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The effect of computerized clinical decision support systems integrated in the electronic health record on the use of laboratory tests: a systematic review.

Thesis neergelegd voor het behalen van de graad van

Master in de huisartsgeneeskunde

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Motivatie

Naar aanleiding van het maken van deze masterproef heb ik diverse onderwerpen gewikt en gewogen. Met veel nieuwsgierigheid heb ik gekozen voor een literatuurstudie rond elektronische besliskundige ondersteunende systemen (*computerized clinical decision support systems, CCDSSs*). Ik heb deze keuze gemaakt omdat deze systemen, mijns inziens, een enorme meerwaarde kunnen betekenen voor de (huis)arts vandaag en misschien nog meer voor die van de toekomst. Dit omdat we overspoeld worden met uitdagingen zoals de vergrijzing van zowel de bevolking als het artsenkorps, een toenemend aantal chronisch zieken, snel evoluerende wetenschappelijke inzichten… Aangezien er ook een evolutie is van technologische ontwikkelingen kan ondersteuning met behulp van betrouwbare systemen een verlichting betekenen voor de werkdruk van de arts en een aanvulling betekenen in het leveren van goede, op wetenschap gebaseerde, zorg voor patiënten.

Ik heb ondervonden dat de technologie op papier (scherm) veelbelovend is (gedeeld medicatieschema, eTarificatie, SumEHRs…) hoewel implementatie in de praktijk voor velen nog niet gebeurd is omwille van achterblijvende softwareleveranciers, onder andere in de praktijk waar ik werk. Een deel artsen, voornamelijk zij die 'de computer' als last zien in plaats van lust, voelt zich hierdoor overweldigd en staat sceptisch tegenover elektronische besliskundige ondersteunende systemen.

Net daarom vind ik het belangrijk om uit te zoeken wat deze systemen kunnen betekenen voor artsen in de praktijk, zodat er realistische verwachtingen zijn. Want willen of niet, de digitale trein is vertrokken en wie niet mee is zal achterblijven en kan geen gebruik maken van de voordelen ervan.

Introduction

Laboratory testing is fundamental in modern medicine. It is used for screening, diagnostics, management and disease monitoring (1). Physicians choose freely the laboratory tests which they need with a large variability in requested laboratory tests for similar indications as a result (2). This variability is among other things influenced by the physician's knowledge (education, guidelines), the physician's experience and fear for responsibility when missing diagnoses (1,3).

This variability leads to *inappropriate testing*: some laboratory tests are being overutilized (tests ordered but not indicated) while others are being underutilized (tests indicated but not ordered). Inappropriate testing is harmful and might lead to medical errors. Overutilization can lead to incorrect diagnoses with unnecessary additional testing and downstream care because of false-positive results while underutilization can result in missed or delayed diagnoses (1,4,5).

The Belgian Healthcare Knowledge Centre (KCE) investigated the use of laboratory tests in the primary care setting. In 2009, laboratory testing (all settings combined) accounted for 5.2% of all healthcare spending (6,7).

The volume of ordered laboratory tests is high and keeps increasing (8). This increase has a direct impact on the costs of healthcare spending, the costs of unneeded downstream care are additional and important. For Belgium, the KCE concluded that interventions such as audit and feedback, clinical computerized decision support systems (CCDSSs) and financial incentives could improve the physician's laboratory testing behaviour (6). However, the KCE has only limited evidence that CCDSSs have an impact on laboratory testing.

Several of these suggestions are being worked on or are already realized. *Domus Medica* created evidence-based guidelines for laboratory testing in the primary care setting (3) and *the public welfare institution (RIZIV/INAMI)* organized audit and feedback campaigns (9). A pilot study which ordered laboratory tests in an evidence-based manner, showed cost savings and additionally time-savings since the tests could be ordered through the electronic health record (EHR) (10). This optimisation of clinical time is in line with findings in the Health Technology Assessment (HTA) of Main et al. (11). Internationally, clinical trials are carried out which make use of CCDSSs to change inappropriate laboratory testing. A report on the effect of CCDSS on laboratory testing aimed at diabetes care (12) showed strong evidence that it was effective in improving healthcare process measures across diverse settings but that evidence for effectiveness on clinical outcomes and costs was minimal. A systematic review done by Roshanov et al. (13) concluded that some CCDSSs can modify the physician's test-

ordering behaviour, but this systematic review, however, did not focus on laboratory testing only (13). This systematic review focusses specifically on the effect of CCDSSs on laboratory testing.

Methods

For this research, a doctoral researcher (general practitioner (GP) and a doctoral researcher at the academic centre for general practice) and a GP trainee cooperated, assisted by a postdoctoral researcher at the academic centre for general practice.

Research question

What is the effect of computerized clinical decision support systems (CCDSSs) integrated in the EHR on appropriate laboratory test ordering?

Search strategy

The search was performed using the following data sources: CINAHL, MEDLINE, EMBASE and MEDLINE In-Process & Other Non-Indexed Citations and additionally the Cochrane Library and the INSPEC database. Furthermore, the clinicaltrial.gov database for relevant protocols and contacted researchers was consulted to obtain unpublished results. Finally, reference lists of included trials and reviews were hand-searched for additional relevant data (snowballing). The search is limited to trials and reviews published until December 2014. A detailed version of the search strategy can be found in appendix 1.

Terms used

The terms used to search the databases were: decision making, computer-assisted; diagnosis, computer-assisted; decision support systems, clinical; hospital information systems, clinical; point-of-care systems; CDSS; CCDSS; clinical decision support system; decision support:.tw.; reminder systems.sh. These terms were combined with additional terms on publication type: clinical trial.mp; clinical trial.pt; radom:.mp; meta analysis.mp; review.pt; review.tw; overview.tw. The content terms were checked by an experienced librarian.

Study selection

Initially, the citations generated after the database search were screened for duplicates. Afterwards, both researchers reviewed this selection independently for potential relevant trials, based on title and abstract using following inclusion criteria:

- Studies focussing on evaluating a CCDSS with the following study design:
    - Randomized controlled trials (RCTs).
    - Non-randomized controlled trials (NRCTs) and controlled before-after (CBA) studies with at least two intervention and two control sites.

    - Interrupted time series (ITS) studies and repeated measures studies with a clearly defined timing of the intervention and minimally three data points before and three after the intervention.
- CCDSS (partially) focusing on laboratory testing and
    - used by a healthcare professional (clinician, physician, nurse) in real, non-simulated clinical settings.
    - providing computerized patient-specific information in the form of an assessment of recommendation.

Disagreement was resolved through debate and if no consensus was reached, a third researcher was consulted. In case of unclear data or an unavailable full text, the authors were contacted for clarification and/or the full text of the article.

Risk of bias assessment

An assessment according to the Cochrane assessment of bias tool was done to check the methodological quality of the selected RCTs (14). The studies were scored 'low risk', 'unclear risk' or 'high risk' on seven potential sources of bias.

- Random sequence generation: selection of participants should happen according to a random sequence (selection bias).
- Allocation concealment: personnel should allocate participants to the control or intervention group in a random and unpredictable manner for both personnel and participants (selection bias).
- Performance bias: personnel and participants should not be aware who participates in which group (blinding of participants and personnel).
- Detection bias: personnel assessing outcomes should not know which results come from which group (blinding of outcome assessment).
- Attrition bias: incomplete outcome data could mean a bias.
- Reporting bias: selective reporting on outcomes.
- Other bias: bias due to problems not covered in any previous topic.

Data extraction and analysis

Data extraction was done on all selected studies to analyse the outcomes in a structured way. Following elements were extracted: study objectives, funding source, details on the study design, study methods, participant characteristics, detailed information on the used CCDSS and effects on outcomes (process, clinical or economical).

For an intervention to be ‘positive’, it needed to show a statistically significant positive change for at least half of the outcomes. Studies reporting a negative effect or a statistically insignificant result, were labelled with ‘no effect’. Most interventions studied process outcomes as primary outcomes and if positive, clinical and/or economic outcomes were analysed. Disagreements and uncertainties were resolved by consensus.

Results

Search results

A total of 5120 references were identified after searching the databases. 5021 appeared unique after separate analysis of author/year/title by both researchers. After reviewing these 5021 articles as described in the methods, 249 articles were withhold for further investigation and 45 articles were added through snowballing. After reviewing the full text of these 294 articles, 55 studies were marked as potentially relevant. After contemplating the inclusion and exclusion criteria, 40 studies were found eligible for inclusion in the systematic review. Figure 1 summarizes our process. These 40 studies included sixteen RCTs, twelve CBAs, nine CRTs, two NRCTs and one ITS. Two studies used data from another included study: Khan et al. (15) used data of the study of Maclean et al. (16) and Smith et al. (17) used data from the study of Feldstein et al. (18). An overview of these 40 studies is shown in table 1.

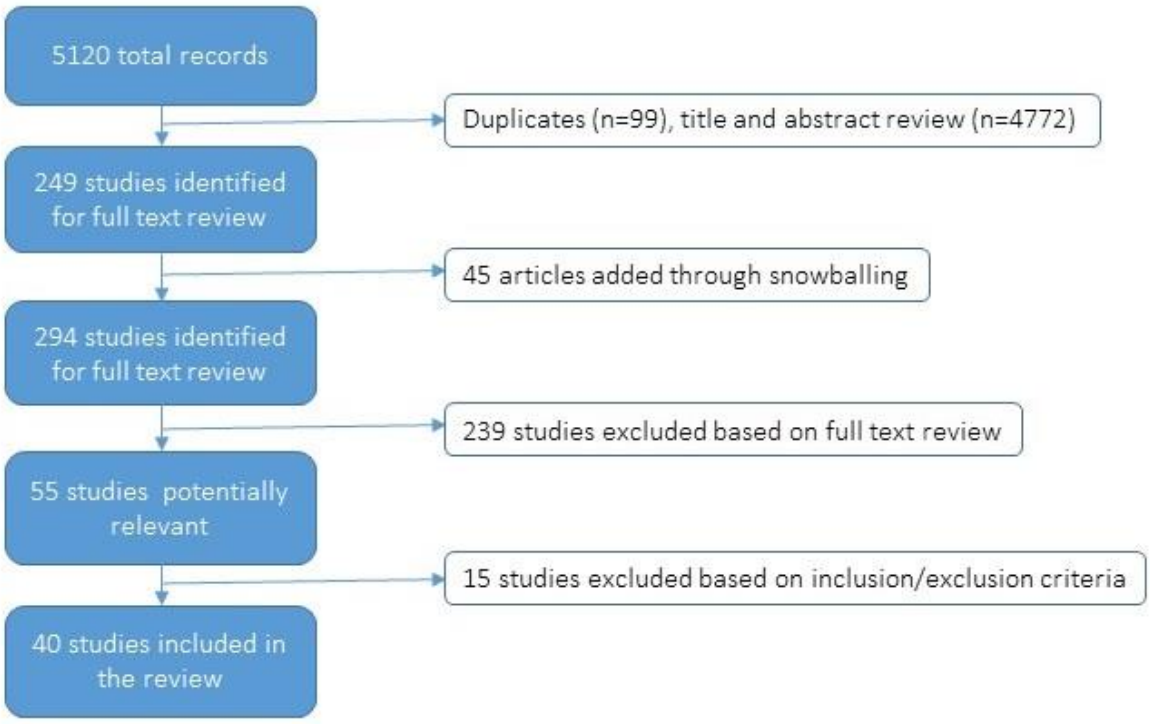

Figure 1. Flow diagram of the search strategy.

Risk of bias assessment

Each assessable item was labelled as described in the methods section. Figure 2 shows the summary of the bias assessment of the included RCTs and CRTs. Additionally, systematic reviews were searched for methodological quality scores for the selected RCTs and CRTs using the database *epistemonikos* (19).

The biggest difficulty for all studies was the blinding of patients and study personnel. Even though personnel was allocated to an intervention or control group, there could be a possible bias since the personnel was aware of the study-setting and perhaps adjusted their behaviour for requesting laboratory tests. On the other hand when blinding patients, personnel possibly gave care to participants in both control and intervention groups with a cross-over bias of their habits.

In four studies, a CCDSS was introduced in both intervention and control group in an attempt to blind all participants. These studies focussed at a different pathology or had a different study design.

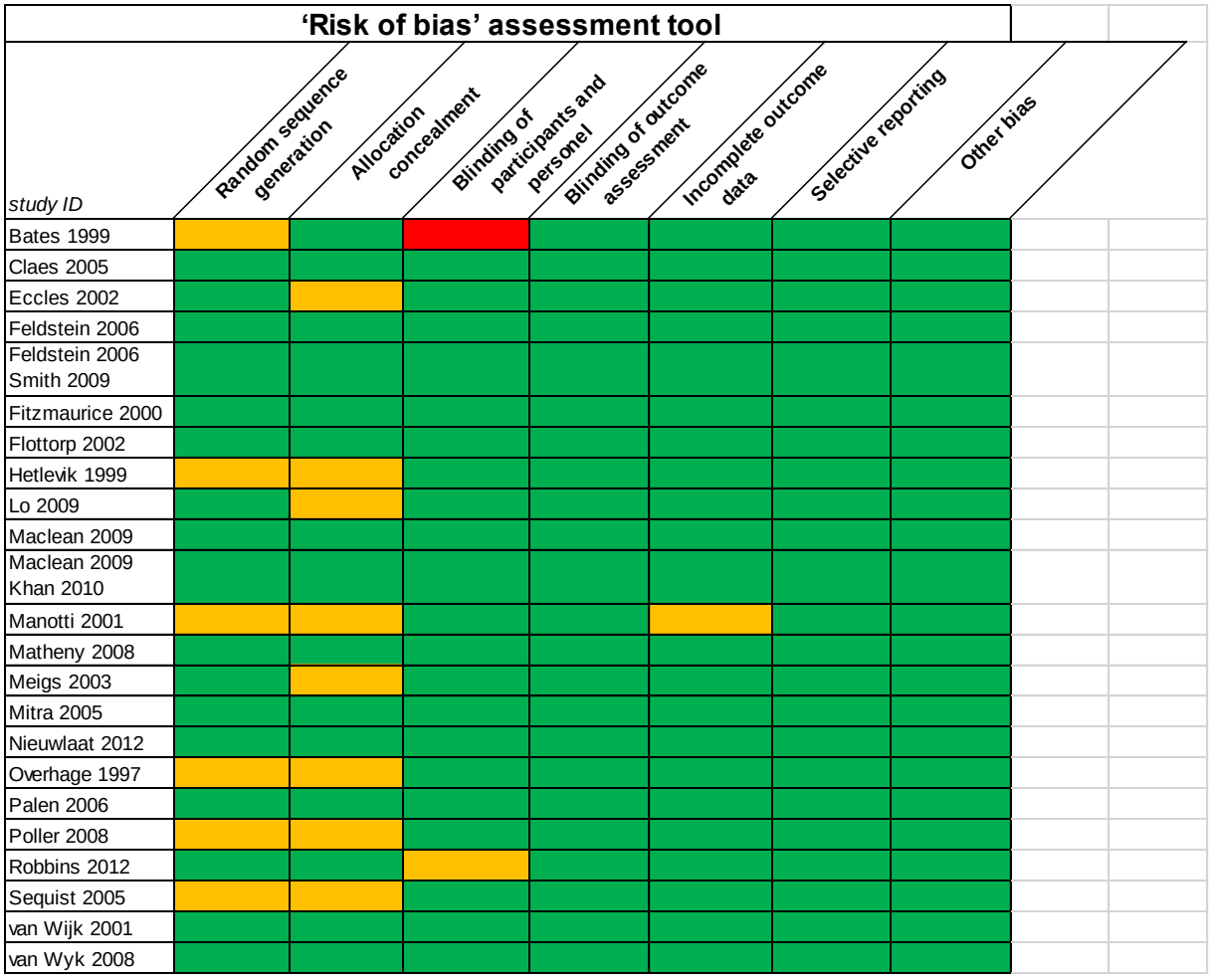

Figure 2. Risk of bias summary.

Overview of selected studies

Study ID	Study design	Country	Setting	number of centers /professionals /patients	Intervention	Outcome		
						Process	Clinical	Economic
Abboud 2006 (20)	CBA	USA	Hospital, inpatient	NR/NR/275	ICIS: Pop-up laboratory suggestions when ordering aminoglycoside medications in children.	x	x	
Bansal 2001 (21)	CBA	USA	Hospital, inpatient	10/NR/1,200	Pop-up alert with previous ABG values and limiting foward duration of tests ordered.	x		
Bates 1999 (22)	RCT	USA	Hospital, inpatient	1/NR/11,586	LMR: Reminder when redundant laboratory tests were ordered in a test-specific interval.	x	x	x
Bridges 2014 (23)	CBA	USA	Hospital, inpatient	1/NR/1,366	Pop-up alert that indicated to the clinician that the AHP-test had recently been ordered.	x		x
Carroll 2011 (24)	CBA	USA	Primary care: GPs	NR/36/173	Automatic prompt for ordering blood tests (CK and transaminases) when newly prescribing a statin medication.	x		
Claes 2005 (25)	RCT	Belgium	Primary care: GPs	NR/96/834	DAWN-AC: calculates dose VKA and time to next INR-control.		x	
Collin 2008 (26)	CBA	UK	Hospital, inpatient and outpatient	4/NR/NR	CPOE (automated form filling, order sets, warnings of possible test duplication, and user defined rules) and browsing previous test results.	x		
Eccles 2002 (27)	CRT	UK	Primary care: GPs	62/279/2,276	PRODIGY: recommendations for blood tests (Hb, Thyroid function, cholesterol or other lipid concentrations and HbA1c) for patients suffering from asthma or angina according to angina guidelines.	x		
Feldstein 2006 (18)	CRT	USA	Primary care	15/253/961	KP EHR: reminders when initiating drugs to order baseline laboratory tests.	x		
Smith 2009 (17)	RCT	USA	Primary care: GPs	15/253/961	KP EHR: reminders when initiating drugs to order baseline laboratory tests.			x
Fitzmaurice 2000 (28)	RCT	UK	Primary care	12/NR/367	AMSS: Intervention practices had practice-based anticoagulation clinics managed by practice nurses supported with decision support software and near patient testing		x	
Flamm 2013 (29)	NRCT	Austria	Hospital, in- and outpatient	1/NR/1,148	PROP: Tool that advises pre-operative tests according to local guidelines: full blood count, liver function tests, coagulation parameters and electrolytes	x		

Flottorp 2002 (30)	RCT	Norway	Primary care	142/620/16,939(sore throat), 9,887(UTI)	MEDIATA: Advice on the use of laboratory tests for patients with sore throat or urinary tract infections.	x		
Heo 2010 (31)	CBA	South-Korea	Hospital, inpatient and ED	10/NR/15,713	BEST: alert for entering predetermined order sets, providing of protocols and guidelines when suspecting a stroke.	x	x	
Hetlevik 1999 (32) Hetlevik 2000 (33)	CRT	Norway	Primary care: GPs	29/53/2,239(AHT), 1,034 (diabetes)	INFOTECH: alerts for diagnosis and treatmnet of AHT, diabetes and dyslipidemia: reminders if data for serum cholesterol and/or HbA1c were missing.	x	x	
Hoch 2003 (34)	CBA	Israel	Hospital, outpatient	551/35,313	Potassium Reminder Project: CCDSS generated an alert for all patients on diuretics without serum potassium measurement.	x		
Lau 2013 (35)	CBA	USA	Hospital, outpatient Primary care: GPs	NR/159/8,646	EPIC's DOT Phrase: noninterruptive alert to improve med-lab monitoring in the context of the 200 most frequently prescribed medications.	x		
Lo 2009 (36)	RCT	USA	Primary care: GPs	22/366/2,765	LMR: alerts when providers initiated an order for a medication and appropriate baseline laboratory tests were missing.	x		
Luo 2013 (37)	CBA	USA	Hospital, inpatient	NR/NR/7,336	When ordering laboratory orders for c. difficile, a pop-up alert reminded for previous results.	x		
Maclean 2009 (16)	CRT	USA	Primary care: GPs	64/132/7,412	VDIS: reminders for overdue diabetes tests.	x	x	x
Khan 2010 (15)	RCT	USA	Hospital, outpatient	64/132/7,412	VDIS: reminders for overdue diabetes tests.			x
Maclean 2013 (38)	CBA	USA	Primary care: GPs	29/55/4,763	PES-D: reminders for overdue proteinuria testing after implementation of newer CCDSS.	x		
Manotti 2001 (39)	RCT	Italy	Hospital, outpatient	NR/NR/1358	PARMA: calculates dose VKA and time to next INR-control.	x	x	
Matheney 2008 (40)	RCT	USA	Primary care: GPs	20/303/1,922	LMR: alerts when providers initiated an order for a medication and appropriate baseline laboratory tests were missing.	x		
Meigs 2003 (41)	CRT	USA	Hospital, outpatient	1/26/1,598	DDMA: Interactive patiënt-specific support (data, treatment and other resources) for patients suffering from diabetes.	x	x	
Mitra 2005 (42)	RCT	USA	Hospital, inpatient	1/NR/30	DAWN-AC: calculates dose VKA and time to next INR-control.	x	x	

Nieuwlaat 2012 (43)	RCT	Canada	Hospital, outpatient	1/NR/1,298	DAWN-AC: calculates dose VKA and time to next INR-control.	x	x	
O'Connor 2005 (44)	NRCT	USA	Primary care: GPs	2/NR/122	CCDSS with reminders and prompts for diabetes care.	x	x	
Overhage 1997 (45)	RCT	USA	Hospital, inpatient	1/89/2,181	RMRS: automatic suggestions for corollary orders (tests to monitor or ameliorate treatments) to prevent errors of omission for any of 87 target tests and treatments.	x		
Palen 2006 (46)	CRT	USA	Primary care: GPs	16/207/26,586	KP EHR: reminders when initiating drugs to order baseline laboratory tests.	x		
Poley 2007 (47)	CBA	Netherlands	Primary care: GPs	118/159/NR	CCDSS suggests usefull blood tests based on chosen patient-symptoms.	x		x
Poller 2008 (48) Poller 2008 (49)	RCT	EU + Australia	Hospital, outpatient	32/NR/13,219	DAWN-AC & PARMA: calculates dose VKA and time to next INR-control.	x	x	
Robbins 2012 (50)	RCT	USA	Hospital, outpatient	NR/33/1,011	Virology FastTrack: alert in case of virologic failure, suboptimal follow-up and abnormal laboratory results.	x	x	
Rosenbloom 2005 (51)	TS	USA	Hospital, inpatient	1/NR/194,192	Alert to discontinue unnecessary tests more than 72 hours ahead + pop-up with recent magnesium, calcium, and phosphorus test results + limited testing to one test instance per order.	x		
Sequist 2005 (52)	CRT	USA	Primary care: GPs	20/194/6,243	LMR: reminders for diabetes care (annual LDL-cholesterol testing and biennial HbA1c testing) and coronary artery disease care (annual LDL-cholesterol testing).	x		
Steele 2005 (53)	CBA	USA	Primary care	NR/NR/19,076	CCDSS presenting an alert when providers ordered medications on a computer if a relevant drug–laboratory interaction existed.	x	x	
van Wijk 2001 (54)	RCT	Netherlands	Primary care: GPs	44/60/NR	BloodLink: restriction in redundant test ordering.	x		
van Wyk 2008 (55)	CRT	Netherlands	Primary care: GPs	38/80/92,054	CholGate: alerting CCDSS or on-demand CCDSS for screening and treatment of dyslipidemia.	x		

Table 1. Overview of selected studies.

Settings and participants

Almost two thirds of the studies were conducted in the USA and one third in Europe. One study was conducted in both Europe and Australia while the last study was conducted in Canada. Sixty percent of the studies took place in primary care setting, a quarter in the hospital outpatient setting and thirteen percent took place in an inpatient hospital setting. Figure 3 shows a diagram of the study location and study setting of the included studies.

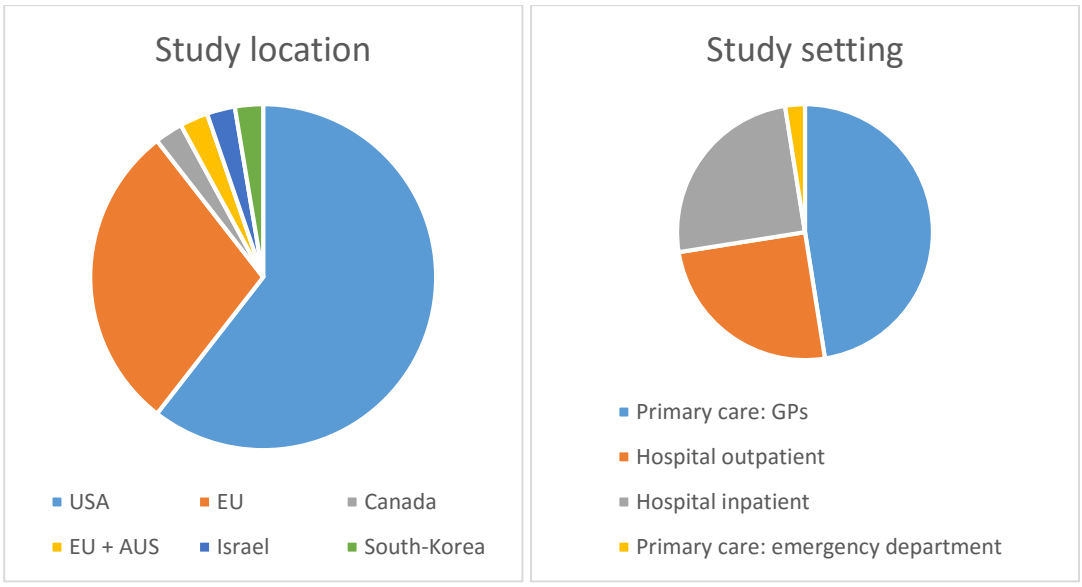

Figure 3. Diagrams of the included study locations and study settings.

Interventions and outcomes

During our analysis, we classified the obtained data into the type of CCDSS and outcome. We only focussed on studies with interventions meant to change laboratory testing, even though some studies also focussed on other domains such as treatment options or medical imaging (15,16,27,30,32,33,41,56). We could group the CCDSSs largely into three types of interventions: restrictive, suggestive or managing of antithrombotic drugs (fig. 4).

We identified sixty two outcomes and differentiated them into three categories: those with an impact on the clinical process, a clinical impact on morbidity or an economic impact. The results are discussed per type of intervention. All the outcomes are shown in appendix 2.

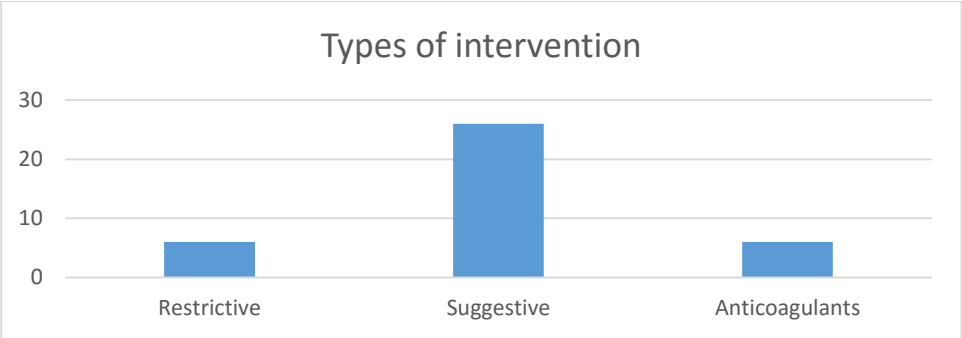

Figure 4. Distribution of intervention types.

Restrictive interventions

The first type of intervention can be seen as restrictive since it aims to prevent overuse of laboratory testing. Eight studies used a CCDSS in order to prevent redundant or duplicate laboratory testing. In these kinds of CCDSS, a pop-up was triggered with the message that the ordered laboratory test was unnecessary and the possibility to cancel the test was given (16,19–24,43). In some CCDSSs, the previous laboratory results were additionally displayed (26) or the possibility to browse these previous results was given (21,37,51). Other trials restricted test ordering with a limitation in the number of orders per form (51) or with a restricted form (54). In six studies, the CCDSSs gave a positive effect in reducing the number of ordered laboratory tests (22,23,30,37,51,54).

The study of Bates et al. used a CCDSS with a pop-up reminder when redundant laboratory tests were ordered in a test-specific interval, with a positive effect. In this study they also studied that a reduction in redundant tests did not increase the number of abnormal tests or did not change the clinical management. They calculated the annual savings of the reduction in inappropriate laboratory testing, without a positive effect (22). Bridges et al. tried to prevent duplicate testing for acute hepatitis profiles (AHP) with a positive effect on both duplicate testing and AHP-associated duplicate test costs (23).

Suggestive interventions

The second group worked suggestive by alerting users when essential laboratory tests were missing (15–18,20,24,27,29–36,38,40,41,44–47,50,52–55).

On the one hand, CCDSSs showed reminders in the follow-up of certain conditions such as diabetes mellitus (16,33,38,41,44,52), asthma (27), angina (27,52) arterial hypertension (AHT) (32) or dyslipidaemia (55). Suggestive reminders also were used in preoperative consults (29), when suspecting a stroke (31) or in the follow-up of HIV patients (50).

Diabetes mellitus

Of six trials studying a CCDSS to improve adherence to testing guidelines for HbA1c and/or LDL-cholesterol, five trials showed a positive effect (16,33,38,41,44) while only one did not (52). Four of these trials studied 'clinical control of diabetes' as a separate outcome, none with a positive effect. The trial of Maclean et al did show a positive effect of the Vermont Diabetes Information System (VDIS) on the number of hospitalisations and the length of stay for patients in the intervention group (16), additionally, Khan et al. studied that the costs for hospital charges and the costs per patient were reduced (15).

Various: HIV, stroke, pre-operative

The study of Robbins et al. (50) gave alerts in case of virologic failure and abnormal laboratory test results for HIV patients. The CCDSS had a positive effect on the CD4-count even though there was no effect on the rate of toxicity(50). Heo et al. (31) studied a CCDSS that suggested the request of essential laboratory tests when suspecting a stroke for a patient on the emergency department. This trial reported a positive effect on the time to availability of the test results and time to thrombolytic treatment for a patient having a stroke (31).

On the other hand, ten CCDSSs used suggestive alerts to improve laboratory monitoring when initiating or prescribing drugs (18,20,24,34–36,40,45,46,53). Five CCDSSs showed pop-ups if **baseline laboratory** orders were missing when initiating a drug treatment (18,24,36,40,46).
In two of these studies the CCDSS gave a positive effect on guideline adherence for laboratory testing (18,24) and in three studies it did not (36,40,46). Smith et al analysed that there was no additional cost of the extra laboratory tests (17) due to improved guideline adherence in the study of Feldstein et al (18).

Four CCDSSs gave an alert when recommended laboratory orders in the follow-up of certain prescribed drugs were not available in a specific time span (20,34,35,45). Three of these studies showed a positive effect on guideline adherence for ordering recommended laboratory tests in monitoring the effect of drugs (34,35,45). Abboud et al. (20) studied a CCDSS to improve laboratory testing when using aminoglycoside antibiotics in children and reported no effect on the guideline adherence for laboratory testing, neither on the aminoglycoside-level itself (20).

Steele et al. (53) studied a CCDSS that presents an alert when available laboratory results conflicted with the prescribed drugs or when these results were missing. The trial showed a positive effect on the guideline adherence for abnormal or missing laboratory results.

Dosing of anticoagulants

The final type of system was used for the *dosing of anticoagulants*. These seven trials used PARMA, DAWN AC or AMSS as CCDSSs (25,28,39,42,43,48,49). The systems suggested the vitamin K antagonist (VKA)-dosing and calculated the time to the next blood draw to monitor the INR. Four of these trials could show a positive effect on the time in therapeutic range (TTR) (39,42,48,49). Claes et al. (25) and Fitzmaurice et al. (28) studied that using a CCDSS to dose VKA did not increase the number of adverse effects such as thromboembolic complications or haemorrhages. Four of these studies analysed the interval between blood draws. Two indicated a positive effect (39,43) and two did not (42,49).

Discussion

In light of the results of our systematic review on CCDSSs used for requesting laboratory tests, there are a few trends we can describe.

Findings

The studied systems mainly gave suggestive or restrictive alerts. Restrictive alerts were aimed at avoiding duplicate or excessive testing. Restrictive alerts were in six out of eight cases successful for lowering the number of laboratory tests (22,23,30,37,51,54). The trial of Bates et al showed that there was no negative impact on the number of abnormal test results and that the economic benefit did not alter the annual laboratory budget significantly. The study of Bridges et al on the other hand, showed a significant reduction in costs for duplicate testing. This suggests that a CCDSS with restrictive alerts may reduce the number of unnecessary laboratory requests without an increase in the number of adverse effects and without changing clinical management.

The economic benefit depends on the perspective: even though a positive effect on certain parts of the budget may exist, the overall budget may not be positively influenced. Perhaps because reductions in indirect expenses, such as costs for downstream care, are not taken into account in the wider perspective of cost savings. It is important to note that the cost effectiveness was most likely only studied for trials with a positive effect on morbidity or the process, which can be seen as a kind of bias. This is consistent with previous research saying that managed care causes a reversal in the upward trend in the number of laboratory tests, without an effect on direct laboratory costs (57). Other research showed that a reduced utilization from 10% and 50% of all laboratory tests produced a modest saving of 3.88% and 21.55% of total expenses respectively (58).

CCDSSs that showed suggestive alerts to monitor a certain condition gave in ten out of thirteen cases a positive effect on the adherence to guidelines (16,18,29,31,38,41,44,47,50,55). Eight of these researched whether there would be a clinical impact on the control of the condition which gave in two trials a positive effect (16,50). Those CCDSSs giving suggestive alerts meant for laboratory testing when initiating or prescribing drugs were in five out of nine cases positive (24,34,35,45,53) without any study showing an effect on the number of adverse effects (53) or the control of the drug dosing (20). It seems that restrictive systems work better to avoid overutilization than suggestive systems which try to improve underutilization. This finding can be useful since the previously mentioned meta-analysis of Zhi et al. (59) revealed that overutilization seems more widespread than underutilization.

Another cluster of studies were those using a CCDSS for the dosing of antithrombotic drugs. As primary outcomes these trials studied whether a CCDSS that ordered the INR-dosing had an effect on the time in therapeutic range (TTR) or on the number of adverse effects under these type of drugs. Half of the studies had a positive effect on the TTR (39,42,49). One of the four trials that studied the number of adverse effects could show a positive effect (48) and the three others showed no effect (25,28,48). Often as a secondary outcome, the number of blood draws was studied, which showed in half of the cases a reduction (39,43).

Strengths and limitations of this systematic review

Several factors limited our analysis. Because of the heterogeneous settings, interventions, indications and results we could not pool and analyse the results quantitatively, meaning that a meta-analysis could not be done. Another weakness is that the magnitudes of effect were not determined but that studies were labelled as *positive* or *without effect*. For an outcome to be positive, at least half of the studied outcomes had to show a statistically significant change. Outcomes with a negative or insignificant result were labelled as 'no effect'. This method is referred to as 'vote counting' and gives an increased risk of underestimating effect (60).

Another possible limitation is the use of possible divergent knowledge bases: are the used bases evidence based medicine or are they made up by the developer of the CCDSS? Ideally, every type of CCDSS would have used the same, evidence-based guidelines. Because of different guidelines in other countries and perhaps diverging views on laboratory testing, this limitation seems unavoidable. The third limitation is also an inevitable one: blinding of the participants. Since participants are aware that they participate in a study, they might adjust their behaviour whether they are in the control or intervention group because they want to prove their abilities or knowledge of the guidelines.

Strengths of our review are the thorough search of several databases and the independent filtering of all the results. An independent third reviewer which guided in resolving disagreement adds even more value to this strength. Also, the selected studies are specific with clear in- and exclusion criteria which allows to make general conclusions per found cluster and makes that the results can be shown clearly.

Conclusions

Restrictive CCDSSs could definitely help to reduce inappropriate laboratory testing such as overuse and duplicate testing, most importantly, without increasing the risk of adverse effects. CCDSSs cause direct cost savings because of reduced inappropriate testing, but cost savings for less downstream care have not been investigated. Suggestive CCDSSs improve guideline adherence but currently, these kinds of CCDSSs do not improve control of morbidity. CCDSSs aimed at dosing VKA for INR-control showed their safety and effectiveness of dosing.

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Abstract

Background: laboratory testing is essential in current medical practice. Inappropriate laboratory testing consists of overuse or underuse and both might cause harm. Overuse might cause harm because of false positive results with unneeded downstream care. Underuse might cause harm because it leads to missed diagnoses. Clinical computerized decision support systems (CCDSSs) have been tested to avoid inappropriate laboratory testing, yet, their effectiveness remains unclear.

Objective: a systematic review to investigate the effect of CCDSSs integrated in EHRs on appropriate laboratory test ordering.

Methods: various databases were searched to find all conducted studies concerning CCDSSs. Next, by using strict in- and exclusion criteria useful studies were selected and a risk of bias assessment was performed to check the methodological quality of the studies. Various data were extracted and outcomes were studied. Every step was independently performed by two researchers.

Results: forty studies were identified, reporting on sixty two outcomes. Thirty four outcomes were about the process of care, more exactly about inappropriate testing, adherence to guidelines and INR-dosing. Twenty two outcomes concerned clinical impacts on morbidity: biochemical control, adverse effects and hospitalization-related effects. Six outcomes described an effect on charge savings or costs related to laboratory testing.

Conclusions: CCDSSs can reduce inappropriate laboratory testing and improve guideline adherence. CCDSSs also affect the time in therapeutic range (TTR) for INR-control. CCDSSs do not increase the risk of adverse effects but currently CCDSSs do not improve control of morbidity either. Direct cost savings due to reduced inappropriate testing are not significant; cost savings for downstream care have not yet been investigated.

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Appendices

Appendix 1: detailed search strategy per database

Search strategy for Pubmed

#1	clinical decision support system OR CDSS OR CCDSS OR medical order entry systems OR computerized physician order entry system OR CPOE OR “order set” OR “order sets” OR "Decision Making, Computer-Assisted"[Mesh:noexp] OR computer assisted decision making[tiab] OR "Diagnosis, Computer-Assisted"[Mesh:NoExp] OR computer assisted diagnosis[tiab] OR reminder system OR decision support[tiab]
#2	clinical laboratory technique OR laboratory diagnosis[tiab] OR laboratory diagnoses[tiab] OR lab test ordering[tiab] OR laboratory test ordering[tiab] OR routine diagnostic
#3	("classification"[MeSH Terms] OR "classification"[All Fields] OR "systematic"[All Fields]) AND ("United Synag Rev"[Journal] OR "review"[All Fields] OR "Rev Patient Focus Care Assoc"[Journal] OR "review"[All Fields] OR "Rev Fed Am Health Syst"[Journal] OR "review"[All Fields] OR "PFCA Rev"[Journal] OR "review"[All Fields] OR "Mod Contemp Fr"[Journal] OR "review"[All Fields] OR "Health Care Financ Rev"[Journal] OR "review"[All Fields] OR "Far East Econ Rev"[Journal] OR "review"[All Fields] OR "Fam Court Rev"[Journal] OR "review"[All Fields] OR "CHAC Rev"[Journal] OR "review"[All Fields])
#4	("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields])
#5	controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields])
#6	"randomized controlled trials as topic"[MeSH Terms] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "randomized controlled trials as topic"[All Fields] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trial"[All Fields]) OR "randomized controlled trial"[All Fields]
#7	after[All Fields] AND ("biomedical research"[MeSH Terms] OR ("biomedical"[All Fields] AND "research"[All Fields]) OR "biomedical research"[All Fields] OR "study"[All Fields])
#8	("time"[MeSH Terms] OR "time"[All Fields]) AND series[All Fields]
#9	"interrupted time series analysis"[MeSH Terms] OR ("interrupted"[All Fields] AND "time"[All Fields] AND "series"[All Fields] AND "analysis"[All Fields]) OR "interrupted time series analysis"[All Fields] OR ("interrupted"[All Fields] AND "time"[All Fields] AND "series"[All Fields]) OR "interrupted time series"[All Fields]
#10	repeated[All Fields] AND ("weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "measure"[All Fields])
#11	"meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]
#12	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	#1 AND #2 AND #12

Search strategy for Embase

#1	'decision support'/exp OR 'decision support' OR 'computerized physician order entry'/exp OR 'computerized physician order entry' OR 'computerized physician order entry system'/exp OR 'computerized physician order entry system' OR 'computerized decision support system' OR 'medical order entry systems'/exp OR 'medical order entry systems' OR 'computer assisted diagnosis'/exp OR 'computer assisted diagnosis' OR 'reminder system'/exp OR 'reminder system'

#2	'laboratory diagnosis' OR 'diagnostic procedure'
#3	'systematic review' OR 'systematic review (topic)' OR 'randomized controlled trial' OR 'randomized controlled trial (topic)' OR 'controlled study' OR 'clinical trial' OR 'clinical trial (topic)' OR 'time series analysis' OR 'meta analysis (topic)' OR 'meta analysis'
#4	#1 AND #2 AND #3

Search strategy for CINAHL

#1	(MH "Decision Support Systems, Clinical") OR (MH "Decision Support Systems, Management") OR (MH "Decision Support Techniques") OR "decision support" OR "cds" OR "ccds" OR "ccdss" OR (MH "Electronic Order Entry") OR (MH "Medical Orders") OR "electronic order" OR (MH "Computerized Patient Record") OR (MH "Decision Making, Computer Assisted") OR (MH "Diagnosis, Computer Assisted") OR "computer assisted" OR (MH "Reminder Systems") OR (MH "Patient Record Systems") OR "reminder system" OR (MH "Clinical Information Systems") OR (MH "Clinical Laboratory Information Systems") OR "clinical information"
#2	(MH "Diagnosis") OR (MH "Diagnosis, Laboratory") OR "laboratory" OR (MH "Clinical Laboratory Information Systems")
#3	#1 AND #2

Search strategy other sources

We used similar search terms for INSPEC, MEDLINE In-process & other non-indexed citations (via Ovid), Cochrane library

Appendix 2: table of process, clinical and economic outcomes

Process outcomes

Study ID	Alert	Intervention	Primary/ secondary outcome	Measurement of intervention	Effect
Abboud 2006 (20)	Suggestive – drugs	Pop-up laboratory suggestions when ordering aminoglycoside medications in children	1	Change in the amount of laboratory tests ordered per antibiotic course.	0
Bansal 2001 (21)	Restrictive – duplicates	Pop-up alert with previous ABG values and limiting foward duration of tests ordered.	1	Change in the number of orderd ABGs.	0
Bates 1999 (22)	Restrictive - redundant testing	Pop-up reminder when redundant laboratory tests were ordered in a test-specific interval.	1	Change in ordering redundant tests.	+
Bridges 2014 (23)	Restrictive – duplicates	The intervention consisted of a computerized alert (pop-up window) that indicated to the clinician that the test had recently been ordered.	1	Change in ordering duplicate tests.	+
Carroll 2011 (24)	Suggestive – drugs	Automatic prompt for ordering blood tests (CK and transaminases) when newly prescribing a statin medication	1	Change in guideline adherence for assessing liver transaminases and CKs.	+
Collin 2008 (26)	Restrictive - redundant + duplicate testing	CPOE (automated form filling, order sets, warnings of possible test duplication, and user defined rules) and browsing previous test results.	1	Change in ordering redundant and duplicate tests for full blood counts, urea and electrolytes and urine cultures.	0
Eccles 2002 (27)	Suggestive – condition	Suggestions for blood tests (Hb, Thyroid function, cholesterol or other lipid concentrations and HbA1c) for patients suffering from asthma or angina	1	Change in guideline adherence for assessing Hb, thyroid function, lipids and HbA1c.	0
Feldstein 2006 (18)	Suggestive – drugs	KP EHR: reminders when initiating drugs to order baseline laboratory tests.	1	Change in guideline adherence for ordering the recommended laboratory monitoring for patients prescribed study medications (statins and gemfibrozil…)	+
Flamm 2013 (29)	Suggestive – condition	Tool that advises pre-operative tests according to local guidelines: full blood count, liver function tests, coagulation parameters and electrolytes	1	Change in guideline adherence for recommended testing and redundant testing without indication.	+
Flottorp 2002 (30)	Restrictive - redundant testing	Advice on the use of laboratory tests for patients consulting with sore throat or urinary tract infections.	1	Change in ordering redundant tests for sore throat and women with symptoms of urinary tract infection.	+
Heo 2010 (31)	Suggestive – condition	BEST: alert for entering predetermined order sets, providing of protocols and guidelines when suspecting a stroke.	1	Change in time from ED arrival to complete blood counts, and prothrombin time testing.	+

Hetlevik 1999 (32) Hetlevik 2000 (33)	Suggestive – condition	INFOTECH: alerts for diagnosis and treatmnet of AHT, diabetes and dyslipidemia: reminders if data for serum cholesterol and/or HbA1c were missing.	1	Change in guideline adherence for HbA1c testing.	0
Hoch 2003 (34)	Suggestive – drugs	CCDSS generated an alert for all patients on diuretics without serum potassium measurement.	1	Change in guideline adherence for potassium blood tests.	+
Lau 2013 (35)	Suggestive – drugs	CCDSS gave noninterruptive alert to improve med-lab monitoring in the context of the 200 most frequently prescribed medications.	1	Change in guideline adherence for hepatic and renal function, myalgias/rhabdomyolysis, LDL and HbA1c monitoring.	+
Lo 2009 (36)	Suggestive – drugs	LMR: alerts when providers initiated an order for a medication and appropriate baseline laboratory tests were missing.	1	Change in guideline adherence for missing laboratory tests when ordering certain medication.	0
Luo 2013 (37)	Restrictive – duplicates	When ordering laboratory orders for c. difficile, a pop-up alert reminded for previous results.	1	Change in number of duplicate PCR tests.	+
Maclean 2009 (16)	Suggestive – condition	VDIS: reminders for overdue diabetes tests.	1	Change in guideline adherence for cholesterol, creatinine and proteinuria.	+
Maclean 2013 (38)	Suggestive – condition	PES-D: reminders for overdue proteinuria testing after implementation of newer CCDSS.	1	Change in guideline adherence for proteinuria testing.	+
Manotti 2001 (39)	INR dosing	PARMA: calculates dose VKA and time to next INR-control.	2	Interval between blood draws.	+
Matheney 2008 (40)	Suggestive – drugs	LMR: alerts when providers initiated an order for a medication and appropriate baseline laboratory tests were missing.	1	Change in guideline adherence for creatinine, potassium, liver function, renal function or therapeutic drug level monitoring.	0
Meigs 2003 (41)	Suggestive – condition	DDMA: Interactive patiënt-specific support (data, treatment and other resources) for patients suffering from diabetes.	1	Change in guideline adherence for HbA1c and LDL-cholesterol testing.	+
Mitra 2005 (42)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	1	Interval between blood draws.	-
Nieuwlaat 2012 (43)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	2	Interval between two blood and number of blood draws.	+
O'Connor 2005 (44)	Suggestive – condition	CCDSS with reminders and prompts for diabetes care.	1	Change in guideline adherence for HbA1c and LDL-cholesterol testing.	+
Overhage 1997 (45)	Suggestive – drugs	RMRS: automatic suggestions for corollary orders (tests to monitor or ameliorate treatments) to prevent errors of omission for any of 87 target tests and treatments.	1	Change in guideline adherence for ordering corollary orders.	+
Palen 2006 (46)	Suggestive – drugs	KP EHR: reminders when initiating drugs to order baseline laboratory tests.	1	Change in guideline adherence for ordering the recommended laboratory monitoring for patients prescribed study medications (statins and gemfibrozil…)	0

Poley 2007 (47)	Suggestive – condition	CCDSS suggests usefull blood tests based on chosen patient-symptoms.	2	Change in laboratory testing and number of blood tests per form when patient suffers from certain symptoms.	+
Poller 2008 (48) Poller 2008 (49)	INR dosing	DAWN-AC & PARMA: calculates dose VKA and time to next INR-control.	2	Interval between blood draws.	-
Robbins 2012 (50)	Suggestive – condition	Virology FastTrack: alert in case of virologic failure, suboptimal follow-up and abnormal laboratory results.	2	Change in follow-up and time-to-next scheduled appointment for patients with abnormal CD4-count.	+
Rosenbloom 2005 (51)	Restrictive - redundant testing	Alert to discontinue unnecessary tests more than 72 hours ahead + pop-up with recent magnesium, calcium, and phosphorus test results + limited testing to one test instance per order.	1	Change in redundant magnesium tests ordering.	+
Sequist 2005 (52)	Suggestive – condition	LMR: reminders for diabetes care (annual LDL-cholesterol testing and biennial HbA1c testing) and coronary artery disease care (annual LDL-cholesterol testing).	1	Change in guideline adherence for LDL and HbA1C in diabetes care and for LDL testing in CAD.	0
Steele 2005 (53)	Suggestive – drugs	CCDS presenting an alert when providers ordered medications on a computer if a relevant drug–laboratory interaction existed.	1	Change in guideline adherence for laboratory/drug ordering in case of abnormal or missing laboratory results.	+
van Wijk 2001 (54)	Restrictive - redundant testing	BloodLink: restriction in redundant test ordering.	1	Change in redundant test ordering.	+
van Wyk 2008 (55)	Suggestive – condition	CholGate: alerting CCDSS or on-demand CCDSS for screening and treatment of dyslipidemia.	1	Change in guideline adherence for dyslipidemia testing.	+

Clinical outcomes

Study ID	Alert	Intervention	Primary/ secondary outcome	Measurement of intervention	Effect
Abboud 2006 (20)	Suggestive - drugs	Pop-up laboratory suggestions when ordering aminoglycoside medications in children	2	Change in aminoglycoside control.	0
Bates 1999 (22)	Restrictive - redundant testing	LMR: Reminder when redundant laboratory tests were ordered in a test-specific interval.	2	Change in number of abnormal test and changes in clinical management.	0
Claes 2005 (25)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	1	Change in TTR.	0
Claes 2005 (25)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	2	Change in number of thrombo-embolic complications and haemorrhages.	0
Fitzmaurice 2000 (28)	INR dosing	AMSS: Intervention practices had practice-based anticoagulation clinics managed by practice nurses supported with decision support software and near patient testing	1	Change in proportion of INR-values and TTR.	0
Fitzmaurice 2000 (28)	INR dosing	AMSS: Intervention practices had practice-based anticoagulation clinics managed by practice nurses supported with decision support software and near patient testing	1	Change in number of adverse effects.	0
Heo 2010 (31)	Suggestive - condition	BEST: alert for entering predetermined order sets, providing of protocols and guidelines when suspecting a stroke.	1	Change in number of IV-thrombolytic treatment.	+
Hetlevik 1999 (32) Hetlevik 2000 (33)	Suggestive - condition	INFOTECH: alerts for diagnosis and treatmnet of AHT, diabetes and dyslipidemia: reminders if data for serum cholesterol and/or HbA1c were missing.	1	Change in HbA1c control.	0
Maclean 2009 (16)	Suggestive - condition	VDIS: reminders for overdue diabetes tests.	2	Change in HbA1c and LDL control.	0
Maclean 2009 (16)	Suggestive - condition	VDIS: reminders for overdue diabetes tests.	2	Change in number of hospital admissions and length of stay.	+
Manotti 2001 (39)	INR dosing	PARMA: calculates dose VKA and time to next INR-control.	1	Change in time to achieve a stable state and TTR.	+
Meigs 2003 (41)	Suggestive - condition	DDMA: Interactive patiënt-specific support (data, treatment and other resources) for patients suffering from diabetes.	1	Change in HbA1c control.	0
Mitra 2005 (42)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	1	Change in TTR.	+

Nieuwlaat 2012 (43)	INR dosing	DAWN-AC: calculates dose VKA and time to next INR-control.	1	Change in TTR.	0
O'Connor 2005 (44)	Suggestive - condition	CCDSS with reminders and prompts for diabetes care.	2	Change in HbA1c control.	0
Poller 2008 (48) Poller 2008 (49)	INR dosing	DAWN-AC & PARMA: calculates dose VKA and time to next INR-control.	2	Change in TTR.	+
Poller 2008 (48) Poller 2008 (49)	INR dosing	DAWN-AC & PARMA: calculates dose VKA and time to next INR-control.	1	Change in number of adverse effects.	0 +
Robbins 2012 (50)	Suggestive - condition	Virology FastTrack: alert in case of virologic failure, suboptimal follow-up and abnormal laboratory results.	1	Change in CD4-count.	+
Robbins 2012 (50)	Suggestive - condition	Virology FastTrack: alert in case of virologic failure, suboptimal follow-up and abnormal laboratory results.	1	Change in rate of grade 3 or 4 toxicities.	0
Steele 2005 (53)	Suggestive - drugs	CCDSS presenting an alert when providers ordered medications on a computer if a relevant drug–laboratory interaction existed.	1	Change in number of adverse effects.	0

Economic outcomes

Study ID	Alert	Intervention	Primary/ secondary outcome	Measurement of intervention	Effect
Bates 1999 (22)	CCDS restrictive alert	LMR: Reminder when redundant laboratory tests were ordered in a test-specific interval.	2	Annual charge savings.	0
Bridges 2014 (23)	CCDS restrictive alert	Pop-up alert that indicated to the clinician that the AHP-test had recently been ordered.	2	Reduction of AHP-associated duplicated tests costs.	+
Smith 2009 (17)	Suggestive – drugs	KP EHR: reminders when initiating drugs to order baseline laboratory tests.	1	Change in cost per patient.	0
Khan 2010 (15)	CCDS suggestive alert	VDIS: reminders for overdue diabetes tests.	1	Change in hospital charges.	+
Khan 2010 (15)	CCDS suggestive alert	VDIS: reminders for overdue diabetes tests.	2	Change in emergency charges.	+
Poley 2007 (47)	CCDS suggestive alert	CCDSS suggests usefull blood tests based on chosen patient-symptoms.	1	Change in cost savings for sampling and testing + salary cost.	0