -	Downstream referral +	Total
Control group	4,219 (92.54%)	340 (7.46%)	4,559
Intervention group	4,854 (94.73%)	270 (5.27%)	5,124
Total	9,073	610	9,683

Columns indicate numbers (proportion) of patients without/with downstream referral and total number of patients included. Rows indicate numbers (proportion) of patients of the control/intervention group and total number of patients.
(Chi-Square statistic = 19.5742; $p < 0.0001$)

Table 5	Downstream functional test -	Downstream functional test +	Total
Control group	4,517 (99.08%)	42 (0.92%)	4,559
Intervention group	5,099 (99.51%)	25 (0.49%)	5,124
Total	9,616	67	9,683

Columns indicate numbers (proportion) of patients without/with downstream functional test and total number of patients included. Rows indicate numbers (proportion) of patients of the control/intervention group and total number of patients.
(Chi-Square statistic = 6.5934; $p = 0.0102$)

Size of laboratory panels and downstream activities

A significant difference in mean laboratory panel size of approximately 7 lab tests was observed between patients from the control (N = 4,192) versus the intervention (N = 4,536) group (mean size = 34.60 lab tests ± 19.83 SD vs mean size = 27.58 lab tests ± 19.69 SD respectively; $p < 0.0001$).

Figure 1 (appendix D) shows the distribution of lab panel size per patient of the control-arm with (N = 844) versus without (N = 3,348) at least one downstream activity.

In the control group, no difference in mean lab panel size was observed between

patients with versus without at least one downstream activity (mean size = 33.50 lab tests ± 18.6 SD vs mean size = 34.87 lab tests ± 20.12 SD respectively; p = 0.1789). No significant difference was observed when excluding lab panels with less than 10 (p = 0.0529), 20 (p = 0.2867) or 50 (p = 0.9587) laboratory tests. Analysis per type of downstream activity showed similar results: downstream lab testing (p = 0.0640), referrals (p = 0.2879), functional testing (p = 0.3119) or imaging (p = 0.1944).

Laboratory tests (clusters) and downstream activities.

Appendix C lists the laboratory tests that encompassed approximately 80% of the total number of tests requested in the ELMO study. These were used to study the relationship between the most common lab tests/clusters (appendix A) and downstream activities. As such, lab panels with and without this test/cluster were compared for 4,192 patients in the control-arm, during the 6-month follow-up period. The two-by-two tables for downstream imaging, lab testing, referrals and functional testing are listed in appendix E. Using the Chi-square test of independence, we observed a significant association ($p < 0,05$) between some individual laboratory tests/clusters and the occurrence of downstream activities: Cholesterol and downstream imaging (RR = 0.6105; 95% CI {0.4314 - 0.8641}; p = 0.0050), Glycemia and downstream imaging (RR = 0.6532; 95% CI {0.4551 - 0.9376}; p = 0.0203), Liver and downstream imaging (RR = 1.8787; 95% CI {1.1808 - 2.9891}; p = 0.0066), CRP and downstream imaging (RR = 1.8529; 95% CI {1.2778 - 2.6869}; p = 0.0009) , ESR and downstream imaging (RR=1.6182; 95% CI {1.1437 - 2.2894}; p = 0.0061), D-dimer and downstream imaging (RR = 8.6364; 95% CI {3.1911 - 23.3731}; p < 0.0001) , ESR and downstream laboratory testing (RR = 1.1677; 95% CI {1.0030 - 1.3596}; p

= 0.0459), troponin and downstream referral (RR = 2.9162; 95% CI {1.7811 - 4.7745}; p < 0.0001) and troponin and downstream functional testing (RR = 8.3475; 95% CI {3.0528 - 22.8253}; p < 0.0001).

Discussion

With this paper we aimed to contribute to the current evidence on downstream activities after laboratory testing in primary care.

We found a small but significant reduction in the proportion of patients undergoing at least one downstream activity in the intervention group compared to the control group (p = 0.0290), 6 months after the initial lab test. This reduction was found for downstream medical imaging (p = 0.0047), referrals (p < 0.0001), and functional testing (p = 0.0102). However, for downstream laboratory testing, no such significant difference (p = 0.5383) was demonstrated. A possible explanation could be that there could be more reflex testing when fewer lab tests are initially requested. A clinical decision support system might help to reduce the volume of downstream diagnostic activities, and, more specifically, of downstream medical imaging, referrals, and functional testing.

In the ELMO study, the average size of laboratory panels was significantly smaller (with a difference of 7 lab tests) in the intervention group versus the control group, which we confirmed in our data-analysis (N = 8,728). The mean size of a lab panel per patient was 34.6 lab tests in the control group versus 27.6 lab tests in the intervention group (p < 0,0001). We observed no association between the size of the laboratory panels and the occurrence of downstream activities in 4,192 patients of the control group: at least one downstream activity (p = 0.1789), lab testing (p = 0.0640), referrals

(p = 0.2879), functional testing (p = 0.3119) and imaging (p = 0.1944). No significant difference was observed when excluding lab panels with less than 10 (p = 0.0529), 20 (p = 0.2867) or 50 (p = 0.9587) laboratory tests. Given that the size of the laboratory panels did not seem to be associated with the occurrence of downstream activities, the data suggest that the size of lab panels might not be a reliable predictor for downstream diagnostic activities in standard primary care.

We studied the association between laboratory tests/clusters in patients' lab panels, and the occurrence of downstream imaging, laboratory testing, referrals, and functional testing for 4,192 patients in the control group of the ELMO study, covering approximately 80% of the most requested lab tests/clusters (appendix C). For patients with liver-related lab tests, CRP, ESR and D-dimer in at least one lab panel, we observed a greater rate of downstream imaging (p = 0.0066, p = 0.0009, p = 0.0061, p < 0.0001 respectively). For patients with troponin in at least one lab panel, we observed a greater rate of downstream referral (p < 0.0001) and functional testing (p < 0.0001). For patients with ESR in at least one lab panel, a higher rate of downstream lab testing was observed (p = 0.0459). However, the absolute volume of tests of troponin and D-dimer was limited. For frequently requested tests such as liver-related lab tests, CRP or ESR, a high volume of downstream activities may pose a burden on health care if used inappropriately. This was studied in a British prospective cohort study, which showed that inflammatory markers as a rule-out test for cancer, infection or auto-immune disease in primary care may generate false positives and lead to an increased rate of lab tests, GP consultations and referrals (8).

To conclude, this research has some important limitations. Our study only observed associations between variables, and no causal relations could be studied. Therefore, the exploration of cascades (as a causal chain of events) in primary care was beyond the scope of this research. Downstream activities were measured as a secondary endpoint in the ELMO study and were registered per patient and not per specific laboratory test, making it impossible to identify the specific laboratory tests/clusters that might have triggered the downstream activity of a patient. Furthermore, there was no information in our datasets on the timing and the frequency of downstream activities for a given patient because the downstream variables were coded as dichotomous variables.

The results of the possible associations between certain lab tests and downstream testing should be interpreted with caution. An important confounder could be that downstream testing might (partly) be triggered by the indication for which the lab tests were ordered, and not by the result of the lab test itself. Likewise, the decision to perform downstream diagnostic testing might have been taken independently of the initial test results. For example, abdominal pain might trigger ultrasound testing, regardless of the results of inflammatory markers in the initial lab test. Our data did not include any information about the decision-making process or results of the lab tests, nor did the databases contain information on the diagnostic outcome.

In our study, we analyzed patients from the ELMO study, where seventeen indications in primary care were studied. Therefore, we cannot extend our results to other indications in primary care. Furthermore, we only conducted descriptive statistics on the data of the ELMO trial. To extrapolate our results to primary care, further inferential statistical analyses are necessary.

We suggest future studies to explore true cascade activities, more specifically, causal relationships between the initial test and downstream activities. Downstream activities could be studied as a primary endpoint. To determine causal relationships between lab tests and downstream activities, a questionnaire for the requesting physician to identify lab results that triggered downstream activities, could be used. To assess the clinical implications of downstream activities, the (change in) diagnostic outcome should be studied as well. Because we identified a significant association between the presence of some frequently requested lab tests (inflammatory markers and liver tests) in lab panels and downstream activities, we suggest future research to further explore the relationship between these lab tests and downstream activities.

Conclusion

This research shows only a small but significant reduction in the proportion of patients undergoing at least one downstream diagnostic activity in the intervention group compared to the control group of the ELMO study, during a 6-month period after initial blood testing. This reduction was found for imaging, functional testing, and referrals, but not for laboratory testing. A clinical decision support system might help to reduce downstream diagnostic activities in primary care. The size of lab panels does not seem to be a reliable predictor for downstream activities. We identified a significant association between the presence of certain frequently requested lab tests (inflammatory markers and liver tests) in lab panels and downstream activities, which could be interesting to explore in future research.

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Appendix

A. Laboratory clusters

Hemoglobin

"Hematocrit (blood)" , "Hemoglobin (blood)" , "Mean corpuscular hemoglobin (erythrocytes)" , "Mean corpuscular hemoglobin concentration (erythrocytes)", "Mean corpuscular volume (erythrocytes)", "Erythrocyte distribution width (erythrocytes)" , "Erythrocytes (blood)", "Erythrocyte morphology - in Blood by automated count", "Erythrocyte morphology - light microscopy", "Erythrocyte morphology: anisocytosis (blood) - light microscopy", "Erythrocyte morphology: poikilocytosis (blood) - light microscopy"

Leucocytes

"Leukocytes (blood) - in #/volume - automated count", "White blood cell differentiation: Basophils (blood) - in %", "White blood cell differentiation: Basophils (blood) - in #/volume", "White blood cell differentiation: Basophils (blood) - in % - automated count" ,"White blood cell differentiation: Basophils (blood) - in #/volume - automated count", "White blood cell differentiation: Eosinophils (blood) - in #/volume","White blood cell differentiation: Eosinophils (blood) - in %", "White blood cell differentiation: Eosinophils (blood) - in #/volume - “automated count", "White blood cell differentiation: Eosinophils (blood) - in % - automated count", "White blood cell differentiation: Lymphocytes (blood) - in #/volume", "White blood cell differentiation: Lymphocytes (blood) - in %","White blood cell differentiation: Lymphocytes

(blood) - in % - automated count", "White blood cell differentiation: Lymphocytes (blood) - in #/volume - automated count", "White blood cell differentiation: Monocytes (blood) - in #/volume", "White blood cell differentiation: Monocytes (blood) - in %", "White blood cell differentiation: Monocytes (blood) - in % - automated count", "White blood cell differentiation: Monocytes (blood) - in #/volume - automated", "White blood cell differentiation: Neutrophils segmented (blood) - in %", "White blood cell differentiation: Neutrophils segmented (blood) - in #", "White blood cell differentiation: Neutrophils segmented (blood) - in %- automated count" ,"White blood cell differentiation: Neutrophils segmented (blood) - in #/volume - automated count", "White blood cell differentiation: Myelocytes (blood) - in %", "White blood cell differentiation: Promyelocytes (blood) - in %", "White blood cell differentiation: Blasts (blood) - in %", "White blood cell differentiation: Metamyelocytes (blood) - in #/volume", "White blood cell differentiation: Metamyelocytes (blood) - in %", "White blood cell differentiation: Lymphocytes (blood) - in % - automated count", "White blood cell differentiation: neutrophils segmented (blood) - in %", "White blood cell differentiation: Eosinophils (blood) - in #/volume - automated count", "White blood cell differentiation: Neutrophils segmented (blood) - in %", "White blood cell differentiation: Neutrophils segmented (blood) - in #", "White blood cell differentiation: Neutrophils (blood) - in #/volume", "White blood cell differentiation: Neutrophils (blood) - in #/volume - automated count"

Liver

"Gamma glutamyl transferase (serum/plasma) [U/L]", "Aspartate aminotransferase (serum/plasma) [U/L]", "Alanine aminotransferase (serum/plasma) [U/L]", "Alkaline phosphatase (serum/plasma) [U/L]", "Bilirubin conjugated (serum/plasma) [mg/dL]", "Bilirubin total (serum/plasma) [mg/dL]", "Bilirubin unconjugated (serum/plasma) [mg/dL]", "Amylase (serum/plasma) [U/L]", "Lipase (serum/plasma)"

Coagulation

"Quick Prothrombin time (platelet poor plasma) - in %", "Quick Prothrombin time (platelet poor plasma) - in INR", "Coagulation tissue factor induced INR"

Glycemia

"Glucose - 60min post 50g challenge (serum/plasma) [mg/dL]", "Glucose – fasted (serum/plasma) [mg/dL]", "Glucose (serum/plasma) [mg/dL]", "Glucose 2 hours post meal (serum/plasma) [mg/dL]", "Glucose post meal (serum/plasma) [mg/dL]", "Hemoglobin A1c (blood) - in %", "Hemoglobin A1c (blood) - in mmol/mol - IFCC protocol

D-dimer

D-dimer (platelet poor plasma) - in mass/volume FEU

Troponin

"Troponin I (serum/plasma)", "Troponin T (serum/plasma)"

Thyroid

"Thyroid Stimulating Hormone (serum/plasma)", "Thyroxine free (serum/plasma) - in mass/volume", "Thyroxine free (serum/plasma) - in moles/volume [pmol/L]", "Triiodothyronine free (serum/plasma) - in moles/volume [pmol/L]", "Thyroid Stimulating Hormone (serum/plasma)"

Cholesterol

"High density lipoprotein cholesterol (serum/plasma) - [mg/dL]", "Cholesterol (serum/plasma) - [mg/dL]", "non-High density lipoprotein cholesterol (serum/plasma)", "Cholesterol total/Cholesterol in HDL", "Low density lipoprotein cholesterol (serum/plasma) - measured", "Triglyceride (serum/plasma) [mg/dL]", "Low density lipoprotein cholesterol (serum/plasma) - [mg/dL] – calculated", "Cholesterol.total/Cholesterol.in HDL", "Low density lipoprotein cholesterol (serum/plasma) - [mg/dL] - calculated"

Kidney

"Estimated glomerular filtration rate - CKD-EPI", "Estimated glomerular filtration rate - MDRD", "Creatinine (serum/plasma) [mg/dL]"

B. Patient demographics

Research question 1

	Control	Intervention	P-value of difference
Mean Age (years)	54.34 (SD 17.61)	58.33 (SD 17.04)	$p < 0.05$
Female sex (absolute number/ proportion)	2578 (56%)	2774 (54%)	$p = 0.018$

Patient demographics for patients included in research question 1. Columns indicate study groups and p-value of difference when comparing study groups.
Rows indicate variables of interest: mean age and patients with female sex.

Research questions 2-3

	Control	Intervention	P-value of difference
Age (years)	54.04 (SD 17.61)	58.15 (SD 17.04)	$p < 0.001$
Female Sex (absolute number/proportion)	2356 (56.2%)	2440 (53.8%)	$p = 0.024$

Patient demographics for patients included in research question 2 and 3. Columns indicate study groups and p-value of difference when comparing study groups.
Rows indicate variables of interest: mean age and patients with female sex.

C. <u>Frequency of tests</u>

Lab test	Frequency	Percentage (%)	Cumulative percentage (%)
Leucocytes*	58697	20,86	20,86
Hemoglobin*	47444	16,86	37,72
Cholesterol*	37452	13,31	51,02
Liver*	19862	7,06	58,08
Kidney*	18517	6,58	64,66
Glycaemia*	13653	4,85	69,51
Thyroid*	8541	3,03	72,55
CRP	4853	1,72	76,34
Potassium	4424	1,57	77,91
Ferritin	3927	1,40	79,31
Sodium	3730	1,33	80,63
ESR	3577	1,27	81,90

Frequency table of lab tests in the ELMO study. Rows indicating the lab test or cluster* included in the ELMO trial, with columns indicating the frequency in absolute numbers, as a percentage of total tests (N = 2,814,27) and the cumulative percentages.

D. Distribution of lab panel sizes

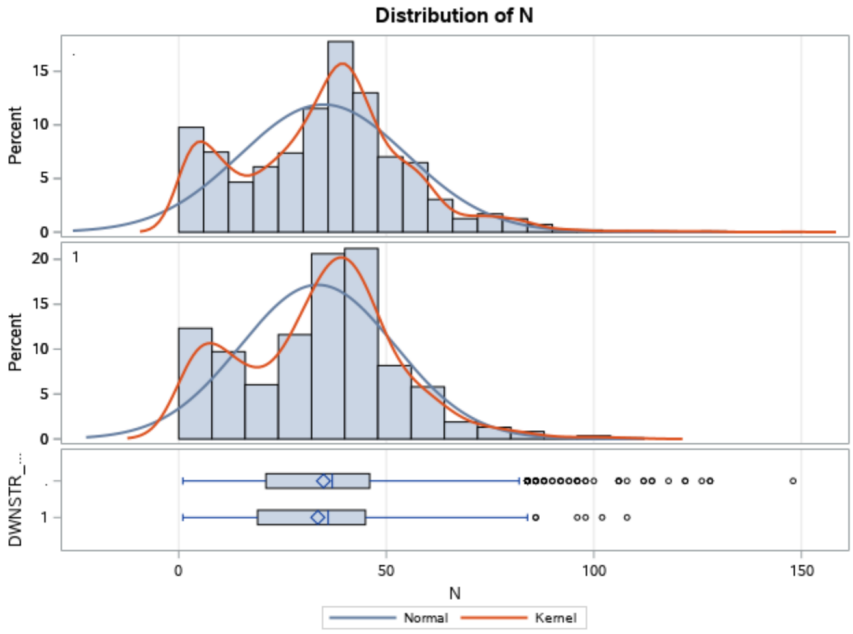


Figure 1: distribution of size of lab panels (= N), comparison between control-arm patients without (.) (top) and with (1) (bottom) downstream activities.

E. Lab tests/clusters versus downstream activities for 4,192 patients in the control-arm of the ELMO study: 2x2-tables

Two-by-two tables for downstream imaging

Lab test (cluster*)	**Lab test included in at least one lab panel?**	**Patients without downstream imaging**	**Patients with downstream imaging**	**Total**
Leucocytes*	no	756	17	773
	yes	3312	107	3419
χ^2 = 1.9010 (p = 0.1680)	Total	4068	124	4192
Hemoglobin*	no	740	15	755
	yes	3328	109	3437
χ^2 = 3.0262 (p = 0.0819)	Total	4068	124	4192

Cholesterol*	no	1376	57	1433
	yes	2692	67	2759
χ^2 = 7.8861 (p = 0.0050)	Total	4068	124	4192
Liver*	no	1140	21	1161
	yes	2928	103	3031
χ^2 = 7.3879 (p = 0.0066)	Total	4068	124	4192
Kidney*	no	981	27	1008
	yes	3087	97	3184
χ^2 = 0.3610 (p = 0.5479)	Total	4068	124	4192
Glycemia*	no	1064	44	1108
	yes	3004	80	3084
χ^2 = 5.3851 (p = 0.0203)	Total	4068	124	4192
Thyroid*	no	1312	43	1355
	yes	2756	81	2837
χ^2 = 0.3237 (p = 0.5694)	Total	4068	124	4192
CRP	no	1925	40	1965
	yes	2143	84	2227
χ^2 = 10.9631 (p = 0.0009)	Total	4068	124	4192
Potassium	no	2113	68	2181
	yes	1955	56	2011
χ^2 = 0.4045 (p = 0.5247)	Total	4068	124	4192
Sodium	no	2173	65	2238
	yes	1895	59	1954

χ^2 = 0.0481 (p = 0.8264)	Total	4068	124	4192
ESR	no	2435	59	2494
	yes	1633	65	1698
χ^2 = 7.5259 (p = 0.0061)	Total	4068	124	4192
INR	no	3939	119	4058
	yes	129	5	134
χ^2 = 0.2884 (p = 0.5913)	Total	4068	124	4192
Troponin	no	4010	122	4132
	yes	58	2	60
χ^2 = 0.0299 (p = 0.8628)	Total	4068	124	4192
D-dimer	no	4059	121	4180
	yes	9	3	12
χ^2 = 20.3689 (p < 0.0001)	Total	4068	124	4192
Platelets	no	1433	34	1467
	yes	2635	90	2725
χ^2 = 3.2238 (p = 0.0726)	Total	4068	124	4192

Two-by-two tables for downstream imaging with rows indicating the specific lab tests or clusters* and columns indicating the presence (yes or no) of the lab test or cluster* in at least one lab panel, the number of patients without downstream imaging, the number of patients with downstream imaging and the total number of patients. P-values of Chi-square statistic are included.

Two-by-two tables for downstream lab testing

Lab test (cluster*)	Lab test in at least one lab panel?	Patients without downstream lab testing	Patients with downstream lab testing	Total
Leucocytes*	no	677	96	773
	yes	2937	482	3419
χ^2 = 1.4943 (p = 0.2215)	Total	3614	578	4192
Hemoglobin*	no	645	110	755
	yes	2969	468	3437
χ^2 = 0.4730 (p = 0.4916)	Total	3614	578	4192
Cholesterol*	no	1221	212	1433
	yes	2393	366	2759
χ^2 = 1.8536 (p = 0.1734)	Total	3614	578	4192
Liver*	no	984	177	1161
	yes	2630	401	3031
χ^2 = 2.8688 (p = 0.0903)	Total	3614	578	4192
Kidney*	no	875	133	1008
	yes	2739	445	3184
χ^2 = 0.3936 (p = 0.5304)	Total	3614	578	4192
Glycemia*	no	959	149	1108
	yes	2655	429	3084
χ^2 = 0.1469 (p = 0.7015)	Total	3614	578	4192
Thyroid*	no	1158	197	1355
	yes	2456	381	2837

χ^2 = 0.9489 (p = 0.3300)	Total	3614	578	4192
CRP	no	1688	277	1965
	yes	1926	301	2227
χ^2 = 0.2962 (p = 0.5863)	Total	3614	578	4192
Potassium	no	1873	308	2181
	yes	1741	270	2011
χ^2 = 0.4261 (p = 0.5139)	Total	3614	578	4192
Sodium	no	1916	322	2238
	yes	1698	256	1954
χ^2 = 1.4525 (p = 0.2281)	Total	3614	578	4192
ESR	no	2172	322	2494
	yes	1442	256	1698
χ^2 = 3.9855 (p = 0.0459)	Total	3614	578	4192
INR*	no	3504	554	4058
	yes	110	24	134
χ^2 = 1.9789 (p = 0.1595)	Total	3614	578	4192
Troponin	no	3561	571	4132
	yes	53	7	60
χ^2 = 0.2305 (p = 0.6312)	Total	3614	578	4192
D-dimer	no	3605	575	4180
	yes	9	3	12
χ^2 =1.2726 (p = 0.2593)	Total	3614	578	4192
Platelets	no	1264	203	1467

	yes	2350	375	2725
χ^2 = 0.0047 (p = 0.9455)	Total	3614	578	4192

Two-by-two tables for downstream lab testing with rows indicating the specific lab tests or clusters* and columns indicating the presence (yes or no) of the lab test or cluster* in at least one lab panel, the number of patients without downstream lab testing, the number of patients with downstream lab testing and the total number of patients. P-values of Chi-square statistics are included.

Two-by-two tables for downstream referrals.

Lab test (cluster*)	**Lab test in at least one lab panel?**	**Patients without downstream referral**	**Patients with downstream referral**	**Total**
Leucocytes*	no	726	47	773
	yes	3146	273	3419
χ^2 = 3.2435 (p = 0.0717)	Total	3872	320	4192
Hemoglobin*	no	709	46	755
	yes	3163	274	3437
χ^2 = 3.1008 (p = 0.0783)	Total	3872	320	4192
Cholesterol*	no	1315	118	1433
	yes	2557	202	2759
χ^2 = 1.1150 (p = 0.2910)	Total	3872	320	4192
Liver*	no	1072	89	1161
	yes	2800	231	3031
χ^2 = 0.0024 (p = 0.9612)	Total	3872	320	4192
Kidney*	no	936	72	1008

	yes	2936	248	3184
χ^2 = 0.4533 (p = 0.5008)	Total	3872	320	4192
Glycemia*	no	1025	83	1108
	yes	2847	237	3084
χ^2 = 0.0434 (p = 0.8349)	Total	3872	320	4192
Thyroid*	no	1251	104	1355
	yes	2621	216	2837
χ^2 = 0.0049 (p = 0.9440)	Total	3872	320	4192
CRP	no	1820	145	1965
	yes	2052	175	2227
χ^2 = 0.3397 (p = 0.5600)	Total	3872	320	4192
Potassium	no	2009	172	2181
	yes	1863	148	2011
χ^2 = 0.4118 (p = 0.5211)	Total	3872	320	4192
Sodium	no	2064	174	2238
	yes	1808	146	1954
χ^2 = 0.1358 (p = 0.7125)	Total	3872	320	4192
ESR	no	2318	176	2494
	yes	1554	144	1698
χ^2 = 2.9038 (p = 0.0884)	Total	3872	320	4192
INR*	no	3748	310	4058
	yes	124	10	134
χ^2 = 0.0057 (p = 0.9396)	Total	3872	320	4192

Troponin	no	3825	307	4132
	yes	47	13	60
χ^2 = 17.0010(p < 0.0001)	Total	3872	320	4192
D-dimer	no	3861	319	4180
	yes	11	1	12
χ^2 = 0.0084 (p = 0.9272)	Total	3872	320	4192
Platelets	no	1369	98	1467
	yes	2503	222	2725
χ^2 = 2.9086 (p = 0.0881)	Total	3872	320	4192

Two-by-two tables for downstream referrals with rows indicating the specific lab tests or clusters* and columns indicating the presence (yes or no) of the lab test or cluster* in at least one lab panel, the number of patients without downstream referrals, the number of patients with downstream referrals and the total number of patients. P-values of Chi-square statistics are included.

Two-by-two tables for functional tests.

Lab test (cluster*)	**Lab test in at least one lab panel?**	**Patients without downstream activity**	**Patients with downstream activity**	**Total**
Leucocytes*	no	770	3	773
	yes	3385	34	3419
χ^2 = 2.6495 (p = 0.1036)	Total	4155	37	4192
Hemoglobin*	no	752	3	755
	yes	3403	34	3437
χ^2 = 2.4788 (p = 0.1154)	Total	4155	37	4192

Cholesterol*	no	1423	10	1433
	yes	2732	27	2759
χ^2 = 0.8499 (p = 0.3566)	Total	4155	37	4192
Liver*	no	1152	9	1161
	yes	3003	28	3031
χ^2 = 0.2119 (p = 0.6453)	Total	4155	37	4192
Kidney*	no	1004	4	1008
	yes	3151	33	3184
χ^2= 3.5802 (p = 0.0585)	Total	4155	37	4192
Glycemia*	no	1102	6	1108
	yes	3053	31	3084
χ^2 = 2.0032 (p = 0.1570)	Total	4155	37	4192
Thyroid*	no	1344	11	1355
	yes	2811	26	2837
χ^2 = 0.1148 (p = 0.7347)	Total	4155	37	4192
CRP	no	1950	15	1965
	yes	2205	22	2227
χ^2 = 0.6015 (p = 0.4380)	Total	4155	37	4192
Potassium	no	2167	14	2181
	yes	1988	23	2011
χ^2 = 3.0115 (p = 0.0827)	Total	4155	37	4192
Sodium	no	2223	15	2238
	yes	1932	22	1954

χ^2= 2.4757 (p = 0.1156)	Total	4155	37	4192
ESR	no	2474	20	2494
	yes	1681	17	1698
χ^2 = 0.4585 (p = 0.4983)	Total	4155	37	4192
INR*	no	4023	35	4058
	yes	132	2	134
χ^2 = 0.5886 (p = 0.4430)	Total	4155	37	4192
Troponin	no	4099	33	4132
	yes	56	4	60
χ^2 = 23.2779 (p < 0.0001)	Total	4155	37	4192
D-dimer	no	4143	37	4180
	yes	12	0	12
χ^2 = 0.1072 (p = 0.7434)	Total	4155	37	4192
Platelets	no	1456	11	1467
	yes	2699	26	2725
χ^2 = 0.4550 (p = 0.5000)	Total	4155	37	4192

Two-by-two tables for downstream functional testing with rows indicating the specific lab tests or clusters* and columns indicating the presence (yes or no) of the lab test or cluster* in at least one lab panel, the number of patients without downstream functional testing, the number of patients with downstream functional testing and the total number of patients. P-values of Chi-square statistics are included.

Personal reflection (persoonlijk reflectieverslag)

In de eerste fase van de master-na-master huisartsgeneeskunde werd ons gevraagd een onderwerp te kiezen voor de masterthesis. Zoals vele andere ambitieuze HAIO's, wilde ik graag een paper schrijven die een bijdrage zou kunnen leveren aan de gezondheidszorg of de bredere maatschappij. Tussen de verschillende mogelijkheden sprak het onderwerp van de ELMO studie me het meest aan om verschillende redenen. Enerzijds vond ik het interessant om verder te kunnen werken aan een grote studie die al veel data had verzameld over het aanvragen van labotesten bij meer dan 70 huisartsenpraktijken in België. Dit maakte het namelijk mogelijk om meteen aan de slag te kunnen gaan om relevante en wetenschappelijk onderbouwde uitspraken te kunnen doen over het aanvraaggedrag van labotesten bij huisartsen. Daarnaast hoopte ik dat het uitvoeren van dit onderzoek ook een actieve investering zou zijn in mijn ontwikkelingsproces als HAIO, niet alleen door het uitvoeren van statistische analyses en het schrijven van een wetenschappelijk artikel, maar ook door op een kritische manier te evalueren hoe we binnen onze dagelijkse praktijk omspringen met de middelen die ons voorhanden zijn. Ik was dan ook zeer tevreden wanneer ik bevestiging kreeg dat ik aan deze masterproef kon beginnen werken.

Tijdens de eerste kennismaking met mijn promotor, Prof. Dr. Geert Goderis, en co-promotor, Dr. Nicolas Delvaux, bespraken we samen het potentieel voor een secundaire analyse op de ELMO studie, en kwamen we overeen om de onderzoeksvraag voor mijn masterproef te formuleren rond het bestuderen van vervolgonderzoeken na labotesten in de ELMO studie. Het was echter een verrassing dat nog een andere HAIO, Thomas Vandekerckhove, ook in dit onderwerp geïnteresseerd was. Thomas en ik hadden elkaar nog niet ontmoet omdat we van

verschillende universiteiten kwamen, maar onze samenwerking is zeker en vast een meerwaarde gebleken voor dit onderzoek. Dit zette echter wel meteen de tijdlijn op scherp, omdat Thomas een half jaar vroeger zou afstuderen en de masterproef daardoor ook vroeger klaar zou moeten zijn.

Aangezien ik binnen de zesjarige opleiding als masterproef een 'systematic review' had geschreven en ter publicatie ingediend, lag mijn ervaring aan het begin van dit proces vooral in het doorzoeken en kritisch evalueren van literatuur. Deze ervaring kon ik dan ook inzetten bij de literatuurstudie die we voor deze masterproef moesten uitvoeren. Nadien maakten we aan de hand van een e-learning traject kennis met het statistische programma dat we zouden gebruiken om de data uit de ELMO studie verwerken. Thomas bleek het meest behendig in het opstellen van de code voor de statistische analyses, waardoor we de afspraak maakten dat hij hiervoor de eindverantwoordelijkheid zou krijgen. Mijn persoonlijke aandeel zou vervolgens voornamelijk liggen in de opbouw van de tekst, het verwerken van de resultaten in tabellen en het uitschrijven van onze voornaamste bevindingen. Daarbij zorgde ik ook voor de vormelijke aspecten van de tekst zoals lay-out en referenties. We planden regelmatig een vergadering via videoconferentie om samen de analyses te overlopen en de resultaten te bekijken om op die manier terug te kunnen koppelen naar onze doelstellingen.

Een van de uitdagingen binnen de samenwerking aan een gemeenschappelijke masterproef, schuilde onder meer in het maken van een goede taakverdeling. Aan het begin hebben we aan den lijve ondervonden dat er regelmatig dubbel werk gebeurt wanneer deze taakverdeling niet duidelijk is opgemaakt. Er kruipt bovendien ook veel werk in het reviseren en vervolledigen van de tekst, omdat er twee partijen zijn die

overeen moeten komen over hoe de masterproef uiteindelijk vorm krijgt. Daarnaast hebben de uitzonderlijke omstandigheden van deze COVID-pandemie ervoor gezorgd dat al deze overlegmomenten volledig digitaal zijn verlopen, wat we ons aan het begin van deze opleiding niet hadden kunnen inbeelden. Toch hebben we zoveel mogelijk geprobeerd om live samen te zitten, via videoconferentie weliswaar, zodat we op een persoonlijke manier elkaars voortgang konden bespreken. Hierin schuilde namelijk het grootste voordeel van een gemeenschappelijke masterproef, de kans om samen het resultaat in vraag te stellen en elkaar kritische maar opbouwende feedback te geven. Dit heeft ervoor gezorgd dat we gedurende het ganse proces ook veel van elkaar konden bijleren. Het schrijven van onze masterproef is dan ook grotendeels vlot verlopen. Bij de bespreking van onze eerste – uiteindelijk niet zo finaal blijkende – versie kregen we nog enkele belangrijke opmerkingen te verwerken over de manier waarop we onze gegevens hadden verwerkt en de conclusies die we hieruit hadden getrokken. Dit heeft ons nog voor een intense eindsprint gezet, maar is de kwaliteit van het resultaat alleen maar ten goede gekomen.

Tenslotte rest er mij nog samen te vatten wat deze masterproef betekent voor mezelf en het werkveld. Wanneer ik terugkijk naar de verwachtingen die ik vooropgesteld had voor deze masterproef, zijn deze naar mijn mening grotendeels ingevuld. Hoewel onze studie enkele beperkingen heeft, zijn we er toch in geslaagd relevante verbanden in het aanvraaggedrag van labotesten bij huisartsen te identificeren en suggesties te doen waar toekomstig onderzoek zich verder in kan verdiepen. Daarnaast heeft het veel aan het licht gebracht over de manier waarop we als arts functioneren. Ik heb meer aandacht gekregen voor de complexiteit van het diagnostische proces en de implicaties die ons medisch handelen kunnen hebben in naloop van een ogenschijnlijk

triviale labotest. Bovendien bevestigt deze reflectie dat ik door het maken van deze masterproef binnen verschillende CANMEDS-rollen vooruitgang heb geboekt. Het meest voor de hand liggend is de rol van wetenschapper die we hebben opgenomen binnen een context van nauwe samenwerking aan een gemeenschappelijke onderzoeksvraag. Waar voor mij het potentieel van deze studie echter voornamelijk in schuilt, is de poging tot gezondheidsbevordering. Hierbij gaat het om trouw blijven aan de eed van Hippocrates door eerst en vooral niet kwaad te doen, en daar bovenop net een verbetering teweeg te brengen en het rationeel gebruik van middelen binnen de gezondheidszorg aan te moedigen. Dit mooie resultaat geeft dan ook een motivatie om te blijven inzetten op die cruciale rollen als arts gedurende de rest van mijn carrière.

Graag zou ik als afsluiter nog enkele dankwoorden willen uitspreken.

Aan onze promotor, Prof. Dr. Geert Goderis, die onze studie met zijn kritische blik op de proef durfde te stellen en nuance bracht in het besluit.

Aan onze co-promotor, Dr. Nicolas Delvaux, die ons wegwijs heeft gemaakt in de data en de doelstellingen van onze masterproef mee heeft vormgegeven.

Aan Thomas, die zijn rug onder dit project heeft gezet en het proces van deze masterproef aangenamer heeft gemaakt.

Tenslotte, aan de steunfiguren uit mijn omgeving die me hebben aangemoedigd om dit project tot een goed einde te brengen.

Hartelijk dank,

An-Marie