Over- and underutilization of laboratory tests on common indications in primary care

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Abstract

(Nederlands)

INLEIDING: Het ongepast gebruik van laboratoriumtesten heeft een belangrijke impact op de kwaliteit-, patientveiligheid en de kost van de gezondheidszorg. Desalniettemin zijn er tot op heden weinig studies die het (on)gepast gebruik van laboratoriumtesten in de eerste lijn systematisch in kaart brengen.

DATA: Deze studie is een retrospectief onderzoek van de dataset van de ELMO-studie, waarin 4370 bloednames getrokken voor 17 indicaties door Vlaamse huisartsen, verzameld werden.

METHODE: Voor iedere indicatie hebben we het over- en ondergebruik van specifieke testen geanalyseerd. Overgebruik werd gedefinieerd als het aanvragen van een niet-geïndiceerde test; ondergebruik als het niet aanvragen van een geïndiceerde test.

RESULTATEN: De tien meest frequent, ongepast aangevraagde indicaties waren algemene check-up , cardiovasculair risico, arteriële hypertensie (AHT), chronische nierinsufficiëntie (CNI), type 2 diabetes mellitus (T2DM), seksueel overdraagbare aandoeningen, vermoeidheid, schildklieraandoeningen, geneesmiddelen follow-up en anemie. Het gemiddelde overgebruiks-percentage was 51.3 % (SD 11.2). Testen die werden overgebruikt op meer dan 25% van alle bloednames: RBC+hct, hemoglobine, WBC, bloedplaatjes; CRP en ESR; serum-creatinine, ureum en urinezuur; natrium en kalium; ALT, AST, GGT en ALP; vitamine D, foliumzuur en B12. Deze testen werden echter ook frequent aangevraagd op hun respectievelijke, gepaste indicaties. Testen voor de complicaties van CNI (PTH en fosfaat), AHT en T2DM (proteïnurie) werden op minder dan 25% en 10% van de respectievelijke stalen aangevraagd.

CONCLUSIE: De frequent overgebruikte testen werden regelmatig door huisartsen aangevraagd, ongeacht of ze gepast waren voor de onderliggende indicatie. Het veralgemeend gebruik van testen moet verminderd en voorbehouden worden voor de strikte onderliggende indicaties. Anderzijds moet het aanvragen van ondergebruikte testen verbeterd worden.

Abstract

(English)

INTRODUCTION: Inappropriate test ordering has an important impact on the quality, patient-safety and cost of healthcare. However, systematic evaluation of (in)appropriate test ordering across prevalent indications in primary care is understudied.

DATA: We retrospectively analyzed the database of the control-group of the ELMO-study, which contained 4370 blood samples drawn for 17 indications by GP's in Flanders (Belgium).

METHODS: For every indication, we analyzed the over- and underutilization rate of specific tests. Overutilization was defined as ordering a non-indicated tests; and underutilization as not ordering an indicated test.

RESULTS: Inappropriate test-ordering most frequently occurred for general check-up, cardiovascular risk management, arterial hypertension (AHT), chronic kidney diseases (CKD), Type 2 diabetes mellitus (T2DM), sexually transmittable infections, fatigue, thyroid dysfunction, medication follow-up and anaemia, at an average overutilization-rate of 51.3% (SD 11.2). Tests overutilized on more than 25% of the panels overall, were: RBC+hct, hemoglobin, WBC, platelets; CRP and ESR; serum-creatinine, urea and urate; sodium and potassium; ALT, AST, GGT, ALP; vitamin D, folate and B12. On their respective appropriate indications, these tests were well utilized. Underutilization occurred for tests of long-term complications of CKD (phosphate, PTH), T2DM and AHT (proteinuria), which were ordered on less than respectively 25% and 10% of their panels.

CONCLUSION: The frequently overutilized tests were routinely ordered regardless whether they were appropriate or not for the ordered indication. The overall ordering-frequency of most tests should be reduced and restricted to clear indications, while the ordering-frequency of underutilized tests should be improved.

Table of contents

Abbreviations 1
Introduction 3
Methods 4
Study design 4
Research question 4
Study setting, selection criteria and data collection 4
Statistical analysis 5
Quantitative variables 5
Selection of inappropriately ordered indications 5
Utilization of laboratory tests 6
Test co-ordering 6
Results 7
Description of the dataset 7
Test-utilization 10
Overutilization 10
Underutilization 13
Test co-ordering 16
Discussion 18
Inappropriately ordered indications 18
Overutilization 18
Underutilization 18
Recommendations for clinical practice 19
Study limitations 19
Modifying factors 19
Methodological limitations 20
Study strengths 20
Conclusion 20
References 21
Supplemental Materials .....
§1.1 Variables in the dataset .....
§1.2 Domains of clinical biology .....
§1.3 Substituted test labels .....
§2.1 Ordering behaviour and utilization on the 7 remaining indications .....
§2.2 Overutilization of tests on the 7 remaining indications .....
§2.3 Underutilization of tests on the 7 remaining indications .....

§3. R-scripts ……
§4. Approval Ethical commision KU Leuven ……

Abbreviations

Ab	Antibody
Ac-Dr	Acute Diarrhoea
ACR	Albumin creatinine ratio
ACS	Acute coronary syndrome
Ag	Antigen
AHT	Arterial Hypertension
ALT	Alanine aminotransferase
ANM	Anaemia
Apr.	Appropriateness
AST	Aspartate aminotransferase
CBC	Complete blood count
Chr-Dr	Chronic Diarrhoea
CK	Creatinine kinase
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CVRM	Cardiovascular risk management
GFR	Glomerular filtration rate
ESR	Erythrocyte sedimentation rate
FTA	Fluorescent Treponema Ab
FTG	Fatigue
GCU	General Check-up
GGT	Gamma glutamyl transferase
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
Hct	Haematocrit
HCV	Hepatitis C
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LE	Lung embolism
LVR	Liver diseases
MFU	Medication Follow-up
N	Number (of)
PCR	Polymerase chain reaction
PSA	Prostate specific antigen
PTH	Parathyroid hormone
RA	Rheumatoid arthritis
RBC	Red blood cells
RPR	Rapid plasma Reagin
STI	Sexually transmittable infection
T2DM	Type 2 diabetes mellitus
T4	Thyroxine free (T4)
T3	Triiodothyronine free (T3)
THD	Thyroid dysfunction
TG	Triglycerides
TIBC	Total iron binding capacity
TPHA	Treponema pallidum haemagglutination
TSH	Thyroid stimulating hormone
Vol.	Volume

Introduction

Laboratory testing is a valuable part of a clinician's decision-making process (1). Of all patient encounters in primary care, approximatively 30% result in laboratory testing . However, inappropriate test ordering is estimated to be as high as 30% (2). Although laboratory testing accounted for 4.6% of total health care spending in Europe in 2016 (3), it often results in more costly downstream activities (4). In addition to the potential economic benefits, improving appropriate testing reduces the risk of unnecessary harm following false-positive test results, missed or delayed diagnoses and improves quality of care without impacting patient safety

There are multiple ways to analyze inappropriate test ordering, depending on the research question of interest (2,5,6). Overutilization refers to ordering a non-indicated test, while underutilization is not ordering an indicated test. Appropriateness can be defined using either restrictive or permissive criteria. The first requires there to be a clear indication for ordering the test, while the latter requires that there is no contra-indication.

Interventions aiming to reduce overall inappropriate testing should address different determining factors of testing behavior (7). First, physician-related factors include theoretical knowledge about clinical indications and the correct understanding of test results, as well as fear of missing diagnoses, attitudes towards evidence-based medicine and knowledge about cost of tests (1,8). Second, patient's insurance restrictions, limited understanding of testing and high expectations can influence physician's decision making (2). Other factors include the increasing number of available tests (8,9).

Interventions targeting clinical indications and the respective tests with high inappropriateness-rates are more likely to be impactful. Previously, several studies measured overall (in)appropriate ordering for selected tests, with no regard to the indications for which the tests were ordered (10–15). However, the clinical significance and appropriateness of laboratory tests differs in various clinical contexts. To date, very little is known about appropriate test ordering coupled to specific indications in primary care (5,9).

This study primary objective is to identify the indications for which primary care physicians most frequently, inappropriately order tests. Second, for those identified indications, we further explored the respective under- and overutilization of tests.

Methods

Study design

We retrospectively analyzed the database of the control group of the ELMO-study (16). The ELMO-study is a randomized clustered trial conducted in 2017 – 2018 primarily designed to assess the effectiveness of clinical decision support systems on inappropriate ordering of laboratory tests for common conditions in primary care.

Research question

Starting from our study objectives, we developed a PEO:

[P] Participants: General practitioners (GP's) working in primary care practices

[E] Exposure: 17 common indications in primary care (table 1)

[O] Outcomes:

- proportions of appropriately ordered tests per indication
- utilization-rates of appropriate and inappropriate tests per indication

Studied clinical indications and used abbreviations			
Acute coronary syndrome	ACS	Gout	Gout
Acute diarrhea	Ac-Dr	Liver disease	LVR
Anemia	ANM	Lung embolism	LE
Arterial hypertension	AHT *	Medication Follow-up	MFU
Cardiovascular risk management	CVRM *	Sexually transmitted infections	STI
Chronic diarrhea	Chr-Dr	Thyroid dysfunction	THD
Chronic kidney disease	CKD	Type 2 diabetes mellitus	T2DM *
General Check-up	GCU *	Rheumatoid arthritis	RA
Fatigue	FTG	*(Other indications) **	*Other*

Table 1. The 17 studied clinical indications (plus 1 undefined 'other indications') and the abbreviations used in this study. * We will refer to AHT, CVRM, GCU and T2DM as indications related to cardiovascular disease diagnosis, prevention and follow-up.

Study setting, selection criteria and data collection

The ELMO-study recruited GP's working in primary care practices in Belgium. The eligibility criteria included GP's working with a computerized system for laboratory orders and an electronic health record. Eligible patients were above 18 years old.

In this study, we analyzed the test panels from the control group, as this reflects the ordering behavior in real-life clinical encounters in primary care practices. Data collected per panel were: anonymized ID's of the patient and physician, age of the patient, test-indications, ordered tests and the computed appropriateness of the test (Supplemental materials§1.1).

GP's were not restricted from ordering any test from any domain of clinical biology (Supplemental materials§1.2). In the dataset, test appropriateness was attributed using a restrictive definition of appropriateness. For instance, if for indication A five tests are considered appropriate, then all additional tests were considered inappropriate. The restrictive criteria of appropriateness were based on indication-specific guidelines for laboratory testing developed by the Flemish College of Family Physicians (5,17,18). GP's could order test panels for one or for

multiple indications. On multiple-indication panels, a test was considered appropriate if it was appropriate for at least one of the ordered indications.

In the dataset, several test labels referred to the same unique test, but had a different name or spelling[1], or other reported units[2]. Regularly, panels included list of tests that originated from one unique test-order entry by a GP[3], such as "white blood cell differentiation", "protein electrophoresis" or "urinary sediment". These test labels were substituted by one indicative test label (Supplemental materials§1.3). To avoid double counting, we deleted duplicate test labels on the same panel.

Statistical analysis

Quantitative variables

The appropriateness per indication was computed by averaging the individual appropriateness's per panel ordered for that indication. The appropriateness for one panel was defined by the ratio (a)/(a+b), where: (a) is the number of appropriate tests for this indication- and (b) the number of inappropriate tests for the respective indication on that panel. Tests that were appropriate for other indications on the same panel, were subtracted from (a).

The average appropriateness-rate of a test, was defined by the ratio (c)/(c+d): (c) number of panels on which the test was appropriately ordered - and (d) the number of panels on which the test was inappropriately ordered.

The overutilization-rate of a test per indication, was defined by the ratio (e)/(f): (e) number of panels on which the test was inappropriately ordered- and (f) total number of panels ordered for the respective indication. Panels on which the studied test was appropriately ordered for at least one other indication, were excluded from the overutilization-rate computation.

For the analysis of underutilization per indication, we reported the ordering-frequencies of the respective appropriate tests, which was defined by the ratio (g)/(h): (g) number of panels on which the appropriate test was ordered and (h) total number of panels ordered for that indication.

Selection of inappropriately ordered indications

To identify the most frequently, inappropriately ordered indications, we used the following selection criteria in consecutive order:

- Exclusion of indications with appropriateness-rates higher than 0.70
- From the remaining indications, inclusion of the 10 indications with the highest number of ordered panels
- Ranking the selected indications starting with the lowest appropriateness ratio

We did not perform further analyses on the undefined 'other indications'.

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[1] E.g. the test labels *choriogonadotropin* and *beta-choriogonadotropin* were substituted by one indicative test label *HCG.*

[2] E.g. the test labels *HbA1c (%)* and *HbA1c (mmol/mol)* were substituted by one indicative test label *HbA1c. In case of infectious serology, labels reporting either the presence or the concentration of immunoglobulins were* replaced the test label by one indicative test IgM/IgG-label

[3] E.g. reported eGFR (MDRD or CKD-EPI), is calculated from serum-creatinine ordered by a GP. Labels reporting *eGFR* and serum-creatinine were substituted by one indicative test label *serum-creatinine+eGFR*

For every indication, we computed the median number of panels ordered per individual GP. To detect uneven representation of GP's ordering behaviour, we summated all the panels ordered by individual GP's under and above this median, and compared their relative contributions to the respective total number of panels.

Utilization of laboratory tests

For the selected indications, we reported overutilization-rates per tests. For summarizing purposes, tests were categorized into 3 groups. Tests with overall appropriateness-ratio's below 0.70 and an overall ordering frequency above 50% were labeled as **High-volume tests (H)**, between 25-49% as **Moderate-volume tests (M)** and between 10-24% as **Low-volume tests (L)**. Tests with ordering-frequencies below 10% were not reported, to obtain a limited yet comprehensive overview of overutilized tests.

For the analysis of test-underutilization, we reported the ordering frequencies of appropriate tests per indication separately. Similarly, high-, moderate- and low utilization referred to ordering frequencies above 50 %, between 25-49% and lower than 25% respectively.

To further optimize the comprehensive overview of the results, we computed a group average of the ordering frequencies and appropriateness for some tests. For example, we reported just one average estimate for the all cholesterol tests (LDL, HDL, total, non-HDL, Total/HDL), for the various reports of albumin- and proteinuria (absolute concentrations and relative to creatinine) and for TIBC and transferrin together. Additionally, we reported the best appropriateness and ordering frequency available for plasma glucose -because time of testing was not always specified- and for bilirubin tests.

The results for the non-selected indications and tests were reported in the supplemental materials (§2.1 and §2.2).

Test co-ordering

We computed the probabilities of ordering different combinations of tests on the same panel. We analyzed combinations containing 2 up to 6 tests, consisting of tests with an overall ordering frequency greater than 10% in the dataset (n=37). The co-ordering probability (p)/(q) was calculated as follows: **(p)** number of panels where all tests from the combination were ordered together; and **(q)** number of panels where at least one test from the combination was ordered, corrected for double counting.

We only selected some test-combinations to present in this paper, due to the large number of possible combinations (more than 2.000.000):

- For high- and moderate volume tests, the co-ordering probabilities for tests from the same domain of clinical biology
- For any test-combination (2 to 6 tests), co-ordering probabilities greater than 70%, in which the CBC-tests and cholesterol-tests were grouped into one element respectively of the test-pool for making combinations.
- A selection of test-combinations of clinical interest: co-ordering probabilities of different combinations of electrolytes and nitrogen metabolism tests.

All planned statistical analyses were run in R.

Results

Description of the dataset

The general characteristics of the dataset are described in table 2. The dataset included 90.523 tests, ordered across 4.370 panels by 125 GP's. The number of panels ordered per GP ranged from 2 to 157 and averaged at 35.0 panels (SD 27.4). Most panels (61%) included just one indication (i.e. single-indication panels). However, the majority of the indications were ordered more frequently on multiple-indication panels, which included 2.43 indications on average (SD 0.82). GP's ordered in total 238 different laboratory tests, but only 45 tests were ordered on more than 10 percent of all panels.

Patients	
Total	4.192
Sex distribution (man/woman)	1836/2356
Average age (years ±1SD)	54.0 ± 17.6
Laboratory panels	
Total	4.370
Single/multiple-indication panels	2682/1688
Average *n* of indications per multiple-indication panel (±1SD)	2.43 ± 0.82 - Range: 2 - 8
General Practitioners	
Total	125
Average *n* patients per GP (±1SD)	33.7 ± 25.8
Average *n* panels per GP (±1SD)	35.0 ± 27.4 - Range 2 - 157
Average *n* tests per panel per GP (±1SD)	18.6 ± 6.8
Laboratory tests	
Total *n* ordered tests	90.523
Unique tests labels in dataset †	238
Average *n* tests per panel (± 1SD)	20.6 ± 10.9 - Range: 1 - 53

Table 2. General characteristics of the dataset. † After substitution of similar test labels referring to the same laboratory test (cfr Methods and Supplemental Materials§1.3).

Appropriateness per clinical indication

The number of panels ordered per indication ranged from 12 for Lung Embolism (LE) to 1787 for General Check-up (GCU, figure 1). The average appropriateness per panel ranged between 0.17 for Acute coronary syndrome (ACS) to 0.66 for Anaemia (ANM, figure 2).

Table 3 ranks the 10 most frequently, inappropriately ordered indications by increasing appropriateness. Of this selection, 4 indications were related to cardiovascular disease prevention, diagnosis and follow-up: GCU, Cardiovascular Risk Management (CVRM), Arterial Hypertension (AHT) and Type 2 Diabetes Mellitus (T2DM). The remaining 6 indications were Chronic Kidney Diseases (CKD), Thyroid dysfunction (THD), Sexually Transmittable Infections (STI), Fatigue (FTG), Medication Follow-up (MFU) and Anaemia (ANM).

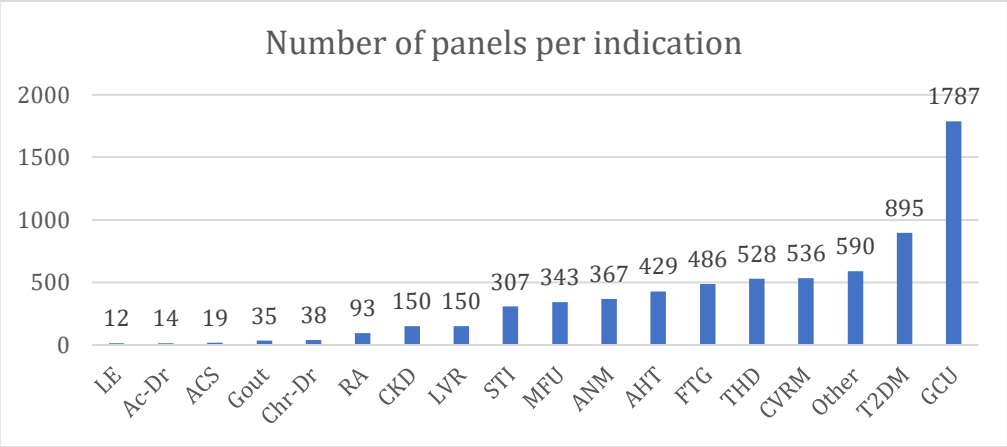

Figure 1. Indications ranked by total number of ordered panels.

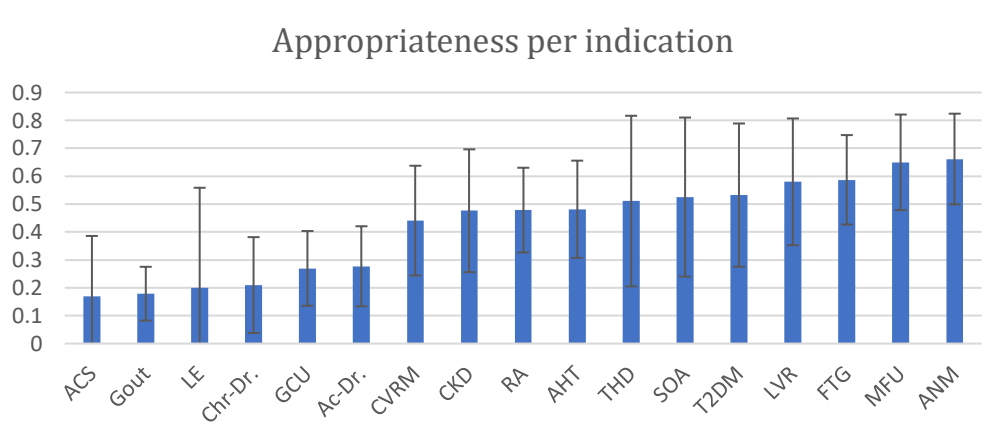

Figure 2. Indications ranked by total average appropriateness per panel (+- 1 SD).

Clinical indications	**Appropriateness**	***n* of panels**
General check-up	0.27 (± 0.13)	1787
Cardiovascular risk management	0.44 (± 0.20)	536
Arterial hypertension	0.48 (± 0.17)	429
Chronic kidney disease	0.48 (± 0.22)	150
Thyroid Dysfunction	0.51 (± 0.30)	528
Type 2 diabetes mellitus	0.53 (± 0.26)	895
Sexually transmittable infections	0.53 (± 0.29)	307
Fatigue	0.59 (± 0.16)	486
Medication Follow-up	0.65 (± 0.17)	343
Anaemia	0.66 (± 0.16)	367

Table 3. The 10 most frequently, inappropriately ordered indications by GP's (increasing average appropriateness per panel (± 1 SD)).

The ordering behaviour of GP's was unevenly represented on these indications. On every indication -except for CKD- half of the GP's contributed to less than a quarter of the total number of panels (figure 3).

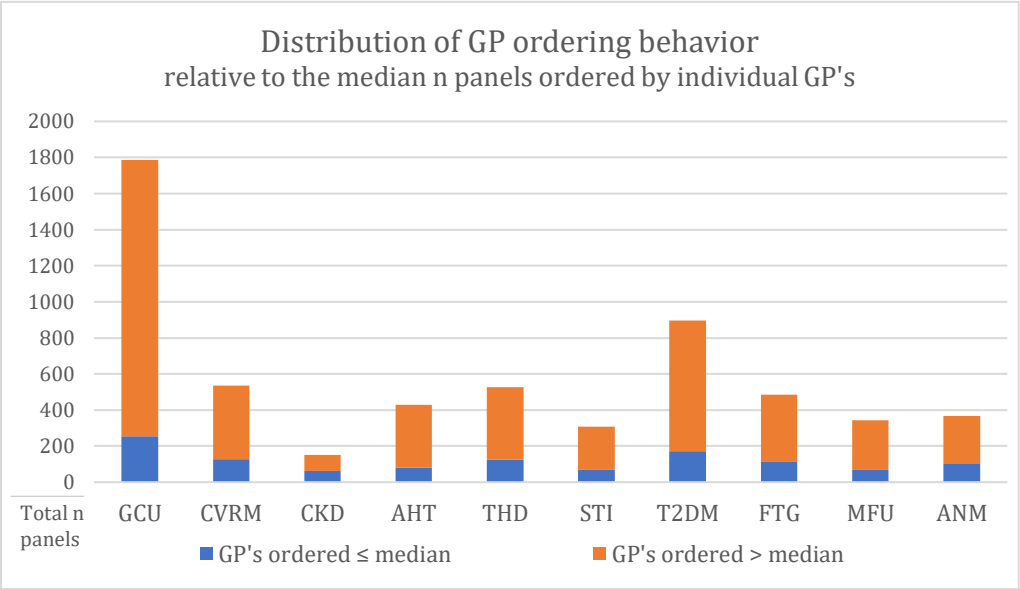

Figure 3. The ordering behaviour of GP's was unevenly distributed, relative to the median number of panels ordered by individual GP's per indication. The blue bar represents the sum of all panels ordered by GP's who each ordered a lesser or equal amount of panels than the median for that indication. The orange bar is the sum of all the panels ordered by GP's who each ordered more than the median.

Test-utilization

Overutilization

The most frequently overutilized tests across all seventeen indications, were grouped into three categories according to their overall ordering frequency. The specific overutilization-rates on the ten selected indications are further specified in table 4 and 5.

- **High volume tests (≥ 50% panels):**
  - Complete blood count (CBC): RBC, haemoglobin, haematocrit, WBC, platelets
  - Inflammation: CRP
  - Nitrogen metabolism: serum creatinine (eGFR)
  - Liver function: ALT, GGT
  - Hormonology: TSH
- **Moderate volume tests (25-49% panels):**
  - Inflammation: ESR
  - Iron status: iron, ferritin
  - Nitrogen metabolism: urea, urate
  - Liver function: ALP, AST
  - Electrolytes: sodium, potassium
  - Vitamins: Folate, vitamin D and B12
- **Low volume tests (10-24% panels):**
  - Haematology: reticulocytes
  - Iron status: TIBC and transferrin
  - Biochemistry: total serum protein and -electrophoresis, LDH, total bilirubin
  - Hormonology and tumour markers: PSA and T4
  - Electrolytes: chloride, magnesium, calcium and bicarbonate

High- and moderate-volume tests were frequently inappropriately ordered across all 10 selected indications (table 4). Where not appropriate, CBC-tests were most frequently overutilized, followed by CRP and ESR, urate, urea, creatinine and sodium and the specific liver function enzymes (AST, ALT, GGT). However, overutilization of these tests was the least pronounced on Sexually transmittable infections and Thyroid dysfunction. Additionally, most of the high- and moderate volume tests were appropriate for Medication Follow-up, Fatigue and Anaemia. However, almost all the respectively non-appropriate tests were overutilized on ≥ 25% of their panels. Vitamin D was inappropriately ordered on more than half of the General Check-up- and Fatigue-panels.

The overutilization of low-volume tests followed a more indication-specific pattern, except for chloride, calcium and bicarbonate, which were overutilized on almost all 10 indications (table 5). Additionally, nearly all low-volume tests were overutilized on panels for General Check-up, Cardiovascular risk management and Fatigue.

Some tests did not fall into the high-, moderate- or low-volume category, but -even so- had overutilization-rates greater than 10% on specific indications (table 5). Specifically, HbA1C was overutilized on General-check up and serum lipids were overutilized on Fatigue and Anaemia. Serology of EBV, CMV and toxoplasmosis showed overutilization on Fatigue-panels, while HCV-antibodies were inappropriately ordered on more than 25% of the STI-panels.

	All indications		GCU	CVRM	AHT	CKD	T2DM	STI	FTG	THD	MFU	ANM
CBC	Vol.	Appr.	Overutilization-rate per indication									
Hematocrit	H	0.2	+++	+++	+++	a	++	++	a	++	a	a
Platelets		0.31	+++	+++	++	++	++	+	a	++	a	a
RBC + ind.		0.32	+++	+++	+++	a	++	++	a	++	a	a
Hemoglobin		0.35	+++	+++	+++	a	++	++	a	++	a	a
WBC diff.		0.36	+++	+++	+++	++	++	++	a	a	a	a
Leukocytes		0.38	+++	+++	+++	++	++	++	a	a	a	a
Inflammation												
CRP	H	0.42	++	++	++	++	++	+	a	a	a	a
ESR	M	0.18	++	++	++	++	+	+	a	+	++	a
Iron status												
Iron	M	0.15	++	+	+	+	+	-	++	+	+	a
Ferritin		0.32	+++	++	++	+	+	+	a	+	++	a
Nitrogen met.												
creat. (eGFR)	H	0.52	+++	++	a	a	a	+	a	++	a	a
Urate	M	0.02	+++	++	+++	++	++	0	++	+	+++	++
Urea		0	+++	++	++	+++	++	+	++	+	++	+
Eletrolytes												
Sodium	M	0.27	+++	++	a	+++	++	+	a	+	++	+
Potassium		0.45	++	+	a	a	a	+	a	+	a	+
Liver												
GGT	H	0.3	+++	a	++	+	++	+	+++	++	a	a
ALT		0.43	+++	a	++	+	++	+	a	+	a	a
ALP	M	0.06	++	++	++	+	+	+	++	+	++	+
AST		0.17	+++	+++	+++	++	++	+	a	++	+++	+
Thyroid												
TSH	H	0.44	+++	++	a	+	++	+	a	a	++	a
Vitamins												
Vitamin D	M	0.03	+++	++	++	a	+	0	+++	++	++	++
Cobalamins		0.12	++	++	++	+	+	+	+++	+	++	a
Folate		0.13	++	+	+	+	+	-	++	+	+	a

Table 4. High- (H) and moderate- (M) volume tests, ordered on respectively more than 50% and 25% of the panels across all 17 indications, and their specified appropriateness-rate. The overutilization-rates on the 10 selected indications are specified as: +++ (>= 50%), ++ (25-49%), + (10-24%), – (<10%), 0 (no overutilization) and "a" (Test is appropriate for the indication).

	All indications		GCU	CVRM	AHT	CKD	T2DM	STI	FTG	THD	MFU	ANM
Hematology	Vol.	Appr.	Overutilization-rate per indication									
Reticulocytes	L	0.17	+	+	-	-	-	-	+	-	+	a
Iron status												
TIBC	L	0.22	+	-	-	-	-	-	+	-	-	a
Biochemistry												
Protein electrophoresis	L	0	+	+	-	-	-	-	+	-	-	-
Protein (serum)		0	+	+	-	+	-	-	+	-	-	-
LDH		0.03	+	+	-	-	+	-	+	-	-	a
Bilirubin total		0	+	-	-	-	-	-	+	-	-	-
Electrolytes												
Chloride	L	0.25	++	++	++	++	+	-	+	+	++	+
Magnesium		0	+	-	-	-	-	-	+	-	-	-
Calcium		0.06	+	+	+	a	+	-	+	+	+	+
Bicarbonate		0.07	+	+	++	a	+	-	+	+	++	-
Phosphate	-	0.09	+	-	-	a	-	-	-	-	-	-
Hormonology												
T4	L	0.45	+	+	+	-	-	-	a	a	+	+
PSA		0	+	+	+	-	-	-	-	-	-	-
Cardiovascular												
Cholesterol (tot., HDL, LDL)	-	0.93	a	a	a	a	a	-	+	-	a	+
Triglycerides		0.93	a	a	a	a	a	-	+	-	a	+
HbA1c		0.74	+	-	-	-	a	-	-	-	-	-
Serology												
HCV Ab	-	0.04	-	-	0	-	-	++	-	-	0	-
CMV IgM + IgG		0.04	-	-	0	0	-	-	+	-	-	-
EBV IgM + IgG		0.04	-	-	0	0	-	-	+	-	-	-
Toxoplasm IgM		0	-	-	0	0	-	-	+	-	-	-
Urinary tests												
Creatinine	-	0	-	-	-	+	+	-	-	-	-	-

Table 5. Low-volume tests (L), ordered on 10-24% of the panels across all 17 indications, and their specified appropriateness-rate. Some tests were ordered on less than 10% of all panels, but had overutilization-rates greater than 10% (Volume -) on the 10 selected indications. The overutilization-rates on the selected indications are specified as: ++ (25-49%), + (10-24%), – (<10%), 0 (no overutilization) and "a" (Test is appropriate for the indication).

Underutilization

The utilization-rates of appropriate tests for the 10 selected indications are presented here below. High-, moderate- and low utilization refers to utilization-rates on more than 50%, between 25-49%, and less than 10-25% of the respective panels.

Cardiovascular disease indications: GCU, CVRM, AHT and T2DM

The serum lipids showed high utilization, while glucose was moderately utilized (table 6). Creatinine kinase was almost never ordered on CVRM-panels. Testing for albumin- or proteinuria occurred on less than 25% of the T2DM- and on less than 10% of the AHT-panels. The urinary tests 'metanephrines' and 'micro-albuminuria' were never ordered.

	GCU	CVRM	AHT	T2DM
Cardiovascular				
Cholesterol (Total, LDL, HDL)	+++	+++	+++	+++
Triglycerides	+++	+++	+++	+++
Glucose	++	++	++	++
HbA1c				+++
Nitrogen metab.				
Creatinine (eGFR)			+++	+++
Liver function				
ALT		+++		
GGT		+++		
Biochemistry				
Creatine kinase		-		
Electrolytes				
Sodium			+++	
Potassium			+++	++*
Thyroid function				
TSH			+++	
Urinary Tests				
Protein (urine)			-	
Albumin or ACR (urine)			-	+
Microalbumin (urine)				0
Metanephrines			0	

Table 6. Appropriate test-utilization for the cardiovascular disease indications. The utilization-rates are specified as: +++ (>=50%), ++ (25-49%), + (10-24%), – (<10%) and 0 (never ordered).

Sexually transmittable infections

The most frequently tested STI-pathogens were HIV and Chlamydia trachomatis (table 7). For Hepatitis B virus (HBV) and syphilis, utilization differed depending on the specific test ordered. For HBV, utilization-rates were high for surface antigen, moderate for surface antibody and low for core antibody. For syphilis, the treponemal tests TPHA and FTA-absorption as well as the non-treponemal tests RPR were moderately used, while VDRL was underused. None of the GP's tested for Trichomonas nor Herpes simplex virus.

	STI
STI-testing	
HIV 1+2 Ab & p24 Ag	+++
HBV c Ab	-
HBV s Ab	++
HBV s Ag	+++
N. gonorrhoeae DNA	++
C. trachomatis DNA	++
TPHA and FTA-abs	++
RPR	++
VDRL	-
Trichomonas Ag	0
HSV culture	0

Table 7. Appropriate test-utilization for STI. The utilization-rates are specified as: +++ (>=50%), ++ (25-49%), + (10-24%) and – (<10%).

Thyroid dysfunction

The thyroid-function tests TSH and T4 were highly utilized (resp. 99 and 80%, table 8). Testing for inflammation (leucocytes and CRP) occurred on 40 to 66% of the panels. Antibodies against 'Thyrotropin receptor' and 'Thyroperoxidase' were ordered on less than 10% of the THD-panels.

Chronic kidney diseases

Most appropriate tests for CKD showed moderate to high utilization (table 8). The serum lipids and glucose were moderately used on CKD-panels. Tests for metabolic complications of CKD had moderate utilization-rates for calcium, bicarbonate and vitamin D, and low utilization-rates for PTH and phosphate. Protein- and albuminuria were ordered on less than 10% of the panels.

Fatigue

GP's frequently ordered the appropriate tests for the fatigue-indication. Glucose, potassium and sodium were slightly less ordered and had a moderate utilization (table 8).

Medication follow-up

Almost all appropriate tests were ordered on more than half of the MFU-panels, except for glucose and CRP which had moderate utilization-rates, and CK and beta-HCG which were ordered on less than 10% of the panels (table 8).

Anaemia

The appropriate test for Anaemia were -depending on the test- well utilized on more than 25 to 50% of the ANM-panels (table 8).

	CKD	FTG	THD	MFU	ANM		CKD	FTG	THD	MFU	ANM
CBC						**Liver function**					
RBC + indices	+++	+++		+++	+++	ALT		+++		+++	++
Hematocrit	+++	+++		+++	+++	AST		+++			
Hemoglobin	+++	+++		+++	+++	GGT				+++	++
Leukocytes		+++	+++	+++	+++	**Biochemistry**					
WBC differentiation		+++	+++	+++	+++	CK				-	
Platelets		+++		+++	+++	**Hormonology**					
Reticulocytes					++	TSH		+++	+++		+++
Iron status						T4		++	+++		
Ferritin		+++			+++	T3			+		
Iron					++	THR and TPO			-		
Transferrin + TIBC					++	PTH	+				
Inflammation						b-HCG				-	
CRP		+++	++		+++	**Vitamins**					
ESR		+++		++	++	Vitamin D	++				
Nitrogen metab.						Cobalamins					+++
Creatinine (eGFR)	+++	+++		+++	+++	Folate					++
Electrolytes						**Urinary tests**					
Potassium	+++	++		+++		Albumin or ACR	-				
Sodium		++				Protein	+				
Calcium	++										
Phosphate	+										
Bicarbonate	++										

Table 8. Appropriate test-utilization for CKD, FTG, MFU and ANM. The utilization-rates are specified as: +++ (>=50%), ++ (25-49%), + (10-24%) and – (<10%).

Test co-ordering

The highest co-ordering probabilities between high- and moderate volume tests from the same domain of clinical biology, was for sodium and potassium with 92%. This means that out of 100 panels including at least sodium or potassium, 92 panels included both tests (table 9A). The cholesterol- and CBC-tests had a co-ordering probability of respectively 88% and 66%. The co-ordering probabilities were lower for nitrogen metabolism tests, the three vitamins and the four liver function enzymes. However, inside these respective domains, several 2-test combinations showed higher co-ordering probabilities. For example: ALT and GGT (83%), folate and vitamin B12 (70%) and urate and urea (54%).

Triglycerides, cholesterol- and CBC-tests dominated the highest probabilities for 3rd- up to 6th-order combinations. In order to detect other meaningful combinations, CBC-tests were grouped into one test-element, as well as cholesterol-tests. Subsequently, co-ordering probabilities greater than 70% were found for 2-test combinations including CBC, serum lipids, GGT, ALT and TSH (table 9B).

Finally, because of the possible clinical relevance, we selectively reported co-ordering probabilities of electrolytes and nitrogen metabolism tests (table 9C). Chloride and bicarbonate were frequently ordered together (76%), as well as calcium and magnesium (57%), and sodium, potassium and creatinine (58%).

CBC-tests	Co-ordering probability
RBC, Hb, Hct, WBC and platelets	66%
Inflammation	
ESR and CRP	52%
Iron status	
Iron and Ferritin	46%
Nitrogen metabolism	
s-creatinine, urea and urate	37%
Electrolytes	
Na and K	92%
Liver function	
ALT and GGT	83%
ALT and AST	60%
GGT and ALP	50%
AST, ALT, GGT and ALP	43%
Cardiovascular	
Cholesterol (total, HDL, non-HDL)	88%
Vitamins	
Vitamin D, Folic acid and B12	36%
Folic acid and B12	70%

Table 9A. The co-ordering probabilities of high- and moderate volume tests from the same domain of clinical biology.

Test combinations (≥70%)	Co-ordering probability
CBC and creatinine	78%
GGT and creatinine	76%
Cholesterol and creatine	75%
ALT and creatinine	74%
Cholesterol and GGT	72%
Triglycerides and creatinine	71%
CBC and GGT	70%
Triglycerides and GGT	70%
Cholesterol and ALT	70%
CBC and TSH	70%

Table 9B. The co-ordering probabilities of 2nd- or more order test-combinations, higher than 70%. The different CBC- and cholesterol tests were grouped. Note that no combination of 3 or more tests fulfilled this criterion.

Nitrogen metabolism	Co-ordering probability
Na, K and s-creatinine	58%
Urate and urea	57%
Urate and s-creatinine	54%
Urea and s-creatinine	46%
Electrolytes	
Cl and HCO3	76%
Ca and Mg	57%
Na, K and Cl	50%
Na, K, Cl and HCO	39%

Table 9C. The co-ordering probabilities of different combinations of electrolytes and nitrogen metabolism tests.

Discussion

Inappropriately ordered indications

Our results show frequent inappropriate test-ordering on 10 prevalent indications in primary care. The average overutilization rate on these indications was 51.3% (SD 11.2), meaning half of the tests ordered for general check-up, cardiovascular risk management, arterial hypertension, chronic kidney diseases, type 2 diabetes mellitus, sexually transmittable infections, fatigue, thyroid dysfunction, medication follow-up and anaemia was not indicated.

Overutilization

We defined overutilization as inappropriately ordering tests on more than 10% of the panels, and as a result, we identified 23 highly- and moderately overutilized tests (table 4). Starting with the most frequently overutilized tests: complete blood count-tests (RBC, Hb, Hct, WBC, platelets), inflammation- (CRP, ESR), nitrogen metabolism- (creatinine, urea, urate), sodium and potassium, liver function- (ALT, AST, GGT, ALP), iron status- (iron, ferritin) and thyroid function-tests (TSH). The vitamins (vitamin D, Folate, B12) were most overutilized on GCU and FTG. Importantly, high- and moderate volume tests, together with the 'low-volume' electrolytes (chloride, calcium an bicarbonate) were overutilized on all ten selected indications. On the contrary, low-volume tests (inappropriately ordered on 10 to 25% of panels) were overutilized on specific indications, but not on all indications (table 5).

Our results suggest that test-overutilization was in part driven by *habitual* co-ordering of tests. Tests from the same domain of clinical biology (cfr. supra), had high co-ordering probabilities. When looking across different domains, CBC-tests, serum lipids, GGT, ALT and TSH were frequently ordered together.

Underutilization

Tests with a limited appropriate use, for example albuminuria for CKD or T2DM, were rarely ordered overall nor on their appropriate indications. In contrast, the discussed overutilized high- and moderate volume tests were -when appropriate- well utilized on their respective indications. Consequently, because many of these tests were appropriate for FTG, MFU and ANM, these indications showed little underutilization and had relatively high appropriateness-rates.

The screening for long-term complications of chronic diseases should be improved. GP's rarely tested for alubumin- or proteinuria in patients with T2DM, AHT and CKD. Additionally, HbA1c was not ordered on 15% of the T2DM-panels, although it is the most important parameter for the follow-up of T2DM (7,22,23). Metabolic complications of CKD were incompletely assessed, as demonstrated by the underutilization of PTH and phosphate. Finally, standard testing for glucose could be further improved for all cardiovascular indications.

Furthermore, usage of diagnostic tests for STI's should be further optimised. For STI, GP's did not consequently test for C. trachomatis and even less for N. gonorrhoeae. Nevertheless, according to the guidelines both should be tested together when suspecting a STI (24). Notably, HIV was tested more often (88%) than any other STI-pathogen, although it is one of the least prevalent STI's and only indicated in the presence of specific risk factors (24). For hepatitis B, surface antibody was much more frequently ordered than core antibody. However, testing for core antibody is needed to differentiate between immunization after vaccination or an acute, chronic or past infection of hepatitis B.

Recommendations for clinical practice

In summary, the test ordering behaviour of GP's was generally too permissive by ordering too many non-indicated tests, and it was not sufficiently specific. High- and moderate volume tests were frequently ordered across all indications, regardless whether they were appropriate or not. GP's also showed a bias towards ordering tests together from the same domain of clinical biology.

Laboratory tests such as CBC-tests, creatinine, thyroid-function tests, CRP and electrolytes do have an appropriate use for several prevalent conditions. However, GP's should be careful when ordering these high- and moderate-volume tests and refine their usage to appropriate indications. Additionally, physicians should be aware of the high probability of co-ordering these tests on most blood samples. Other tests would tests would benefit from being significantly less ordered overall. This includes liver function tests, protein electrophoresis, platelets, PSA, vitamin D, B12 and folate, which only have sufficient predictive values -and thus an appropriate use- for a more limited number of less common indications (5,17,18).

Finally, tests with a limited number of appropriate indications were generally underutilized. Specifically, testing for long-term complications of T2DM, AHT and CKD should be improved to decrease the risk of under, mis- or delayed diagnosis of complications.

Study limitations

Modifying factors

The presence of panels ordered for multiple indications in the dataset lead to underestimation of inappropriateness- and overutilization-rates. On the contrary, to eliminate overestimation of our indication-specific variables, we excluded tests that were appropriate for at least one other indication on multiple-indication panels.

Other factors lead to over- and underestimation of the appropriateness-rates. Factors of overestimation could include GP's adjusting their test ordering behavior, knowing they participated to a study on inappropriate test-ordering. Underestimation-factors could include inadequate registration of every indication a GP was testing for. For example, if GP's did not register all the indications they were testing for or if their clinical hypothesis was not adequately reflected the 17 available indications on the order sets of the study. Importantly, GP's could not include infective illnesses as an ordered indication. This probably lead an inaccurate estimation of the appropriateness-rate of WBC and CRP.

Patient recruiting factors also possibly affected our results. The number of recruited patients per GP had a wide distribution leading to an uneven representation of GP ordering behavior across the dataset. Also, the total number of panels varied per indication. As a consequence, the accuracy of our estimates is for example higher for GCU than for AHT.

Additionally, differences in the set of appropriate tests per indication used by GP's and the ones defined by the ELMO-study, probably affected our estimates. The list of appropriate tests defined in the ELMO-study was based on guidelines from the Flemish college of Family Physicians, but there were differences on some tests. For GCU, Flemish and Dutch guidelines suggest a broader panel of appropriate tests for GCU, including RBC, haematocrit, haemoglobin, creatinine, TSH and even inflammatory indicators as CRP and ESR depending on the clinical context (5,17,18).

Furthermore, guidelines cannot conceive all possible clinical contexts in which GP's are operating.

Finally, precise rates of underutilization could not be estimated, because testing for an indication does not always require the inclusion of all possible appropriate tests. Instead, the selection of appropriate tests is directed by the specific clinical context and the advised testing frequency in guidelines (once versus multiple times a year).

Methodological limitations

We used a restrictive definition for (in)appropriateness, both for the analysis of over- and underutilization. However, the ELMO-study did not include timing of repeat (inappropriate) testing as a variable.

Study strengths

The dataset provided us with a large sample of laboratory tests ordered in real clinical encounters in primary care. Additionally, it offered the possibility to differentiate between over- and underutilization of tests respective to specific clinical indications. Moreover, our study adds evidence to the research of underutilization which is thought to be widespread but understudied (10).

Further research of over- and underutilization should investigate time-related factors, such as the difference between initial and (advised ordering frequency of) repeat testing. Next, the determining factors of inappropriate ordering behaviour should be further explored. Surveys could specifically address tests and indications with high over- and underutilization rates *identified* in this study.

Conclusion

Half of the tests ordered for prevalent indications in primary care are inappropriate on average. An increased awareness of habituated patterns of test ordering could improve overall appropriateness. The overall ordering-frequency of most tests should be reduced and the use of more prevalent tests (such as CBC, cholesterol and serum creatinine) should be restricted to clear indications. Finally, diagnostic test-ordering for STI and underutilization of screenings-tests for long-term complications of chronic diseases should be improved.

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§1. Supplemental Materials: Variables

§1.1 Variables in the dataset

Columns

TXT_WRKFLOW_IDN	Unique label per laboratory panel
LAB_APPROP	Appropriateness of the test (0 or 1)
IDC_PAT	Unique label per patient
CD_PAT_SEX	Patient gender
CD_RIZIV_TREAT_PHYS	Unique label per GP (social security number)
DT_LAB_TST	Date of ordering the laboratory panel
LAB_NAME	Name of laboratory analysing the panel
GROUP_ID	Original group studied in the ELMO-RCT (control vs intervention; we only selected data from the control group)
AGE	Patient age
CD_COD_TREAT_PHYS	?
INDIC_ALL	Ordered indication(s) on the panel
TX_LBL_EN	Ordered laboratory test in the original ELMO-dataset (351 unique test-labels)
Test_unique_aanvraag	Indicative test label respective to test labels in TX_LBL_EN, to avoid double counting

Rows

Every row represents one unique laboratory test ordered on a specific panel.

§1.2 Domains of clinical biology

Domains of clinical biology		
Hematology	**Coagulation**	**Immunology**
> Complete blood count > Iron status > Blood group	> PT, aPTT, coagulation factors > D-dimers	> Infectious serology > Auto-immunity and immunoglobulins > Allergology
Biochemistry	**Hormonology**	**Microbiology**
> Nitrogen metabolism (kidney, urea, urate) > Liver- and pancreas function > Cardiac markers > Plasma proteins and electrophoresis > Electrolytes	> Thyroid function > Sex hormones > Calcium metabolism > Adrenal > Tumor markers	> Urine > Stool > Genital > Skin, punctures
Inflammatory status	**Cardiovascular follow-up**	**Biochemistry of body fluids**
> CRP > Erythrocyte sedimentation rate	> Cholesterol and triglycerides > Glucose metabolism	> Urine > Stool > Punctured fluids
Drug monitoring and toxicology of body fluids	**Vitamins**	**Varia**

In the study, GP's were not restricted from ordering any test, from any domain of clinical biology.

§1.3 Substituted test labels (3 conditions)

In the dataset, test labels referring to the same laboratory test, were substituted by one indicative test label if the following conditions were present:

1. Test labels were named or spelled differently
2. Test labels have different reported units
3. List of test labels originate from one laboratory-order entry by a GP

1. Test labels were named or spelled differently

Original test label	**Substituted by indicative test label…**
25 hydroxycholecalciferol D2 + D3 (serum/plasma)	25-OH-vitamin D
Cholecalciferol (serum/plasma)	25-OH-vitamin D
25 hydroxycholecalciferol (serum/plasma)	25-OH-vitamin D
Nuclear Ab (serum) - presence	Antinuclear antibodies
Antinuclear antibodies (serum) - presence	Antinuclear antibodies
Cholesterol total/Cholesterol in HDL	Cholesterol total/Cholesterol in HDL
Cholesterol.total/Cholesterol.in HDL	Cholesterol total/Cholesterol in HDL
Glucose - fasted (serum/plasma) [mg/dL]	Glucose fasted
Glucose - fasted (serum/plasma) [mg/dL]	Glucose fasted
Glucose 2 hours post meal (serum/plasma) [mg/dL]	Glucose postprandial
Glucose post meal (serum/plasma) [mg/dL]	Glucose postprandial
Choriogonadotropin (serum/plasma)	HCG
Beta human choriogonadotropin (serum/plasma)	HCG
Magnesium (serum/plasma)	Magnesium (serum/plasma)
Magnesium (serum/plasma) - in moles/volume [mmol/L]	Magnesium (serum/plasma)
Phosphate (serum/plasma)	Phosphate (serum/plasma)
Phosphate (serum/plasma) - in moles/volume [mmol/L]	Phosphate (serum/plasma)
Thyroid Stimulating Hormone (serum/plasma	Thyroid Stimulating Hormone (serum/plasma)
Thyroid Stimulating Hormone (serum/plasma)	Thyroid Stimulating Hormone (serum/plasma)
Thyroperoxidase IgG Ab (serum/plasma)	Thyroperoxidase IgG Ab (serum/plasma)
Thyroperoxidase Ab (serum/plasma)	Thyroperoxidase IgG Ab (serum/plasma)

2. Test labels have different reported units

Original test label	Substituted by indicative test label…
Albumin (urine) - presence	Albumine (urine)
Albumin (urine) - in mass/volume	Albumine (urine)
Borrelia burgdorferi Ab (serum) - presence	Borrelia burgdorferi Ab
Borrelia burgdorferi IgM + IgG (serum) - immunoblot	Borrelia burgdorferi Ab
Borrelia burgdorferi IgM (serum) - immunoblot	Borrelia burgdorferi IgM
Borrelia burgdorferi IgM (serum) - in units/volume	Borrelia burgdorferi IgM
Borrelia burgdorferi IgG (serum) - immunoblot	Borrelia burgdorferi IgG
Borrelia burgdorferi IgG (serum) - units/volume	Borrelia burgdorferi IgG
Cortisol (serum/plasma) - morning peak [nmol/L]	Cortisol (serum/plasma) - morning peak [nmol/L]
Cortisol 08:00 (serum/plasma) - in mass/volume	Cortisol (serum/plasma) - morning peak [nmol/L]
Cytomegalovirus IgM (serum)	CMV IgM
Cytomegalovirus IgM (serum) - in units/volume	CMV IgM
Cytomegalovirus IgM (serum) - in units/volume	CMV IgM
Cytomegalovirus IgG (serum)	CMV IgG
Cytomegalovirus IgG (serum) - presence	CMV IgG
Hemoglobin A1c (blood) - in %	HbA1c (mmol/mol and %)
Hemoglobin A1c (blood) - in mmol/mol - IFCC protocol	HbA1c (mmol/mol and %)
Hepatitis A virus IgM (serum) - presence	Hepatitis A IgM
Hepatitis A virus IgM (serum) - in units/volume	Hepatitis A IgM
Hepatitis A virus IgG (serum) - presence	Hepatitis A IgG
Hepatitis A virus IgG (serum) - in units/volume	Hepatitis A IgG
Hepatitis B virus core Ab (serum) - presence	HBV c Ab
Hepatitis B virus core Ab (serum) - in units/volume	HBV c Ab
Hepatitis B virus e Ag (serum) - presence	HBV e Ag
Hepatitis B e-antigen Ab (serum) - presence	HBV e Ag
Hepatitis B virus surface Ag (serum) - in units/volume	HBV s Ag
Hepatitis B virus surface Ag (serum) - presence	HBV s Ag
Hepatitis C virus Ab (serum) - in units/volume	HCV Ab
Hepatitis C virus Ab (serum) - presence	HCV Ab
Hepatitis C virus Ab signal/cutoff (serum) - in units/volume	HCV Ab
Mycoplasma pneumoniae IgM (serum) - presence	Mycoplasma pneumoniae IgM
Mycoplasma pneumoniae IgM (serum) - in units/volume	Mycoplasma pneumoniae IgM
Mycoplasma pneumoniae IgG (serum) - presence	Mycoplasma pneumoniae IgG
Mycoplasma pneumoniae IgG (serum) - in units/volume	Mycoplasma pneumoniae IgG
Coagulation tissue factor induced INR	PT and INR
Quick Prothrombin time (platelet poor plasma) - in %	PT and INR

Quick Prothrombin time (platelet poor plasma) - in INR	PT and INR
Rubella IgM (serum) - in units/volume	Rubella IgM
Rubella IgM (serum)- presence	Rubella IgM
Rubella IgG (serum) - in units/volume	Rubella IgG
Rubella IgG (serum)- presence	Rubella IgG
Thyroxine free (serum/plasma) - in mass/volume	Thyroxine free (serum/plasma)
Thyroxine free (serum/plasma) - in moles/volume [pmol/L]	Thyroxine free (serum/plasma)
Toxoplasma gondii IgM (serum) - in units/volume	Toxoplasma gondii IgM (serum)
Toxoplasma gondii IgM (serum) - presence	Toxoplasma gondii IgM (serum)
Toxoplasma gondii IgG (serum) - in units/volume	Toxoplasma gondii IgG (serum)
Toxoplasma gondii IgG (serum) - presence	Toxoplasma gondii IgG (serum)
Treponema pallidum Ab (serum) - immunofluorescence	Treponema pallidum Ab
Treponema pallidum Ab (serum) - presence	Treponema pallidum Ab
Treponema pallidum particle agglutination - TP-PA (serum)	Treponema pallidum TPHA
Treponema pallidum Ab (serum) - titer - TPHA	Treponema pallidum TPHA
Varicella zoster virus IgM (serum)	Varicella zoster virus IgM
Varicella zoster virus IgM (serum) - presence	Varicella zoster virus IgM

3. List of test labels originate from one laboratory-order entry by a GP

Original test label	**Substituted by indicative test label…**
Creatinine (serum/plasma) [mg/dL]	creatinine (serum) + EGFR
Estimated glomerular filtration rate - CKD-EPI	creatinine (serum) + EGFR
Estimated glomerular filtration rate - MDRD	creatinine (serum) + EGFR
Epstein Barr virus capsid Ag IgG (serum) - in units/volume	EBV IgG
Epstein Barr virus nuclear IgG Ab (serum) - in units/volume	EBV IgG
Epstein Barr virus capsid Ag IgM (serum) - in units/volume	EBV IgM
Epstein Barr virus nuclear IgM Ab (serum) - in units/volume	EBV IgM
Epstein-Barr virus capside antigen IgM (serum) - in units/volume	EBV IgM
parasites (stool)	parasites (stool)
parasites after concentration (stool)	parasites (stool)
Protein electrophoresis: albumin (serum/plasma) - in %	Protein electrophoresis
Protein electrophoresis: albumin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: alpha 1 globulin (serum/plasma) - in %	Protein electrophoresis

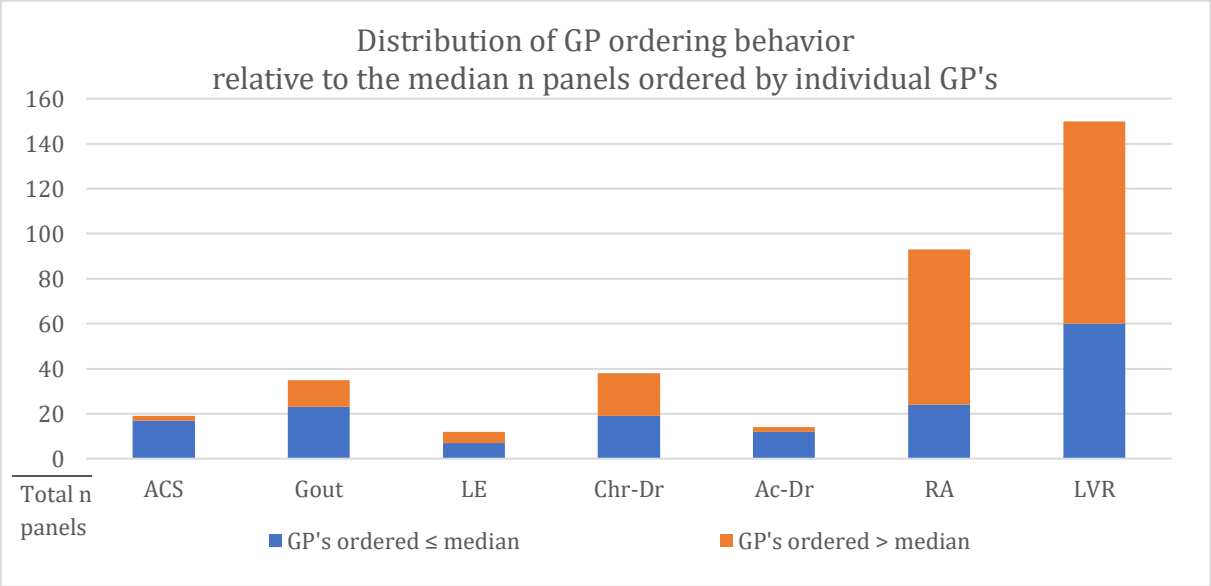
Protein electrophoresis: alpha 1 globulin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: alpha 2 globulin (serum/plasma) - in %	Protein electrophoresis
Protein electrophoresis: alpha 2 globulin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: beta 1 globulin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: beta 2 globulin (serum/plasma) - in %	Protein electrophoresis
Protein electrophoresis: beta 2 globulin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: beta globulin (serum/plasma) - in %	Protein electrophoresis
Protein electrophoresis: gamma globulin (serum/plasma) - in %	Protein electrophoresis
Protein electrophoresis: gamma globulin (serum/plasma) - in mass/volume	Protein electrophoresis
Protein electrophoresis: interpretation (serum/plasma)	Protein electrophoresis
Prostate specific Ag (serum/plasma) [µg/L]	PSA + ratio
Prostate specific Ag free (serum/plasma) [µg/L]	PSA + ratio
Prostate specific Ag free / Prostate specific Ag total (serum/plasma)	PSA + ratio
Erythrocyte distribution width (erythrocytes)	RBC + indices
Erythrocyte morphology - in Blood by automated count	RBC + indices
Erythrocyte morphology - light microscopy	RBC + indices
Erythrocyte morphology: anisocytosis (blood) - light microscopy	RBC + indices
Erythrocyte morphology: poikilocytosis (blood) - light microscopy	RBC + indices
Erythrocytes (blood)	RBC + indices
Mean corpuscular hemoglobin (erythrocytes)	RBC + indices
Mean corpuscular hemoglobin concentration (erythrocytes)	RBC + indices
Mean corpuscular volume (erythrocytes)	RBC + indices
Reticulocytes (blood) - in #/volume	Reticulocytes
Reticulocytes (blood) - in %	Reticulocytes
Rhesus big C Ag (erythrocytes)	Rhesus subgroups
Rhesus E Ag (erythrocytes)	Rhesus subgroups
Rhesus little c Ag (erythrocytes)	Rhesus subgroups
Rhesus little e Ag (erythrocytes)	Rhesus subgroups
Culture: micro organisms (urine)	Urine Culture
Epithelial cells squamous (urine) - in #/volume - automatic count	Urine Culture
Bacteria (urine) - in #/volume - automated count	Urine Culture

Yeasts (urine) - in #/volume - automated count	Urine Culture
Casts (urine) - in #/volume - automatic count	Urine sediment + microscopy
Epithelial cells (urine sediment) - in #/area - light microsc	Urine sediment + microscopy
Epithelial cells renal (urine sediment) - in #/area - light microsc	Urine sediment + microscopy
Erythrocytes (urine) - in #/volume - automated count	Urine sediment + microscopy
Leukocytes (urine) - in #/volume - automated count	Urine sediment + microscopy
Hyaline Casts (urine) - in #/volume - automatic count	Urine sediment + microscopy
Bilirubin (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Glucose (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Hemoglobin (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Ketones (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Leukocyte esterase (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Nitrite (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
pH (urine) - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Protein (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Specific gravity (urine) - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
Urobilinogen (urine) - presence - test strip	Urine test strip (pH, specific gravity, protein, urobilinogen glucose, ketones, nitrite, leucocytes esterase, Hb)
White blood cell differentiation: Basophils (blood) - in #/volume	White blood cell differentiation
White blood cell differentiation: Basophils (blood) - in #/volume - automated count	White blood cell differentiation
White blood cell differentiation: Basophils (blood) - in %	White blood cell differentiation
White blood cell differentiation: Basophils (blood) - in % - automated count	White blood cell differentiation
White blood cell differentiation:	White blood cell differentiation

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

§2. Supplemental Materials: Results remaining indications

§2.1 Ordering behaviour and utilization on the 7 remaining indications



The ordering behaviour of GP's was unevenly distributed, relative to the median number of panels ordered by individual GP's per indication. The blue bar represents the sum of all panels ordered by GP's who each ordered a lesser or equal amount of panels than the median for that indication. The orange bar is the sum of all the panels ordered by GP's who each ordered more than the median.

§2.2 Overutilization of tests on the 7 remaining indications

1. Overutilization-rates of high- and moderate volume tests

	All indications		LVR	RA	Gout	Ac-Dr	ACS	ChrDr	LE	other
CBC	Vol.	Appr.	Overutilization-rate per indication							
Hematocrit	H	0.2	+++	a	+++	a	+++	a	+++	+++
Platelets		0.31	++	a	+++	++	+++	++	++	++
RBC + ind.		0.32	+++	a	+++	a	+++	a	+++	+++
Hemoglobin		0.35	++	a	+++	a	+++	a	+++	+++
WBC diff.		0.36	+++	a	+++	+++	+++	++	+++	+++
Leukocytes		0.38	++	a	+++	+++	+++	a	+++	+++
Inflammation										
CRP	H	0.42	++	a	+++	++	++	a	+++	++
ESR	M	0.18	++	+++	++	++	+++	++	++	++
Iron status										
Iron	M	0.15	a	+	+	+	+	++	-	+
Ferritin		0.32	a	++	++	+	+	++	-	++
Nitrogen metab.										
creat. (eGFR)	H	0.52	++	a	a	a	++	++	++	++
Urate	M	0.02	+	+++	a	+	++	+	-	++
Urea		0	+	++	+++	a	+++	++	+	++
Electrolytes										
Sodium	M	0.27	++	++	++	a	++	++	+	++
Potassium	M	0.45	+	++	+	+	++	++	+	++
Liver										
GGT	H	0.3	a	+++	++	++	++	++	++	++
ALT		0.43	a	a	++	++	+	++	++	++
ALP	M	0.06	a	++	+	++	+	+	+	++
AST		0.17	a	+++	++	+++	++	++	++	++
Thyroid										
TSH	H	0.44	++	++	++	++	++	++	+	++
Vitamins										
Vitamin D	M	0.03	++	++	+	-	++	++	-	++
Cobalamins	M	0.12	+	++	+	++	+	++	-	++
Folate	M	0.13	+	++	+	+	+	+	0	+

High- (H) and moderate- (M) volume tests, ordered on respectively more than 50% and 25% of the panels across all 17 indications, and their specified appropriateness-rates. The overutilization-rates on the 7 remaining indications are specified as: +++ (>= 50%), ++ (25-49%), + (10-24%), – (<10%), 0 (no overutilization) and "a" (Test is appropriate for the indication).

2. Overutilization-rates of low-volume tests

	All indications		Liver	RA	Gout	AcD	ACS	ChrD	LE	other
Hematology	Vol.	Appr.	Overutilization-rate per indication							
Reticulocytes	L	0.17	+	+	-	+	+	+	0	+
Iron status										
TIBC	L	0.22	a	+	+	0	-	+	-	-
Biochemistry										
Protein electrophoresis	L	0	-	+	-	0	-	+	0	+
Protein (serum)	L	0	-	+	-	0	-	+	0	+
LDH	L	0.03	+	++	-	+	++	+	+	+
Bilirubin total	L	0.12	a	-	-	-	-	+	0	+
Electrolytes										
Chloride	L	0	+	+	+	+	+	++	0	++
Magnesium	L	0	-	-	-	-	0	+	-	+
Calcium	L	0.06	-	-	+	0	+	+	-	+
Bicarbonate	L	0.07	+	+	-	-	+	+	0	+
Thyroid										
T4	L	0.45	-	+	-	+	-	+	-	+

Low-volume tests (L), ordered on 10-24% of the panels across all 17 indications, and their specified appropriateness-rate. The overutilization-rates on the 7 remaining indications (and the undefined 'other indications') are specified as: ++ (25-49%), + (10-24%), – (<10%), 0 (no overutilization) and "a" (Test is appropriate for the indication).

3. Overutilization of other tests on > 10% of the panels

	All indications		LVR	RA	Gout	AcD	ACS	Chr-D	LE	other
Biochemistry	Vol.	Appr.	Overutilization-rate per indication							
Lipase	-	0	+	-	-	+	+	-	0	-
Amylase		0.08	a	-	0	+	+	+	0	-
Albumin		0.04	a	+	-	0	-	+	0	-
CK		0.49	-	-	0	-	+	-	0	-
Electrolytes										
Phosphate	-	0.09	-	-	-	-	-	+	0	-
Cardiovascular										
CK-MB	-	0	-	0	-	0	+++	-	0	-
NT-pro-BNP		0	0	0	0	0	+	0	0	-
HbA1c		0.74	-	-	+	0	0	+	0	-
Glucose		0.92	a	+	-	0	+	+	0	-
Cholesterol		0.92	a	+	-	0	+	+	0	-
Immunology										
ANF	-	0	0	++	0	0	0	0	0	-
Deamidated gliadin IgG		0	-	0	0	0	0	++	0	-
Allergology										
Total IgE	-	0	-	0	-	-	0	+	-	-
Cow milk IgE (serum)		0	-	0	0	0	0	+	0	-
Wheat IgE		0	0	0	0	0	0	+	0	-
Serology										
HCV Ab	-	0.04	a	0	0	+	+	-	-	-
HBV s Ab		0.85	a	0	0	0	+	-	-	-
Tumor markers										
CEA	-	0	0	0	0	+	0	0	0	-
Stool tests										
Hemoglobin	-	0	-	-	0	0	0	+	0	-
parasites		0.16	-	0	0	a	0	+	0	0
Cryptosp. Ag		0	-	0	0	+	0	a	0	0
Gram stain		0	-	0	0	+	0	+	0	-
Genital tests										
Gram stain	-	0	-	0	0	++	0	+	0	-

Tests ordered on more than 10% of the panels of the 7 remaining indications (and the undefined 'other indications'), which did not fall into the high, moderate or low overutilized category. The overutilization-rates are specified as: ++ (25-49%), + (10-24%), – (<10%), 0 (no overutilization) and "a" (Test is appropriate for the indication).

§2.3 Underutilization of tests on the 7 remaining indications

	LVR	RA	Gout	Ac-Dr	ACS	ChrDr	LE
Blood cells							
RBC + indices		+++		+++		+++	
Hematocrit		+++		+++		+++	
Hemoglobin		+++		+++		+++	
Leukocytes		+++				+++	
WBC differentiation		+++					
Platelets		+++					
Inflammation							
CRP		+++				+++	
ESR							
Iron status							
Iron	++						
Ferritin	+						
Transferrin + TIBC	-						
Coagulation							
PT and INR	-						
Nitrogen metab.							
Creatinine (eGFR)		+++	+++	++			
Urea				+			
Urate			+++				
Electrolytes							
Sodium				+			
Liver function							
ALT	+++	+++					
AST, GGT, ALP	+++						
Biochemistry							
Amylase	+						
Albumine	+						
Billirubin (best)	++						
Cardiovascular							
Cholesterol tests	++						
Triglycerides	++						
Glucose	++						
Serology							
Hepatitis A, B and C	-						
EBV	-						
CMV	-						
Immunology							
RA factor		+++					
Anti-CCP		++					
t-transglutaminase IgA						+	

Appropriate test-utilization for LVR, RA, Gout, Acute and chronic diarrhea , ACS and LE. The utilization-rates are specified as: +++ (>=50%), ++ (25-49%), + (10-24%) and – (<10%).

```
################################################################################
############################## R-script 1#######################################
################## Appropriateness per indication ##############################
################################################################################

## load packages and data ####
install.packages("plotrix")
library(tidyr) # to install run: install.packages("tidyr")
library(plotrix)


# LOAD DATA
setwd(dir = "C:/Users/nemoz/Dropbox/Masterpaper - Labotesten gepast en ongepast gebruik/DATA/ELMO Dataset/
Dataset_zonder_duplicates/CSV/Unique_test_aanvraag")
dat <- read.csv("XX_dataset_wod30402_wod45758uniqueTestopAanvraag.csv" , sep = ",", check.names = FALSE,
stringsAsFactors = FALSE)
dat <- separate_rows(dat, INDIC_ALL)
dat$ind <- NA


## Rename indication codes ####
q <- which(dat$INDIC_ALL == "A")
dat$ind[q] <- "GCU"
q <- which(dat$INDIC_ALL == "49601007")
dat$ind[q] <- "CVRM"
q <- which(dat$INDIC_ALL == "44054006")
dat$ind[q] <- "T2DM"
q <- which(dat$INDIC_ALL == "38341003")
dat$ind[q] <- "AHT"
q <- which(dat$INDIC_ALL == "709044004")
dat$ind[q] <- "CKD"
q <- which(dat$INDIC_ALL == "8098009")
dat$ind[q] <- "SOA"
q <- which(dat$INDIC_ALL == "69896004")
dat$ind[q] <- "RA"
q <- which(dat$INDIC_ALL == "264580006")
dat$ind[q] <- "THD"
q <- which(dat$INDIC_ALL == "235856003")
dat$ind[q] <- "Liver"
q <- which(dat$INDIC_ALL == "84229001")
dat$ind[q] <- "Fatigue"
q <- which(dat$INDIC_ALL == "B")
dat$ind[q] <- "MFU"
q <- which(dat$INDIC_ALL == "271737000")
dat$ind[q] <- "Anemia"
q <- which(dat$INDIC_ALL == "59282003")
dat$ind[q] <- "LE"
q <- which(dat$INDIC_ALL == "394659003")
dat$ind[q] <- "ACS"
q <- which(dat$INDIC_ALL == "409966000")
dat$ind[q] <- "Acute-D"
q <- which(dat$INDIC_ALL == "236071009")
dat$ind[q] <- "Chr-D"
q <- which(dat$INDIC_ALL == "90560007")
dat$ind[q] <- "Gout"
```

```
q <- which(dat$INDIC_ALL == "99")
dat$ind[q] <- "Other"



# Appropriateness-prop per indication, corrected for appropriate tests of other indications on multiple-indication pan
els
IDs <- unique(dat$ind)
results <- data.frame(ind = IDs, totaal = NA, prop = NA, sd = NA)
# for-loop
for (i in 1:nrow(results)) {
  j <- which(dat$ind == results$ind[i])
  dat_subset <- dat[j,]
  Aanvr <- unique(dat_subset$TXT_WRKFLOW_IDN)
  dat_Aanvr <- data.frame(Aanvr = Aanvr, prop = NA , sd = NA)
  for (k in 1:nrow(dat_Aanvr)) {                          #alternative aggregate(dat_subset$LAB_APPROP, by = list(d
at_subset$TXT_WRKFLOW_IDN), FUN = mean)
    l <- which(dat_subset$TXT_WRKFLOW_IDN == dat_Aanvr$Aanvr[k])
    dat_subset_Aanvr <- dat_subset[l,]
    p <- which(dat_subset_Aanvr$LAB_APPROP == 1)

    # T2DM
    if (results$ind[i] == "T2DM") {
      a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
      a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
      a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
      a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
      a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
      a <- append(a,grep("HbA1C", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
      a <- append(a,grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
      a <- append(a,grep("potassium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
      a <- append(a,grep("albumin/creatinine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
      a <- append(a,grep("albumine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))  #komt overee
n met albumine urine
      a <- unique(a)
      b <- which(a %in% p)
      p <- p[-b]
      if (length(p) >0) {
        dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
        dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
        dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
      } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
    }

    #GCU
    if (results$ind[i] == "GCU") {
      a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
      a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
      a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
```

```
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
     dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
     dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
     dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
   }

   #CVRM
   if (results$ind[i] =="CVRM") {
    a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("alanine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("gamma", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Creatine kinase (serum/plasma)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = T
RUE, fixed = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
     dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
     dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
     dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
   }

   #AHT
   if (results$ind[i] == "AHT") {
    a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("potassium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("sodium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("TSH", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("albumin/creatinine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
```

```
    a <- append(a,grep("albumine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))  #komt overee
n met albumine urine
    a <- append(a,agrep("Protein (urine)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Protein/Creatinine (urine)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRU
E))
    a <- append(a,grep("meta", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  # CKD
  if (results$ind[i] == "CKD") {
    a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("potassium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("albumin/creatinine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("albumine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))  #komt overee
n met albumine urine
    a <- append(a,agrep("Protein (urine)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Protein/Creatinine (urine)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRU
E))
    a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Parathyrin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("25-OH-vitamin D", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Calcium (serum/plasma) - in moles/volume [mmol/L]", dat_subset_Aanvr$Test_unique_aan
vraag, ignore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Phosphate (serum/plasma)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE
, fixed = TRUE))
    a <- append(a,grep("bicarb", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }
```

```
  #THD
  if (results$ind[i] == "THD") {
    a <- grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("differentiation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("c reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("TSH", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("T4", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("triiodo", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("thyropero", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  # Fatigue
  if (results$ind[i] == "Fatigue") {
    a <- grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case =
TRUE, fixed = TRUE)
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("differentiation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("c reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("TSH", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("T4", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("potassium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("sodium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("alanine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("platelets", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("sedimentation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("ferritin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("aspartate", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
```

```
  }

  #MFU
  if (results$ind[i] == "MFU") {
    a <- grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case =
TRUE, fixed = TRUE)
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("differentiation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("c reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("alanine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("platelets", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Creatine kinase (serum/plasma)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = T
RUE, fixed = TRUE))
    a <- append(a,grep("HCG", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("gamma", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("potassium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
     dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
     dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
     dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  # Anemia
  if (results$ind[i] == "Anemia") {
    a <- grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("differentiation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("c reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("TSH", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("alanine", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("platelets", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("sedimentation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("ferritin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Total iron-binding capacity saturation (serum/plasma) - in %", dat_subset_Aanvr$Test_uniq
ue_aanvraag, ignore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Iron binding capacity (serum/plasma)  [µg/dL]", dat_subset_Aanvr$Test_unique_aanvraag,
ignore.case = TRUE, fixed =TRUE))
```

```
    a <- append(a,grep("transferrin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Iron (serum/plasma) - in mass/volume [µg/dl]", dat_subset_Aanvr$Test_unique_aanvraag, f
ixed = TRUE))
    a <- append(a,grep("reticulo", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("lactate", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("folate", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("cobalamin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("gamma", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  #Liver
  if (results$ind[i] == "Liver") {
    a <- grep("cholesterol", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("Glucose (serum/plasma) - unspecified time", dat_subset_Aanvr$Test_unique_aanvraag, ign
ore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Glucose postprandial", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixe
d = TRUE))
    a <- append(a,grep("Glucose fasted", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE, fixed = T
RUE))
    a <- append(a,grep("triglyceride", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("alanin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("ferritin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("aspartate", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hbv", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hepatitis", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("gamma", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Total iron-binding capacity saturation (serum/plasma) - in %", dat_subset_Aanvr$Test_uniq
ue_aanvraag, ignore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("Iron binding capacity (serum/plasma)  [µg/dL]", dat_subset_Aanvr$Test_unique_aanvraag,
ignore.case = TRUE, fixed =TRUE))
    a <- append(a,grep("transferrin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Iron (serum/plasma) - in mass/volume [µg/dl]", dat_subset_Aanvr$Test_unique_aanvraag, f
ixed = TRUE))
    a <- append(a,grep("Alkaline phosphatase (serum/plasma) [U/L]", dat_subset_Aanvr$Test_unique_aanvraag, fix
ed = TRUE))
    a <- append(a,grep("bilirub", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("amylase", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("hcv", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("inr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Albumin (serum/plasma) - [g/L]", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case =
TRUE,fixed=TRUE))
    a <- append(a,grep("ebv", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("cmv", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
```

```
  if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
  } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
  dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
}

#SOA
if (results$ind[i] == "SOA") {
  a <- grep("HIV", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
  a <- append(a,grep("HBV", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("gono", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("chlamy", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("RPR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("TPHA", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("Trepo", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("VDRL", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("Tricho", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("Herpes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- unique(a)
  b <- which(a %in% p)
  p <- p[-b]
  if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
  } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
  dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
}

#Gout
if (results$ind[i] == "Gout") {
  a <- grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
  a <- append(a,grep("urate", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- append(a,grep("urate crystals", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
  a <- unique(a)
  b <- which(a %in% p)
  p <- p[-b]
  if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
  } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
  dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
}

#ACS
if (results$ind[i] == "ACS") {
  a <- grep("Tropo", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
  b <- which(a %in% p)
  p <- p[-b]
  if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
```

```
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
   } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
   dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  #LE
  if (results$ind[i] == "LE") {
   a <- grep("dimer", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
   b <- which(a %in% p)
   p <- p[-b]
   if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
   } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
   dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  #RA
  if (results$ind[i] == "RA") {
   a <- grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
   a <- append(a,grep("differentiation", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("C reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("platelets", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("citrullinated ", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Rheumatoid", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Alanin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- unique(a)
   b <- which(a %in% p)
   p <- p[-b]
   if (length(p) >0) {
    dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
    dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
   } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
   dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
  }

  # Acute diarree
  if (results$ind[i] == "Acute-D") {
   a <- grep("eGFR", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
   a <- append(a,grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Sodium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Clostridium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Giardia", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,agrep("Culture: micro organisms (stool)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case =
TRUE, fixed = TRUE))
   a <- append(a,grep("Parasites", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
   a <- append(a,grep("Rotavirus", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
```

```
    a <- append(a,grep("urea", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Adeno", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
   }

   #Chronische diarrhee
   if (results$ind[i] == "Chr-D") {
    a <- grep("RBC", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE)
    a <- append(a,grep("hematocr", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Hemoglobin (blood)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("c reactive", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Clostridium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Giardia", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Culture: micro organisms (stool)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case =
 TRUE, fixed = TRUE))
    a <- append(a,grep("calprotectin", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("Cryptosporidium", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,grep("leukocytes", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- append(a,agrep("Tissue transglutaminase IgA (serum) - in units/volume", dat_subset_Aanvr$Test_unique_a
anvraag, ignore.case = TRUE, fixed = TRUE))
    a <- append(a,grep("iga (total)", dat_subset_Aanvr$Test_unique_aanvraag, ignore.case = TRUE))
    a <- unique(a)
    b <- which(a %in% p)
    p <- p[-b]
    if (length(p) >0) {
      dat_subset_Aanvr <- dat_subset_Aanvr[-p,]
      dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
      dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)
    } else {dat_Aanvr$prop[k] <- mean(dat_subset_Aanvr$LAB_APPROP)
    dat_Aanvr$sd[k] <- sd(dat_subset_Aanvr$LAB_APPROP)}
   }

  }
  results$prop[i] <- mean(dat_Aanvr$prop)
  results$sd[i] <- sd(dat_Aanvr$prop)
  results$totaal[i] <- length(unique(dat_subset$TXT_WRKFLOW_IDN))
}

write.csv(results, "COR_prop_ind.csv" )


################################################################################
################################ R script 2 ####################################
####################### Analysis of overutilization ############################
################################################################################
```

```
## load and install packages ####
install.packages("tidyverse")
install.packages("ggpubr")
library(tidyverse)
library(tidyr) # to install run: install.packages("tidyr")
library(car)
library(ggpubr)
library(rstatix)
library(ggplot2)
library(dunn.test)
library(MASS)

## LOAD DATA ####
setwd(dir = "C:/Users/nemoz/Dropbox/Masterpaper - Labotesten gepast en ongepast gebruik/DATA/ELMO Dataset/
Dataset_zonder_duplicates/CSV/Unique_test_aanvraag")
dat <- read.csv("XX_dataset_wod30402_wod45758uniqueTestopAanvraag.csv" , sep = ",", check.names = FALSE,
stringsAsFactors = FALSE)

## Distribution of tests across all-single-multiple indication panels ####
# PS: Analysis must be BEFORE separation of multiple-indication rows!
# All panels
Testen <- unique(dat$Test_unique_aanvraag)
test_d <- data.frame (test = Testen, totaal = NA, proc = NA, prop= NA, sd = NA, SE = NA)
for (i in 1:nrow(test_d)) {
  j <- which(dat$Test_unique_aanvraag == test_d$test[i])
  dat_subset <- dat[j,]
  test_d$totaal[i] <- length(dat_subset$Test_unique_aanvraag)
  test_d$prop[i] <- mean(dat_subset$LAB_APPROP)
  test_d$sd[i] <- sd(dat_subset$LAB_APPROP)
  test_d$SE[i] <- ((sd(dat_subset$LAB_APPROP))/(sqrt((length(dat_subset$Test_unique_aanvraag)))))
  test_d$proc[i] <- ((length(dat_subset$Test_unique_aanvraag))/(length(unique(dat$TXT_WRKFLOW_IDN))))
}



## Separation of multiple-indication rows -> 1 indication per test per row ####
dat <- separate_rows(dat, INDIC_ALL)

## Analysis per indication: all panels ####
# A General Check-up
GCU <- which(dat$INDIC_ALL=="A")
dat_GCU <- dat[GCU,]
test_GCU <- unique(dat_GCU$Test_unique_aanvraag)
results_GCU <- data.frame(test = test_GCU , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_GCU)) {
  j <- which(dat_GCU$Test_unique_aanvraag == results_GCU$test[i])
  dat_subset_GCU <- dat_GCU[j,]
  k <- which(dat_subset_GCU$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_GCU <- dat_subset_GCU[-k,]
  } else {  dat_subset_GCU <- dat_subset_GCU}
  results_GCU$totaal[i] <- length(dat_subset_GCU$Test_unique_aanvraag)
  results_GCU$totaal_pc[i] <- length(dat_subset_GCU$Test_unique_aanvraag)/length(unique(dat_GCU$TXT_WR
KFLOW_IDN))
}
```

```
# Cardiovascular disease management (49601007)
CVRM <- which(dat$INDIC_ALL=="49601007")
dat_CVRM <- dat[CVRM,]
test_CVRM <- unique(dat_CVRM$Test_unique_aanvraag)
results_CVRM <- data.frame(test = test_CVRM , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_CVRM)) {
  j <- which(dat_CVRM$Test_unique_aanvraag == results_CVRM$test[i])
  dat_subset_CVRM <- dat_CVRM[j,]
  k <- which(dat_subset_CVRM$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_CVRM <- dat_subset_CVRM[-k,]
  } else {  dat_subset_CVRM <- dat_subset_CVRM}
  results_CVRM$totaal[i] <- length(dat_subset_CVRM$Test_unique_aanvraag)
  results_CVRM$totaal_pc[i] <- length(dat_subset_CVRM$Test_unique_aanvraag)/length(unique(dat_CVRM$TXT
_WRKFLOW_IDN))
}


# Hypertensie (38341003)
AHT <- which(dat$INDIC_ALL=="38341003")
dat_AHT <- dat[AHT,]
test_AHT <- unique(dat_AHT$Test_unique_aanvraag)
results_AHT <- data.frame(test = test_AHT , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_AHT)) {
  j <- which(dat_AHT$Test_unique_aanvraag == results_AHT$test[i])
  dat_subset_AHT <- dat_AHT[j,]
  k <- which(dat_subset_AHT$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_AHT <- dat_subset_AHT[-k,]
  } else {  dat_subset_AHT <- dat_subset_AHT}
  results_AHT$totaal[i] <- length(dat_subset_AHT$Test_unique_aanvraag)
  results_AHT$totaal_pc[i] <- length(dat_subset_AHT$Test_unique_aanvraag)/length(unique(dat_AHT$TXT_WR
KFLOW_IDN))
}



# Chronische Nierinsufficiëntie (709044004)
CKD <- which(dat$INDIC_ALL=="709044004")
dat_CKD <- dat[CKD,]
test_CKD <- unique(dat_CKD$Test_unique_aanvraag)
results_CKD <- data.frame(test = test_CKD , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_CKD)) {
  j <- which(dat_CKD$Test_unique_aanvraag == results_CKD$test[i])
  dat_subset_CKD <- dat_CKD[j,]
  k <- which(dat_subset_CKD$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_CKD <- dat_subset_CKD[-k,]
  } else {  dat_subset_CKD <- dat_subset_CKD}
  results_CKD$totaal[i] <- length(dat_subset_CKD$Test_unique_aanvraag)
  results_CKD$totaal_pc[i] <- length(dat_subset_CKD$Test_unique_aanvraag)/length(unique(dat_CKD$TXT_WR
KFLOW_IDN))
```

```
}


# Type 2 Diabetes (44054006)
T2DM <- which(dat$INDIC_ALL=="44054006")
dat_T2DM <- dat[T2DM,]
test_T2DM <- unique(dat_T2DM$Test_unique_aanvraag)
results_T2DM <- data.frame(test = test_T2DM , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_T2DM)) {
  j <- which(dat_T2DM$Test_unique_aanvraag == results_T2DM$test[i])
  dat_subset_T2DM <- dat_T2DM[j,]
  k <- which(dat_subset_T2DM$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_T2DM <- dat_subset_T2DM[-k,]
  } else {  dat_subset_T2DM <- dat_subset_T2DM}
  results_T2DM$totaal[i] <- length(dat_subset_T2DM$Test_unique_aanvraag)
  results_T2DM$totaal_pc[i] <- length(dat_subset_T2DM$Test_unique_aanvraag)/length(unique(dat_T2DM$TXT_
WRKFLOW_IDN))
}

# STI (8098009)
STI <- which(dat$INDIC_ALL=="8098009")
dat_STI <- dat[STI,]
k <- unique(dat$TXT_WRKFLOW_IDN)
test_STI <- unique(dat_STI$Test_unique_aanvraag)
results_STI <- data.frame(test = test_STI , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_STI)) {
  j <- which(dat_STI$Test_unique_aanvraag == results_STI$test[i])
  dat_subset_STI <- dat_STI[j,]
  k <- which(dat_subset_STI$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_STI <- dat_subset_STI[-k,]
  } else {  dat_subset_STI <- dat_subset_STI}
  results_STI$totaal[i] <- length(dat_subset_STI$Test_unique_aanvraag)
  results_STI$totaal_pc[i] <- length(dat_subset_STI$Test_unique_aanvraag)/length(unique(dat_STI$TXT_WRKFL
OW_IDN))
}


# Fatigue (84229001)
Fatigue <- which(dat$INDIC_ALL=="84229001")
dat_Fatigue <- dat[Fatigue,]
test_Fatigue <- unique(dat_Fatigue$Test_unique_aanvraag)
results_Fatigue <- data.frame(test = test_Fatigue , totaal = NA)
for (i in 1:nrow(results_Fatigue)) {
  j <- which(dat_Fatigue$Test_unique_aanvraag == results_Fatigue$test[i])
  dat_subset_Fatigue <- dat_Fatigue[j,]
  k <- which(dat_subset_Fatigue$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_Fatigue <- dat_subset_Fatigue[-k,]
  } else {  dat_subset_Fatigue <- dat_subset_Fatigue}
  results_Fatigue$totaal[i] <- length(dat_subset_Fatigue$Test_unique_aanvraag)
  results_Fatigue$totaal_pc[i] <- length(dat_subset_Fatigue$Test_unique_aanvraag)/length(unique(dat_Fatigue$TX
T_WRKFLOW_IDN))
}
```

```
# Schiklklier (264580006)
THD <- which(dat$INDIC_ALL=="264580006")
dat_THD <- dat[THD,]
test_THD <- unique(dat_THD$Test_unique_aanvraag)
results_THD <- data.frame(test = test_THD , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_THD)) {
  j <- which(dat_THD$Test_unique_aanvraag == results_THD$test[i])
  dat_subset_THD <- dat_THD[j,]
  k <- which(dat_subset_THD$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_THD <- dat_subset_THD[-k,]
  } else {  dat_subset_THD <- dat_subset_THD}

  results_THD$totaal[i] <- length(dat_subset_THD$Test_unique_aanvraag)
  results_THD$totaal_pc[i] <- length(dat_subset_THD$Test_unique_aanvraag)/length(unique(dat_THD$TXT_WR
KFLOW_IDN))
}


# Liverlijden (235856003)
Liver <- which(dat$INDIC_ALL=="235856003")
dat_Liver <- dat[Liver,]
test_Liver <- unique(dat_Liver$Test_unique_aanvraag)
results_Liver <- data.frame(test = test_Liver , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_Liver)) {
  j <- which(dat_Liver$Test_unique_aanvraag == results_Liver$test[i])
  dat_subset_Liver <- dat_Liver[j,]
  k <- which(dat_subset_Liver$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_Liver <- dat_subset_Liver[-k,]
  } else {  dat_subset_Liver <- dat_subset_Liver}
  results_Liver$totaal[i] <- length(dat_subset_Liver$Test_unique_aanvraag)
  results_Liver$totaal_pc[i] <- length(dat_subset_Liver$Test_unique_aanvraag)/length(unique(dat_Liver$TXT_WR
KFLOW_IDN))
}


# MFU Follow up (B)
MFU <- which(dat$INDIC_ALL=="B")
dat_MFU <- dat[MFU,]
test_MFU <- unique(dat_MFU$Test_unique_aanvraag)
results_MFU <- data.frame(test = test_MFU , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_MFU)) {
  j <- which(dat_MFU$Test_unique_aanvraag == results_MFU$test[i])
  dat_subset_MFU <- dat_MFU[j,]
  k <- which(dat_subset_MFU$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_MFU <- dat_subset_MFU[-k,]
  } else {  dat_subset_MFU <- dat_subset_MFU}
  results_MFU$totaal[i] <- length(dat_subset_MFU$Test_unique_aanvraag)
  results_MFU$totaal_pc[i] <- length(dat_subset_MFU$Test_unique_aanvraag)/length(unique(dat_MFU$TXT_WR
KFLOW_IDN))
}
```

```
# Anemia (271737000)
Anem <- which(dat$INDIC_ALL=="271737000")
dat_Anem <- dat[Anem,]
test_Anem <- unique(dat_Anem$Test_unique_aanvraag)
results_Anem <- data.frame(test = test_Anem , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_Anem)) {
  j <- which(dat_Anem$Test_unique_aanvraag == results_Anem$test[i])
  dat_subset_Anem <- dat_Anem[j,]
  k <- which(dat_subset_Anem$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_Anem <- dat_subset_Anem[-k,]
  } else {  dat_subset_Anem <- dat_subset_Anem}
  results_Anem$totaal[i] <- length(dat_subset_Anem$Test_unique_aanvraag)
  results_Anem$totaal_pc[i] <- length(dat_subset_Anem$Test_unique_aanvraag)/length(unique(dat_Anem$TXT_W
RKFLOW_IDN))
}


# Reumatoïde Arthritis (69896004)
RA <- which(dat$INDIC_ALL=="69896004")
dat_RA <- dat[RA,]
test_RA <- unique(dat_RA$Test_unique_aanvraag)
results_RA <- data.frame(test = test_RA , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_RA)) {
  j <- which(dat_RA$Test_unique_aanvraag == results_RA$test[i])
  dat_subset_RA <- dat_RA[j,]
  k <- which(dat_subset_RA$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_RA <- dat_subset_RA[-k,]
  } else {  dat_subset_RA <- dat_subset_RA}
  results_RA$totaal[i] <- length(dat_subset_RA$Test_unique_aanvraag)
  results_RA$totaal_pc[i] <- length(dat_subset_RA$Test_unique_aanvraag)/length(unique(dat_RA$TXT_WRKFLO
W_IDN))
}


# Gout (90560007)
gout <- which(dat$INDIC_ALL=="90560007")
dat_gout <- dat[gout,]
test_gout <- unique(dat_gout$Test_unique_aanvraag)
results_gout <- data.frame(test = test_gout , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_gout)) {
  j <- which(dat_gout$Test_unique_aanvraag == results_gout$test[i])
  dat_subset_gout <- dat_gout[j,]
  k <- which(dat_subset_gout$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_gout <- dat_subset_gout[-k,]
  } else {  dat_subset_gout <- dat_subset_gout}
  results_gout$totaal[i] <- length(dat_subset_gout$Test_unique_aanvraag)
  results_gout$totaal_pc[i] <- length(dat_subset_gout$Test_unique_aanvraag)/length(unique(dat_gout$TXT_WRKF
LOW_IDN))
}
```

```
# Acute diarree (409966000)
AcD <- which(dat$INDIC_ALL=="409966000")
dat_AcD <- dat[AcD,]
test_AcD <- unique(dat_AcD$Test_unique_aanvraag)
results_AcD <- data.frame(test = test_AcD , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_AcD)) {
  j <- which(dat_AcD$Test_unique_aanvraag == results_AcD$test[i])
  dat_subset_AcD <- dat_AcD[j,]
  k <- which(dat_subset_AcD$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_AcD <- dat_subset_AcD[-k,]
  } else {  dat_subset_AcD <- dat_subset_AcD}
  results_AcD$totaal[i] <- length(dat_subset_AcD$Test_unique_aanvraag)
  results_AcD$totaal_pc[i] <- length(dat_subset_AcD$Test_unique_aanvraag)/length(unique(dat_AcD$TXT_WRK
FLOW_IDN))
}


# Acute Coronary Syndrome (394659003)
ACS <- which(dat$INDIC_ALL=="394659003")
dat_ACS <- dat[ACS,]
test_ACS <- unique(dat_ACS$Test_unique_aanvraag)
results_ACS <- data.frame(test = test_ACS , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_ACS)) {
  j <- which(dat_ACS$Test_unique_aanvraag == results_ACS$test[i])
  dat_subset_ACS <- dat_ACS[j,]
  k <- which(dat_subset_ACS$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_ACS <- dat_subset_ACS[-k,]
  } else {  dat_subset_ACS <- dat_subset_ACS}
  results_ACS$totaal[i] <- length(dat_subset_ACS$Test_unique_aanvraag)
  results_ACS$totaal_pc[i] <- length(dat_subset_ACS$Test_unique_aanvraag)/length(unique(dat_ACS$TXT_WRK
FLOW_IDN))
}


# Chronische diarree (236071009)
ChrD <- which(dat$INDIC_ALL=="236071009")
dat_ChrD <- dat[ChrD,]
test_ChrD <- unique(dat_ChrD$Test_unique_aanvraag)
results_ChrD <- data.frame(test = test_ChrD , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_ChrD)) {
  j <- which(dat_ChrD$Test_unique_aanvraag == results_ChrD$test[i])
  dat_subset_ChrD <- dat_ChrD[j,]
  k <- which(dat_subset_ChrD$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_ChrD <- dat_subset_ChrD[-k,]
  } else {  dat_subset_ChrD <- dat_subset_ChrD}
  results_ChrD$totaal[i] <- length(dat_subset_ChrD$Test_unique_aanvraag)
  results_ChrD$totaal_pc[i] <- length(dat_subset_ChrD$Test_unique_aanvraag)/length(unique(dat_ChrD$TXT_WR
KFLOW_IDN))
}
```

```
# Long embolen (59282003)
LE <- which(dat$INDIC_ALL=="59282003")
dat_LE <- dat[LE,]
test_LE <- unique(dat_LE$Test_unique_aanvraag)
results_LE <- data.frame(test = test_LE , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_LE)) {
  j <- which(dat_LE$Test_unique_aanvraag == results_LE$test[i])
  dat_subset_LE <- dat_LE[j,]
  k <- which(dat_subset_LE$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_LE <- dat_subset_LE[-k,]
  } else {  dat_subset_LE <- dat_subset_LE}
  results_LE$totaal[i] <- length(dat_subset_LE$Test_unique_aanvraag)
  results_LE$totaal_pc[i] <- length(dat_subset_LE$Test_unique_aanvraag)/length(unique(dat_LE$TXT_WRKFLO
W_IDN))
}


# Overige (99)
other <- which(dat$INDIC_ALL=="99")
dat_other <- dat[other,]
test_other <- unique(dat_other$Test_unique_aanvraag)
results_other <- data.frame(test = test_other , totaal = NA, totaal_pc = NA)
for (i in 1:nrow(results_other)) {
  j <- which(dat_other$Test_unique_aanvraag == results_other$test[i])
  dat_subset_other <- dat_other[j,]
  k <- which(dat_subset_other$LAB_APPROP == 1)
  if (length(k) > 0) {
    dat_subset_other <- dat_subset_other[-k,]
  } else {  dat_subset_other <- dat_subset_other}
  results_other$totaal[i] <- length(dat_subset_other$Test_unique_aanvraag)
  results_other$totaal_pc[i] <- length(dat_subset_other$Test_unique_aanvraag)/length(unique(dat_other$TXT_WR
KFLOW_IDN))
}



## Resulting dataframe: test ordering frequencies per indication  ####
results <- data.frame(test = test_d$test , proc = NA , class = NA , appr = NA , sd = NA ,
                      GCU = NA , CVRM = NA , AHT = NA , CKD = NA, T2DM = NA ,  STI = NA, Fatigue = NA ,
                      THD = NA , Liver = NA,  MFU = NA, Anem = NA , RA = NA , gout = NA ,
                      AcD = NA, ACS = NA , ChrD = NA , LE = NA , other = NA )
ind <- c("GCU", "CVRM" ,"AHT","CKD","T2DM","STI","Fatigue","THD","Liver","MFU","Anem","RA","Gout",
"AcD","ACS","ChrD","LE","other")
results[is.na(results)] = 0
for (i in 1:nrow(test_d)) {
  j <- which(results$test == test_d$test[i])
  results$proc[j] <- test_d$proc[i]
  results$appr[j] <- test_d$prop[i]
  results$sd[j] <- test_d$sd[i]
}

# Overutilization according to High-, Moderate- and Low-volume criteria ####
for (i in 1:nrow(results)) {
  j <- which (results$proc >= 0.50)
```

```
  results$class[j] <- 'H'
}
for (i in 1:nrow(results)) {
  j <- which (results$proc <0.50 & results$proc >= 0.25)
  results$class[j] <- 'M'
}
for (i in 1:nrow(results)) {
  j <- which (results$proc <0.25 & results$proc >= 0.1)
  results$class[j] <- 'L'
}
for (i in 1:nrow(results)) {
  j <- which (results$proc <0.10)
  results$class[j] <- '-'
}


# Fill Restulting dataframe with data from every indication ####
for (i in 1:nrow(results_GCU)) {
  j <- which(results$test == results_GCU$test[i])
  results$GCU[j] <- results_GCU$totaal_pc[i]
}
for (i in 1:nrow(results_CVRM)) {
  j <- which(results$test == results_CVRM$test[i])
  results$CVRM[j] <- results_CVRM$totaal_pc[i]
}
for (i in 1:nrow(results_AHT)) {
  j <- which(results$test == results_AHT$test[i])
  results$AHT[j] <- results_AHT$totaal_pc[i]
}
for (i in 1:nrow(results_CKD)) {
  j <- which(results$test == results_CKD$test[i])
  results$CKD[j] <- results_CKD$totaal_pc[i]
}
for (i in 1:nrow(results_T2DM)) {
  j <- which(results$test == results_T2DM$test[i])
  results$T2DM[j] <- results_T2DM$totaal_pc[i]
}
for (i in 1:nrow(results_STI)) {
  j <- which(results$test == results_STI$test[i])
  results$STI[j] <- results_STI$totaal_pc[i]
}
for (i in 1:nrow(results_Fatigue)) {
  j <- which(results$test == results_Fatigue$test[i])
  results$Fatigue[j] <- results_Fatigue$totaal_pc[i]
}
for (i in 1:nrow(results_THD)) {
  j <- which(results$test == results_THD$test[i])
  results$THD[j] <- results_THD$totaal_pc[i]
}
for (i in 1:nrow(results_Liver)) {
  j <- which(results$test == results_Liver$test[i])
  results$Liver[j] <- results_Liver$totaal_pc[i]
}
for (i in 1:nrow(results_MFU)) {
  j <- which(results$test == results_MFU$test[i])
```

```
  results$MFU[j] <- results_MFU$totaal_pc[i]
}
for (i in 1:nrow(results_Anem)) {
  j <- which(results$test == results_Anem$test[i])
  results$Anem[j] <- results_Anem$totaal_pc[i]
}
for (i in 1:nrow(results_RA)) {
  j <- which(results$test == results_RA$test[i])
  results$RA[j] <- results_RA$totaal_pc[i]
}
for (i in 1:nrow(results_gout)) {
  j <- which(results$test == results_gout$test[i])
  results$gout[j] <- results_gout$totaal_pc[i]
}
for (i in 1:nrow(results_AcD)) {
  j <- which(results$test == results_AcD$test[i])
  results$AcD[j] <- results_AcD$totaal_pc[i]
}
for (i in 1:nrow(results_ACS)) {
  j <- which(results$test == results_ACS$test[i])
  results$ACS[j] <- results_ACS$totaal_pc[i]
}
for (i in 1:nrow(results_ChrD)) {
  j <- which(results$test == results_ChrD$test[i])
  results$ChrD[j] <- results_ChrD$totaal_pc[i]
}
for (i in 1:nrow(results_LE)) {
  j <- which(results$test == results_LE$test[i])
  results$LE[j] <- results_LE$totaal_pc[i]
}
for (i in 1:nrow(results_other)) {
  j <- which(results$test == results_other$test[i])
  results$other[j] <- results_other$totaal_pc[i]
}

write.csv(results, "XX_Alle_testen_indicaties.csv")



################################################################################
################################## R script 3 ##################################
####################### Analysis of underutilization ###########################
################################################################################



## Underutilization: dataframe ####
results_ap <- data.frame(     test=results$test,  GCU = NA , CVRM = NA , AHT = NA , CKD = NA, T2DM = NA ,
STI = NA, Fatigue = NA ,
                              THD = NA , Liver = NA,  MFU = NA, Anem = NA , RA = NA , gout = NA ,
                              AcD = NA, ACS = NA , ChrD = NA , LE = NA )
results_ap[is.na(results_ap)] = 0.000000

## Defining Appropriate tests per indication ####
# GCU
```

```
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$GCU[a] <- results$GCU[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$GCU[a] <- results$GCU[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$GCU[a] <- results$GCU[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$GCU[a] <- results$GCU[a]
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$GCU[a] <- results$GCU[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$GCU[a] <- results$GCU[a]


# CVRM
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("alanine", results_ap$test, ignore.case = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("gamma", results_ap$test, ignore.case = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]
a <- grep("Creatine kinase (serum/plasma)", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CVRM[a] <- results$CVRM[a]


# T2DM
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("HbA1C", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("potassium", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("albumin/creatinine", results_ap$test, ignore.case = TRUE)
results_ap$T2DM[a] <- results$T2DM[a]
a <- grep("albumine", results_ap$test, ignore.case = TRUE)  #komt overeen met albumine urine
results_ap$T2DM[a] <- results$T2DM[a]
```

```
# AHT
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("potassium", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("sodium", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("TSH", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("albumin/creatinine", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("albumine", results_ap$test, ignore.case = TRUE)  #komt overeen met albumine urine
results_ap$AHT[a] <- results$AHT[a]
a <- agrep("Protein (urine)", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- agrep("Protein/Creatinine (urine)", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- results$AHT[a]
a <- grep("meta", results_ap$test, ignore.case = TRUE)
results_ap$AHT[a] <- "?a?"

# CKD
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("potassium", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("albumin/creatinine", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("albumine", results_ap$test, ignore.case = TRUE)  #komt overeen met albumine urine
results_ap$CKD[a] <- results$CKD[a]
a <- agrep("Protein (urine)", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- agrep("Protein/Creatinine (urine)", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
```

```
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Parathyrin", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- agrep("25-OH-vitamin D", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Calcium (serum/plasma) - in moles/volume [mmol/L]", results_ap$test, ignore.case = TRUE, fixed = TR
UE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("Phosphate (serum/plasma)", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$CKD[a] <- results$CKD[a]
a <- grep("bicarb", results_ap$test, ignore.case = TRUE)
results_ap$CKD[a] <- results$CKD[a]



# THD
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("differentiation", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("c reactive", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("TSH", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("T4", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("triiodo", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]
a <- grep("thyropero", results_ap$test, ignore.case = TRUE)
results_ap$THD[a] <- results$THD[a]



# Fatigue
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("differentiation", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
```

```
a <- grep("c reactive", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("TSH", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("T4", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("potassium", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("sodium", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("alanine", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("platelets", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("sedimentation", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("ferritin", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]
a <- grep("aspartate", results_ap$test, ignore.case = TRUE)
results_ap$Fatigue[a] <- results$Fatigue[a]


# MFU
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("differentiation", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("c reactive", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("alanine", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("platelets", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("Creatine kinase (serum/plasma)", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("HCG", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a]
```

```
a <- grep("gamma", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]
a <- grep("potassium", results_ap$test, ignore.case = TRUE)
results_ap$MFU[a] <- results$MFU[a]



# Anemia
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("differentiation", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("c reactive", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("TSH", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("alanine", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("platelets", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("sedimentation", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("ferritin", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("Total iron-binding capacity saturation (serum/plasma) - in %", results_ap$test, ignore.case = TRUE, fixed
 = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("Iron binding capacity (serum/plasma)  [µg/dL]", results_ap$test, ignore.case = TRUE, fixed =TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("transferrin", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("Iron (serum/plasma) - in mass/volume [µg/dl]", results_ap$test, fixed = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("reticulo", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("lactate", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("folate", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("cobalamin", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]
a <- grep("gamma", results_ap$test, ignore.case = TRUE)
results_ap$Anem[a] <- results$Anem[a]



# Liver
a <- grep("cholesterol", results_ap$test, ignore.case = TRUE)
```

```
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Glucose (serum/plasma) - unspecified time", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Glucose postprandial", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Glucose fasted", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("triglyceride", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("alanin", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("ferritin", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("aspartate", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("hbv", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("hepatitis", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("gamma", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Total iron-binding capacity saturation (serum/plasma) - in %", results_ap$test, ignore.case = TRUE, fixed
 = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Iron binding capacity (serum/plasma)  [µg/dL]", results_ap$test, ignore.case = TRUE, fixed =TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("transferrin", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Iron (serum/plasma) - in mass/volume [µg/dl]", results_ap$test, fixed = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Alkaline phosphatase (serum/plasma) [U/L]", results_ap$test, fixed = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("bilirub", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("amylase", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("hcv", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("inr", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("Albumin (serum/plasma) - [g/L]", results_ap$test, ignore.case = TRUE,fixed=TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("ebv", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]
a <- grep("cmv", results_ap$test, ignore.case = TRUE)
results_ap$Liver[a] <- results$Liver[a]


# STI
a <- grep("HIV", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("HBV", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("gono", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
```

```
a <- grep("chlamy", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("RPR", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("TPHA", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("Trepo", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("VDRL", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("Tricho", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]
a <- grep("Herpes", results_ap$test, ignore.case = TRUE)
results_ap$STI[a] <- results$STI[a]


# Gout [3]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$gout[a] <- results$gout[a]
a <- grep("urate", results_ap$test, ignore.case = TRUE)
results_ap$gout[a] <- results$gout[a]
a <- grep("urate crystals", results_ap$test, ignore.case = TRUE)
results_ap$gout[a] <- results$gout[a]

# ACS [2]
a <- grep("Tropo", results_ap$test, ignore.case = TRUE)
results_ap$ACS[a] <- results$ACS[a]

# LE [1]
a <- grep("dimer", results_ap$test, ignore.case = TRUE)
results_ap$LE[a] <- results$LE[a]



# RA [11]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("differentiation", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("C reactive", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("platelets", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("citrullinated ", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
a <- grep("Rheumatoid", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]
```

```
a <- grep("Alanin", results_ap$test, ignore.case = TRUE)
results_ap$RA[a] <- results$RA[a]


# AcD [12]
a <- grep("eGFR", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Sodium", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Clostridium", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Giardia", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- agrep("Culture: micro organisms (stool)", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Parasites", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Rotavirus", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("urea", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]
a <- grep("Adeno", results_ap$test, ignore.case = TRUE)
results_ap$AcD[a] <- results$AcD[a]


# ChrD [12]
a <- grep("RBC", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("hematocr", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- agrep("Hemoglobin (blood)", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("c reactive", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("Clostridium", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("Giardia", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- agrep("Culture: micro organisms (stool)", results_ap$test, ignore.case = TRUE, fixed = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("calprotectin", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("Cryptosporidium", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- grep("leukocytes", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]
a <- agrep("Tissue transglutaminase IgA (serum) - in units/volume", results_ap$test, ignore.case = TRUE, fixed = T
RUE)
results_ap$ChrD[a] <- results$ChrD[a]
```

```
a <- grep("iga (total)", results_ap$test, ignore.case = TRUE)
results_ap$ChrD[a] <- results$ChrD[a]

##################################################################################
############################### R script 3 ####################################
######################## Co-ordering probabilities ############################
##################################################################################
setwd(dir = "C:/Users/nemoz/Dropbox/Masterpaper - Labotesten gepast en ongepast gebruik/DATA/ELMO Dataset/
Dataset_zonder_duplicates/CSV/Unique_test_aanvraag")
dat <- read.csv("XX_dataset_wod30402_wod45758uniqueTestopAanvraag.csv" , sep = ",", check.names = FALSE,
stringsAsFactors = FALSE)
Test <- read.csv("XX_tests_paper.csv" , sep = ",", check.names = FALSE, stringsAsFactors = FALSE, encoding = "
UTF-8")

## get the unique indicators
Aanvragen <- unique(dat$TXT_WRKFLOW_IDN)
Test_c <- unique(Test[,1])

## get the unique triple indicators  C(n, k)= n!/[k!( n-k)!]
v_comb2 <- combn(Test_c, m = 2, simplify = FALSE)
v_comb2 <- sapply(v_comb2[!!lengths(v_comb2)], toString)
v_comb2 <- gsub(", ", ";", v_comb2)

v_comb3 <- combn(Test_c, m = 3, simplify = FALSE)
v_comb3 <- sapply(v_comb3[!!lengths(v_comb3)], toString)
v_comb3 <- gsub(", ", ";", v_comb3)

v_comb4 <- combn(Test_c, m = 4, simplify = FALSE)
v_comb4 <- sapply(v_comb4[!!lengths(v_comb4)], toString)
v_comb4 <- gsub(", ", ";", v_comb4)

v_comb5 <- combn(Test_c, m = 5, simplify = FALSE)
v_comb5 <- sapply(v_comb5[!!lengths(v_comb5)], toString)
v_comb5 <- gsub(", ", ";", v_comb5)

v_comb6 <- combn(Test_c, m = 6, simplify = FALSE)
v_comb6 <- sapply(v_comb6[!!lengths(v_comb6)], toString)
v_comb6 <- gsub(", ", ";", v_comb6)


##  Comb 2 - Data Frame
df2p <- data.frame(Test_comb2 = v_comb2, minimum = NA, tot = NA, p = NA)
for (i in 1:nrow(df2p)) {
  print(i)
  t_i <- strsplit(df2p$Test_comb2[i], split = ";")[[1]]
  v <- c()
  for (j in 1:length(Aanvragen)) {
    k <- which(dat$TXT_WRKFLOW_IDN == Aanvragen[j])
    data_subset <- dat[k,]
    testen_subset <- unique(data_subset$Test_unique_aanvraag)
    if(t_i[[1]] %in% testen_subset) {
      if (t_i[[2]] %in% testen_subset) {
        v <- append(v,1)
      }
    }
```

```
  }
  t1 <- which(t_i[[1]] == dat$Test_unique_aanvraag)
  t1 <- dat$TXT_WRKFLOW_IDN[t1]
  t2 <- which(t_i[[2]] == dat$Test_unique_aanvraag)
  t2 <- dat$TXT_WRKFLOW_IDN[t2]
  t2 <- setdiff(t2,t1)

  s <- sum(v)
  df2p$minimum[i] <- (length(t1)+length(t2))
  df2p$tot[i] <- s
  df2p$p[i] <- df2p$tot[i]/df2p$minimum[i]
}



##  Comb 3 - Data Frame
df3p <- data.frame(Test_comb3 = v_comb3, minimum = NA , tot = NA, p = NA)
for (i in 1:nrow(df3p)) {
  print(i)
  t_i <- strsplit(df3p$Test_comb3[i], split = ";")[[1]]
  v <- c()
  for (j in 1:length(Aanvragen)) {
    k <- which(dat$TXT_WRKFLOW_IDN == Aanvragen[j])
    data_subset <- dat[k,]
    testen_subset <- unique(data_subset$Test_unique_aanvraag)
    if(t_i[[1]] %in% testen_subset) {
      if (t_i[[2]] %in% testen_subset) {
        if (t_i[[3]] %in% testen_subset) {
          v <- append(v,1)
        }
      }
    }
  }
  t1 <- which(t_i[[1]] == dat$Test_unique_aanvraag)
  t1 <- dat$TXT_WRKFLOW_IDN[t1]
  t2 <- which(t_i[[2]] == dat$Test_unique_aanvraag)
  t2 <- dat$TXT_WRKFLOW_IDN[t2]
  t2 <- setdiff(t2,t1)
  t3 <- which(t_i[[3]] == dat$Test_unique_aanvraag)
  t3 <- dat$TXT_WRKFLOW_IDN[t3]
  t3 <- setdiff(t3,t1)
  t3 <- setdiff(t3,t2)
  s <- sum(v)
  df3p$minimum[i] <- (length(t1)+length(t2)+length(t3))
  df3p$tot[i] <- s
  df3p$p[i] <- df3p$tot[i]/df3p$minimum[i]
}



##  Comb 4 - Data Frame
df4p <- data.frame(Test_comb4 = v_comb4, minimum = NA, tot = NA, p = NA)
for (i in 1:nrow(df4p)) {
  print(i)
  t_i <- strsplit(df4p$Test_comb4[i], split = ";")[[1]]
```

```
  v <- c()
  for (j in 1:length(Aanvragen)) {
    k <- which(dat$TXT_WRKFLOW_IDN == Aanvragen[j])
    data_subset <- dat[k,]
    testen_subset <- unique(data_subset$Test_unique_aanvraag)
    if(t_i[[1]] %in% testen_subset) {
      if (t_i[[2]] %in% testen_subset) {
        if (t_i[[3]] %in% testen_subset) {
          if (t_i[[4]] %in% testen_subset) {
            v <- append(v,1)
          }
        }
      }
    }
  }
  t1 <- which(t_i[[1]] == dat$Test_unique_aanvraag)
  t1 <- dat$TXT_WRKFLOW_IDN[t1]
  t2 <- which(t_i[[2]] == dat$Test_unique_aanvraag)
  t2 <- dat$TXT_WRKFLOW_IDN[t2]
  t2 <- setdiff(t2,t1)
  t3 <- which(t_i[[3]] == dat$Test_unique_aanvraag)
  t3 <- dat$TXT_WRKFLOW_IDN[t3]
  t3 <- setdiff(t3,t1)
  t3 <- setdiff(t3,t2)
  t4 <- which(t_i[[4]] == dat$Test_unique_aanvraag)
  t4 <- dat$TXT_WRKFLOW_IDN[t4]
  t4 <- setdiff(t4,t1)
  t4 <- setdiff(t4,t2)
  t4 <- setdiff(t4,t3)
  s <- sum(v)
  df4p$minimum[i] <- (length(t1)+length(t2)+length(t3)+length(t4))
  df4p$tot[i] <- s
  df4p$p[i] <- df4p$tot[i]/df4p$minimum[i]
}


##  Comb 5 - Data Frame
df5p <- data.frame(Test_comb5 = v_comb5, minimum = NA, tot = NA, p = NA)
for (i in 1:nrow(df5p)) {
  print(i)
  t_i <- strsplit(df5p$Test_comb5[i], split = ";")[[1]]
  v <- c()
  for (j in 1:length(Aanvragen)) {
    k <- which(dat$TXT_WRKFLOW_IDN == Aanvragen[j])
    data_subset <- dat[k,]
    testen_subset <- unique(data_subset$Test_unique_aanvraag)
    if(t_i[[1]] %in% testen_subset) {
      if (t_i[[2]] %in% testen_subset) {
        if (t_i[[3]] %in% testen_subset) {
          if (t_i[[4]] %in% testen_subset) {
            if (t_i[[5]] %in% testen_subset) {
              v <- append(v,1)
            }
          }
        }
```

```
    }
   }
  }
  t1 <- which(t_i[[1]] == dat$Test_unique_aanvraag)
  t1 <- dat$TXT_WRKFLOW_IDN[t1]
  t2 <- which(t_i[[2]] == dat$Test_unique_aanvraag)
  t2 <- dat$TXT_WRKFLOW_IDN[t2]
  t2 <- setdiff(t2,t1)
  t3 <- which(t_i[[3]] == dat$Test_unique_aanvraag)
  t3 <- dat$TXT_WRKFLOW_IDN[t3]
  t3 <- setdiff(t3,t1)
  t3 <- setdiff(t3,t2)
  t4 <- which(t_i[[4]] == dat$Test_unique_aanvraag)
  t4 <- dat$TXT_WRKFLOW_IDN[t4]
  t4 <- setdiff(t4,t1)
  t4 <- setdiff(t4,t2)
  t4 <- setdiff(t4,t3)
  t5 <- which(t_i[[5]] == dat$Test_unique_aanvraag)
  t5 <- dat$TXT_WRKFLOW_IDN[t5]
  t5 <- setdiff(t5,t1)
  t5 <- setdiff(t5,t2)
  t5 <- setdiff(t5,t3)
  t5 <- setdiff(t5,t4)
  s <- sum(v)
  df5p$minimum[i] <- (length(t1)+length(t2)+length(t3)+length(t4)+length(t5))
  df5p$tot[i] <- s
  df5p$p[i] <- df5p$tot[i]/df5p$minimum[i]
}



##  Comb 6 - Data Frame
df6p <- data.frame(Test_comb6 = v_comb6, minimum = NA, tot = NA, p = NA)
for (i in 1:nrow(df6p)) {
  print(i)
  t_i <- strsplit(df6p$Test_comb6[i], split = ";")[[1]]
  v <- c()
  for (j in 1:length(Aanvragen)) {
    k <- which(dat$TXT_WRKFLOW_IDN == Aanvragen[j])
    data_subset <- dat[k,]
    testen_subset <- unique(data_subset$Test_unique_aanvraag)
    if(t_i[[1]] %in% testen_subset) {
      if (t_i[[2]] %in% testen_subset) {
        if (t_i[[3]] %in% testen_subset) {
          if (t_i[[4]] %in% testen_subset) {
            if (t_i[[5]] %in% testen_subset) {
              if (t_i[[6]] %in% testen_subset) {
                v <- append(v,1)
              }
            }
          }
        }
      }
    }
  }
```

```
  t1 <- which(t_i[[1]] == dat$Test_unique_aanvraag)
  t1 <- dat$TXT_WRKFLOW_IDN[t1]
  t2 <- which(t_i[[2]] == dat$Test_unique_aanvraag)
  t2 <- dat$TXT_WRKFLOW_IDN[t2]
  t2 <- setdiff(t2,t1)
  t3 <- which(t_i[[3]] == dat$Test_unique_aanvraag)
  t3 <- dat$TXT_WRKFLOW_IDN[t3]
  t3 <- setdiff(t3,t1)
  t3 <- setdiff(t3,t2)
  t4 <- which(t_i[[4]] == dat$Test_unique_aanvraag)
  t4 <- dat$TXT_WRKFLOW_IDN[t4]
  t4 <- setdiff(t4,t1)
  t4 <- setdiff(t4,t2)
  t4 <- setdiff(t4,t3)
  t5 <- which(t_i[[5]] == dat$Test_unique_aanvraag)
  t5 <- dat$TXT_WRKFLOW_IDN[t5]
  t5 <- setdiff(t5,t1)
  t5 <- setdiff(t5,t2)
  t5 <- setdiff(t5,t3)
  t5 <- setdiff(t5,t4)
  t6 <- which(t_i[[6]] == dat$Test_unique_aanvraag)
  t6 <- dat$TXT_WRKFLOW_IDN[t6]
  t6 <- setdiff(t6,t1)
  t6 <- setdiff(t6,t2)
  t6 <- setdiff(t6,t3)
  t6 <- setdiff(t6,t4)
  t6 <- setdiff(t6,t5)
  s <- sum(v)
  df6p$minimum[i] <- (length(t1)+length(t2)+length(t3)+length(t4)+length(t5)+length(t6))
  df6p$tot[i] <- s
  df6p$p[i] <- df6p$tot[i]/df6p$minimum[i]
}
```

§4. Goedkeuring Ethische commissie

Ongepast gebruik van labotesten in de huisartsenpraktijk: een analyse van de testen en gedragsdeterminanten

Dossiernr.:	MP017170
Masterproef:	Masterproef I HAIO, 2019-2022
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2020-2021
Korte omschrijving / abstract:	Labotesten zijn onlosmakelijk verbonden met de dagelijkse klinische praktijkvoering van huisartsen. Bij een derde van alle patiëntencontacten worden labotesten aangevraagd, terwijl naar schatting een derde van deze testen ongepast worden aangevraagd. Ongepast gebruik wordt gedefinieerd als het aanvragen van een test dat voor deze indicatie niet geïndiceerd is volgens de huidige EBM-richtlijnen in de 1ste lijn (cfr KCE richtlijn). In deze studie analyseren we een dataset van 300.000 labotesten, genomen voor 18 frequente indicaties. De dataset is afkomstig van de ELMO-RCT (Delvaux, zie publicaties infra). De primaire onderzoeksvraag beoogt de identificatie van de meest frequent ongepast aangevraagde test-indicaties, en een analyse van de respectievelijke meest frequent ongepast aangevraagde labotesten. Een secundair studiedoel is de exploratie van de determinanten die het ongepast schrijfgedrag van de huisarts beïnvloeden.
Website:	https://www.medischcentrumhuisartsen.be/documents/labo/studie.xml
Toegepaste technieken:	Descriptieve statistische analyses in R: Onderzoeksvraag [1]: retrospectief op de ELMO-dataset // Onderzoeksvraag [2]: gestandaardiseerde interviews bij deelnemende huisartsen van de ELMO-trial afnemen, met descriptieve analyse van de resultaten
Key publication:	Delvaux et al. Electronic Laboratory Medicine ordering with evidence-based Order sets in primarycare (ELMO study): protocol for a cluster randomised trial. Implementation Science 2017, 12(147)
Trefwoorden:	labotesten huisartsgeneeskunde
Gewenste taal van communicatie:	nl
Promotor:	Dr Nicolas Delvaux (u0099109)
Organisatie:	KU Leuven
Dienst:	Maatschappelijke Gezondheidszorg en Eerstelijnszorg, Campus Kulak Kortrijk
Discipline:	Masterproef
Extra groepsleden:	Théophane Némoz nemoz.theophane@student.kuleuven.be r0296657

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.

UZ LEUVEN

Leuven, 25 augustus 2017

Commissie Medische Ethiek
UZ KU Leuven / Onderzoek
U.Z. Gasthuisberg
Herestraat 49
B 3000 Leuven (Belgium)

prof. dr. Bert Aertgeerts
CC ARTSEN - FUNDAMENTALISTEN

Ons kenmerk:	EudraCT-nr:	Belg. Regnr:
S59472		B322201733217

The effect of evidence-based order sets within a CPOE (computerised physician order entry) system on the quantity and quality of laboratory test ordering in family practice : a cluster randomised trial.

DEFINITIEF GUNSTIG ADVIES

Geachte Collega,

De Commissie Medische Ethiek van UZ KU Leuven / Onderzoek heeft vermeld protocol onderzocht en besproken op haar vergadering van 26 juli 2017.

Na inzage van de bijkomende informatie en/of aangepaste documenten met betrekking tot dit dossier is de Commissie van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Na raadpleging van de ethische commissie van de andere deelnemende centra verleent ze dan ook een gunstig advies over deze studie.

Bij het beoordelen van dit dossier werd rekening gehouden met de documenten en informatie gerelateerd aan deze studie, ingediend op 29 juni 2017, 3 juli 2017 en 17 augustus 2017.

Dit gunstig advies betreft:

Protocol:
version 3.6 dd 07 August 2017
Informatie en toestemmingsformulier:
ICF versie 1 dd 28/06/2017 (ontvangen op 17/8/2017) Nl
Bewijs van "no-fault" verzekering:
valid 01/01/2017 - 31/12/2017
Rekruteringsmateriaal:
rekrutering flyer : versie ontvangen dd 29/06/2017 Nl
rekrutering flyer per labo : versie ontvangen dd 29/06/2017 Nl
rekrutering studiepopulatie : versie ontvangen dd 29/06/2017 Nl

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e-mail : ec@uzleuven.be

De Commissie bevestigt dat ze werkt in overeenstemming met de ICH-GCP principes (International Conference on Harmonization Guidelines on Good Clinical Practice), met de meest recente versie van de Verklaring van Helsinki en met de van toepassing zijnde wetten en regelgeving.

De Commissie bevestigt dat in geval van belangenconflict, de betrokken leden niet deelnemen aan de besluitvorming omtrent de studie.

Een ledenlijst wordt bijgevoegd.

De Ethische Commissie Onderzoek UZ/KU Leuven verwacht voor de start van de studie een lijst te ontvangen van de 300 deelnemende huisartsen waarin RIZIV-nummer, adresgegevens en identificatiegegevens vermeld worden.

Aandachtspunten: (indien van toepassing)

De opdrachtgever is verantwoordelijk voor de conformiteit van de anderstalige documenten met de Nederlandstalige documenten.

*Indien er een **Clinical Trial Agreement** is, kan de studie in ons centrum pas aangevat worden wanneer dit Clinical Trial Agreement goedgekeurd en ondertekend is door de gedelegeerde bestuurder van UZ Leuven (en/of desgevallend door bevoegde vertegenwoordiger(s) van KU Leuven R&D).*

Studies met geneesmiddelen en sommige studies met "medische hulpmiddelen" dienen door de opdrachtgever aangemeld te worden bij het FAGG.
Studies met geneesmiddelen mogen slechts aanvangen op voorwaarde dat de minister (FAGG) geen bezwaren heeft kenbaar gemaakt binnen de wettelijke termijnen zoals beschreven in art.13 van de Belgische wet van 7/5/2004 inzake experimenten op de menselijke persoon.
Voor bepaalde studies met medische hulpmiddelen gelden eveneens wettelijke termijnen (zie KB van 17/3/2009). Voor meer informatie hieromtrent verwijzen we naar de website van het FAGG www.fagg-afmps.be.

Onderzoek op embryo's in vitro valt onder de wet van 11 mei 2003. Voor dergelijk onderzoek is er naast een positief advies van het Ethisch Comité ook een goedkeuring van de Federale Commissie voor medisch en wetenschappelijk onderzoek op embryo's in vitro noodzakelijk vooraleer dit onderzoeksproject kan doorgaan.

Gelieve ook rekening te houden met de regelgeving van het ziekenhuis betreffende weefselbeheer en met de beschikkingen van de wet van 19 december 2008.

Dit gunstig advies van de Commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor dus zelf verantwoordelijk. Bovendien dient U erover te waken dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.
U dient ongewenste voorvallen en ernstige bijwerkingen te rapporteren zoals aangegeven door de Belgische Wet aangaande Experimenten op de menselijke persoon van 7 mei 2004 (Art 27 en 28) en de omzendbrief 586 van het FAGG.

Gelieve ons mee te delen indien een studie niet wordt aangevat of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van reden).

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*Indien de studie niet binnen het jaar beëindigd is, vereist de ICH-GCP dat een **jaarlijks vorderingsrapport** aan de commissie wordt bezorgd.*

*Gelieve tenslotte het (vroegtijdige of geplande) stopzetten van een studie binnen de door de wet vastgestelde termijnen mee te delen en een **Clinical Study Report** aan de Commissie te bezorgen.*

Met vriendelijke groet,

Prof. dr. Minne Casteels
Voorzitter Commissie Medische Ethiek
UZ KU Leuven / Onderzoek

Prof. Dr. Minne Casteels
Voorzitter
Commissie Medische Ethiek UZ KU Leuven / Onderzoek

Cc:
FAGG (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)

CTC (Clinical Trial Center UZ Leuven)

Externe Commissie(s) :

1- De Commissie heeft rekening gehouden met het advies van de volgende lokale commissie(s). De Commissie gaat er dan ook van uit dat deze centra de studie aanvaarden, tenzij tegenbericht:
Lokale Commissie *Onderzoeker*

2- De volgende commissie(s) heeft (hebben) een negatief advies uitgebracht:
Lokale Commissie *Onderzoeker*

3- Van onderstaande commissie(s) ontvingen wij geen advies. Bijgevolg kunnen deze centra niet deelnemen aan deze studie (cfr. Wet van 7 mei 2004 inzake experimenten op de menselijke persoon). Deze centra kunnen enkel via amendement aan de studie worden toegevoegd.
Lokale Commissie *Onderzoeker*

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Ledenlijst/Samenstelling van de Commissie op 26 juli 2017 (datum van de laatste bespreking van het dossier):

Voorzitter	prof. dr. Maria-Reinhilde Casteels	Clinical Pharmacology
Vice-voorzitter	prof. dr. em. Guido Verhoeven	Experimental Medicine
	De heer Jean-Jacques Derèze	Medical Legislation
	Mevr. Els Raets	Nurse
	Mevr. Godelieve Goossens	Nurse
	Mevr. Hélène De Somer	Nurse
	Mevr. Joke De Vocht	Psychologist
	Mevr. Stefanie Goris	Pharmacist
	apr. J.R. Thomas	Clinical Pharmacology
	dr. Anne Smits	Paediatrics
	dr. José Thomas	Medical Oncology
	dr. Lut De Groote	General Practitioner
	dr. Sabine Graux	Physician
	prof. Ben Van Calster	Statistics
	prof. dr. Dominique Bullens	Paediatrics
	prof. dr. Gregor Verhoef	Haematology
	prof. dr. Jan Van Hemelrijck	Anesthesiology
	prof. dr. Jan de Hoon	Clinical Pharmacology
	prof. dr. Xavier Bossuyt	Immunology
	prof. dr. em. Raymond Verhaeghe	Cardiology
	prof. dr. em. Willem Daenen	Cardiac Surgery

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