DATA-DRIVEN DECISION SUPPORT FOR MULTIDISCIPLINARY CLINICAL DECISION-MAKING & REPORTING IN BREAST CANCER

Mathijs Pieter Hendriks

Data-driven decision support for multidisciplinary clinical decision-making & reporting in breast cancer

Mathijs Pieter Hendriks

Dit proefschrift is goedgekeurd door:

Promotor
prof.dr. S. Siesling

Co-promotor
dr. A. Jager

This thesis is part of the Health Sciences Series, HSS 24-54, department Health Technology and Services Research, University of Twente, Enschede, the Netherlands.
ISSN: 1878-4968

Printing of this thesis was supported by:
Noordwest Academie part of Noordwest Ziekenhuisgroep
Integraal Kankercentrum Nederland (IKNL)

Cover design: Mathijs P. Hendriks
Printed by: Ridderprint
Lay-out: Ninke van Wiggen, persoonlijkproefschrift.nl
ISBN (print): 978-90-365-6338-3
ISBN (digitaal): 978-90-365-6339-0
URL: https://doi.org/10.3990/1.9789036563390

Data-driven decision support for multidisciplinary clinical decision-making & reporting in breast cancer

PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. ir. A. Veldkamp,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op dinsdag 3 december 2024 om 16.45 uur

door

Mathijs Pieter Hendriks
geboren op 1 april 1977
in Tiel, Nederland

PROMOTIECOMMISSIE:

Voorzitter / secretaris:	prof.dr. T. Bondarouk
Promotor:	prof.dr. S. Siesling Universiteit Twente, BMS, Health Technology & Services Research
Co-promotor:	dr. A. Jager Erasmus Medical Centre, Medical Oncology
Leden:	prof.dr. T.J.M. Ruers Universiteit Twente, TNW, Nanobiophysics
	prof.dr. M.C. Mikkers Universiteit Twente, BMS, Health Technology & Services Research
	prof. dr. M. Koopman University Medical Centre Utrecht, Medical Oncology
	prof. dr. I.H.J.T. De Hingh Maastricht University, Fac. Health, Medicine and Life Sciences, Epidemiologie GROW - Innovative Cancer Diagnostics & Therapy
	prof. dr. M.A.W. Merkx Radboud University Medical Centre, IQ Health
	dr. H.J.G.D. Van Den Bongard Amsterdam University Medical Centre, Radiation Oncology

Table of contents

PART I

Introduction

CHAPTER 1

General introduction

General introduction and thesis outline

The burden and variety of breast cancer

Breast cancer is the most common cancer worldwide. In 2022, 2.3 million women have been diagnosed with this disease, and 670.000 women died from breast cancer.[1] In the Netherlands, breast cancer is the most common cancer in women with 15.618 invasive breast cancer diagnoses in 2022.[2] Importantly, breast cancer is a very heterogeneous disease.[3,4] There are many subtypes of breast cancer, based on clinicopathological and molecular features. Treatment of breast cancer is multidisciplinary teamwork, and each disease trajectory is unique. Therefore, all patients are discussed within the multidisciplinary team in the hospital for tailored diagnostic and treatment advice (before and after breast cancer surgery), and the individualized recommendations of the multidisciplinary team are then discussed with the patient. In the Netherlands, multidisciplinary teams must consist of at least a breast care nurse and/or nursing specialist in oncology, a surgical oncologist, a plastic surgeon, a radiologist, a pathologist, a radiation oncologist, a medical oncologist, a specialist in nuclear medicine, all with special expertise in breast pathology.[5]

Multidisciplinary decision-making and clinical practice guidelines

For a multidisciplinary team it is challenging to tailor a growing amount of breast cancer knowledge to each unique patient. A recent meta-analysis showed evidence of a strong positive effect of multidisciplinary team management on overall survival for various types of cancer including breast cancer.[6] Multidisciplinary teams should base their recommendations on clinical evidence as described in clinical practice guidelines. However classical textual guidelines have practical limitations by their extensive size and huge efforts needed to keep them up-to-date (timely revisions), which makes implementation by clinicians in clinical practice challenging. This requires innovation to improve the availability of relevant guideline information during the clinical decision-making process. Computer technology can help to represent guideline knowledge to support guideline implementation.[7] Further to learn from actually administered care in daily practice, there is need for a data-driven methodology to analyze these real-world data.

To illustrate the many faces of breast cancer and the complexity of decision-making, two patient cases will be discussed below. This will elucidate the foundations of this thesis and main questions to be answered.

Two women with breast cancer

The story of Jessie

Jessie is a 39-year-old woman who noticed a palpable mass in her left breast with bra size B. The swelling had been there for a week when she consulted her general practitioner. The lesion was suspicious for breast cancer and Jessie was referred to the hospital. The lab technician of the radiology department performed a mammography

which revealed a breast imaging-reporting and data system (BI-RADS) 5 lesion of 1.9 cm in the upper medial quadrant of the left breast, and evaluated the tumor and the axilla with ultrasound. In the same session, a biopsy for pathological examination was performed of the tumor in de left breast and a suspicious lymph node in the left axilla. Jessie was sent to the breast care nurse to explain the further trajectory and to answer some questions about her medical history, family history and endocrine history. Later that day, Jessie was informed by the breast surgeon that rapid diagnostic testing of the lesion in her left breast turned out to be a triple negative basal-like breast cancer Bloom-Richardson grade 3.[8] The next day, the pathologist completed the pathological examination and reported adenocarcinoma in the punctured lymph node. The nursing specialist ordered a magnetic resonance imaging (MRI) of the breast and a fluorodeoxyglucose (FDG)-positron emission tomography (PET) at the nuclear department.

One week after the mammography, Jessie was discussed in the multidisciplinary team, which consisted of a radiologist, a breast surgeon, a medical oncologist, a pathologist, a plastic surgeon, a nursing specialist and a breast cancer nurse. The MRI showed that the known tumor had a size of 2.3 cm and a satellite lesion of 5mm was seen. The FDG PET revealed three FDG avid lymph nodes in the left axilla without signs of distant metastases. The multidisciplinary team concluded that Jessie's tumor stage was a cT2N1 triple negative breast cancer and recommended a second look ultrasound of the satellite lesion, referral to the medical oncologist to discuss neoadjuvant chemotherapy (with the goals to improve her prognosis and to increase the chance for breast conserving surgery if appropriate and to increase the chance of an axilla conserving surgery), referral to the radiation oncologist, genetic investigation (because of Jessie's age <40 years old, Jessie's mother had been diagnosed with breast cancer when she was 38-years old and her sister had ovarian cancer at age 51).

After the multidisciplinary team meeting, the surgeon was discussing the recommendations of the team to Jessie. The news was disappointing and Jessie stated firmly that she wanted to do everything to improve her prognosis and that she wanted ablative surgery of both her breasts. After the visit, the second look ultrasound confirmed the satellite lesion, and a biopsy was performed which showed triple negative breast cancer as well. Rapid genetic testing showed a *BRCA-1* gene mutation. After careful consideration, including genetic counseling with a clinical geneticist, Jessie decided to start neo-adjuvant chemotherapy followed by bilateral ablative surgery with breast reconstruction, a left-sided sentinel node procedure and a targeted axillary dissection of a marked positive lymph node.

The story of Emily

Emily is a 66-year-old woman with a screen-detected breast cancer of her right breast of 2.0 cm on the mammography. A tumor biopsy revealed an invasive carcinoma NST (No Special Type) Bloom Richardson grade 2, estrogen receptor 100% positive, progesterone receptor 80% positive and HER2 negative. Ultrasound of the axilla did not show suspected lymph nodes.

The multidisciplinary team recommended breast conserving surgery (in cooperation with the plastic surgeon considering Emily's bra size A) with a sentinel node procedure for this cT1cN0 hormone receptor positive invasive breast cancer NST, with the alternative of ablative surgery with a sentinel node procedure.

After discussing the treatment options for her clinical low risk breast cancer, Emily opted for breast conserving surgery with a sentinel node procedure. Pathology examination showed a 2.2cm Bloom-Richardson grade 2, hormone receptor positive and HER2negative invasive carcinoma NST. The sentinel node contained two lymph nodes, with a micro-metastasis in one of them.

The multidisciplinary team discussed Emily's case again after surgery, and advised adjuvant radiotherapy, endocrine therapy and chemotherapy in case of a high-risk MammaPrint.[9,10] It was disappointing for Emily that now, her breast cancer was clinically high risk. She agreed to use the MammaPrint, and this 70-gene signature test predicted a genetically low risk profile. Therefore, adjuvant chemotherapy was omitted.

Review of Jessie's and Emily's case

In a short period of time, many health care professionals are involved in the diagnostic trajectory. Information about the patient (e.g. family history) and the tumor (e.g. final tumor size, genetic profile) is accumulating over time, which is important for the decision process and subsequent treatment options. Many data were categorized using international accepted classification systems like BI-RADS and TNM.[11,12] The data originate from different sources. For instance from patients themselves and/or the reports of the radiologist and pathologist. All these data are discussed in a multidisciplinary team meeting to make an individualized recommendation for primary treatment: neoadjuvant chemotherapy in Jessie's case and surgery in Emily's case. After completion of this primary treatment, patients are discussed again in the multidisciplinary team. All data are interpreted by the multidisciplinary team in the context of everything known about the patient's case. New added data may alter the multidisciplinary team recommendation. For example, after identification of Jessie's axillary lymph node metastasis, an indication for performing a PET CT follows. And the finding of triple negative breast cancer with a size of 1.9cm alone implies an indication for neoadjuvant chemotherapy with an MRI preoperatively. Another example: when genetic testing identified a *BRCA-1* mutation, the multidisciplinary team recommended ablative surgery of the left breast and preventive ablative surgery of the right breast, despite breast conserving therapy was technically feasible.

The multidisciplinary team is expected to formulate recommendations based on clinical practice guidelines. In the Netherlands, the Dutch breast cancer guideline is leading. This guideline is currently (version 2023) divided into 145 modules and consist of 495 pages.[13] This means that the multidisciplinary team must include guideline texts from different modules in order to reach a recommendation for an individual patient at any point in the disease trajectory. Diagnosis and treatment of cancer is teamwork, as illustrated by both cases. Multidisciplinary teams congregate, judge and validate all information of each patient. The team is the central place for decision-making in oncology and

are expected to deliver personalized state of the art recommendations, based on all cumulative data known about an individual patient at the time of the meeting.[14] These data include characteristics of the patient and the disease. Multidisciplinary teams base their recommendations on clinical practice guidelines, personal experience and patient factors (e.g., comorbidity and patient preferences). It has been shown that the implementation of clinical practice guidelines reduces unwanted variability in clinical practice and improves outcome, and therefore improving the quality of care.[6,15,16] However, patient cases will not always fit within clinical practice guidelines, and clinicians may deliberately deviate from the guideline based on patient's clinical and psychological conditions.[17] Further, patients preferences influence the final treatment choice. Learning from these patients may be helpful for *similar patients* and future guideline updates.

Multidisciplinary team decisions are based on data. Clinical practice guidelines are based on data, with an indication for the level of evidence for each recommendation.[18] Routine explicit guideline utilization for each patient is cumbersome due to ambiguity of guideline texts that are often drawn up in unequivocally terms. This thesis investigates the role of data-driven decision support to optimize and implement personalized data-driven clinical decision making in breast cancer on two levels: clinical decision support systems for Multidisciplinary teams and for the evaluation of actually delivered care using real-world data.

Clinical decision support systems for multidisciplinary teams

Incorporation of up-to-date guidelines during multidisciplinary team meetings is essential but challenging as traditional clinical practice guidelines are large textual documents, which are often not revised in a timely manner.[19] Further, the amount of medical knowledge is increasing rapidly (in 2023 there were 29.962 publications about breast cancer in PubMed, versus 24.936, 20.194 and 13.806 in 2018, 2013 and 2008 respectively).[20] New knowledge about etiology, diagnostics and treatment of breast cancer as such should be applied to each unique patient, leading to more and more specific patient subpopulations. Consider for example tumor subtypes, molecular tumor characteristics and genetic risk profiles. To overview all relevant patient and disease characteristics to optimize clinical decision-making and subsequent treatment options, multidisciplinary teams may benefit from clinical decision support tools for multidisciplinary clinical decision-making in cancer.[21,22] Clinical decision support systems can be an effective tool to increase clinician accordance with clinical practice guidelines.[23,24] Clinical decision support system usage is associated with improved process outcomes and guideline adherence.[25] In **Chapter 2** we review the available clinical decision support systems for multidisciplinary decision-making in solid cancer. Based on this review, an implementation model has been composed aiming to improve implementation of these systems in the clinical workflow.

Clinical decision support using clinical decision trees

To assist multidisciplinary teams with clinical decision-making for breast cancer real-time, the Dutch national breast cancer guideline at the time with 199 pages of text needed a transformation to a more compact format that should be clinically interpretable and suitable for implementation in clinical decision support systems.[2]

However, this transition requested for a different methodology to structure a guideline. **Chapter 3** describes the transformation of the Dutch national breast cancer guideline into data-drive clinical decision trees, a novel methodology to capture guideline recommendations in an unambiguous way without losing nuances.

An important prerequisite for adequate decision-making during multidisciplinary team meetings includes the availability of relevant data to make a certain decision. The clinical decision trees display for each decision what data should be known. In **Chapter 4** we present a retrospective single-center study where the availability of data for four pivotal clinical decision trees are analyzed.

The methodology of clinical decision trees is scalable towards other tumor types. Clinical decision trees have been developed for colorectal cancer and prostate cancer, among others. **Chapter 5** describes a prospective multicenter study analyzing the concordance between recommendations of the multidisciplinary teams versus the clinical decision trees in breast cancer, colorectal cancer and prostate cancer.

Clinical decision trees for the evaluation of actually delivered care using national real-world data

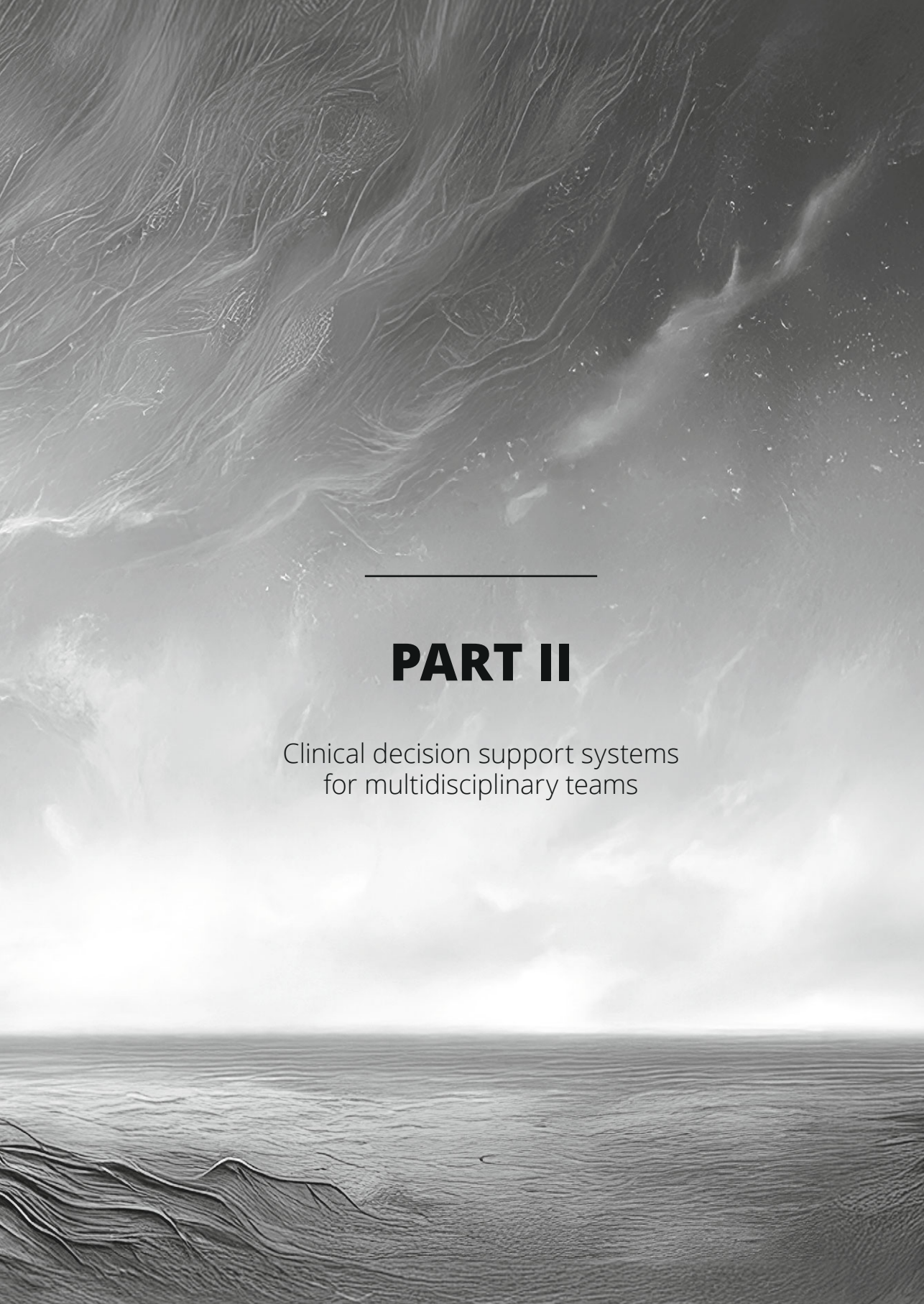
By projecting the data of the Netherlands Cancer Registry on the clinical decision trees, the clinical decision trees can analyze for each treatment decision what should have been done according to the guideline and what has been done in practice. Insights in real-world data can facilitate valuable feed-back for guideline working parties and speed-up guideline updates. Learning from these data can improve the quality of care. **Chapter 6** describes implementation of data-driven clinical decision trees for national evaluation of real-world breast cancer care**.** This chapter explores the feasibility of projecting national cancer registry data onto the CDTs aiming to monitor real-world practice. Because CDTs encode real-world practice data, CDTs can act as a self-learning health system. This concept is explained by a clinical example.

Chapter 7 discusses the main findings of the conducted research for this thesis, and provides a viewpoint about how CDTs can be implemented in daily care. A new conceptual model will be proposed for evidence-based multidisciplinary decision support in breast cancer with CDTs as a platform for a self-learning health care system.

References

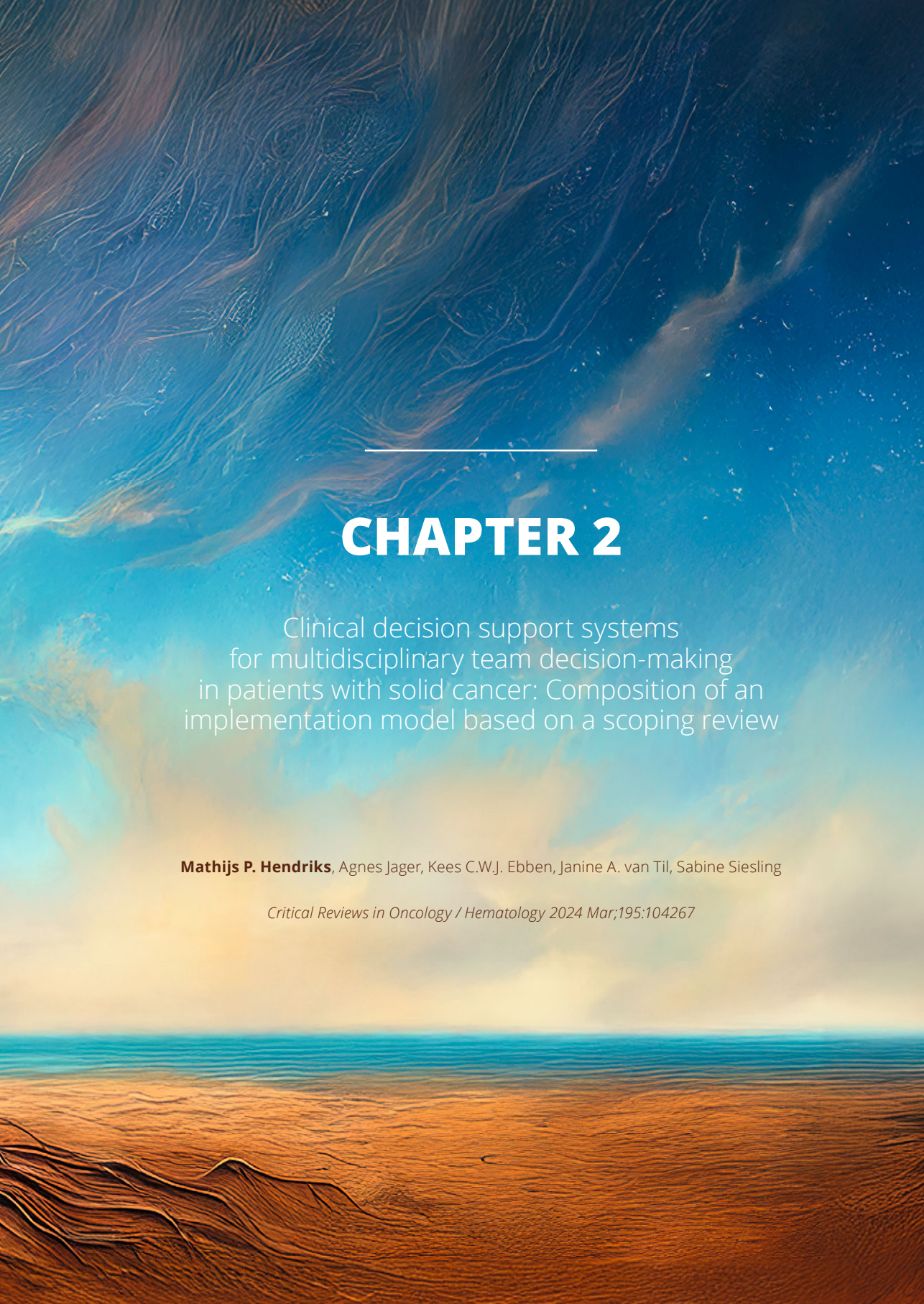
1. World Health Organization factsheet breast cancer. 2021.
2. Dutch Breast Cancer Guideline version 2.0. 2012.
3. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet 2021;397:1750-69.
4. Guo L, Kong D, Liu J, et al. Breast cancer heterogeneity and its implication in personalized precision therapy. Exp Hematol Oncol 2023;12:3.
5. SONCOS normeringsrapport 11-2023. Multidisciplinaire normering oncologische zorg in Nederland. 2023. at www.soncos.org.)
6. Huang RS, Mihalache A, Nafees A, et al. The Impact of Multidisciplinary Cancer Conferences on Overall Survival: A Meta-Analysis. J Natl Cancer Inst 2023.
7. Li XH, Liao JP, Chen MK, et al. The Application of Computer Technology to Clinical Practice Guideline Implementation: A Scoping Review. J Med Syst 2023;48:6.
8. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957;11:359-77.
9. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530-6.
10. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375:717-29.
11. D'Orsi CJ SE, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology. 2013.
12. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:290-303.
13. Dutch Breast Cancer Guideline 2023.
14. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev 2016;42:56-72.
15. Panella M, Marchisio S, Di Stanislao F. Reducing clinical variations with clinical pathways: do pathways work? Int J Qual Health Care 2003;15:509-21.
16. Brown GTF, Bekker HL, Young AL. Quality and efficacy of Multidisciplinary Team (MDT) quality assessment tools and discussion checklists: a systematic review. BMC Cancer 2022;22:286.
17. Bortot L, Targato G, Noto C, et al. Multidisciplinary Team Meeting Proposal and Final Therapeutic Choice in Early Breast Cancer: Is There an Agreement? Front Oncol 2022;12:885992.
18. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-10.
19. Martinez Garcia L, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. CMAJ 2014;186:1211-9.
20. PubMed. at https://pubmed.ncbi.nlm.nih.gov/?term=breast+cancer&sort=date.)
21. Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. Ann Surg Oncol 2011;18:2116-25.
22. Ebben K, Sieswerda MS, Luiten EJT, et al. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. JCO Clin Cancer Inform 2020;4:346-56.

23. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293:1223-38.
24. Roshanov PS, Fernandes N, Wilczynski JM, et al. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. BMJ 2013;346:f657.
25. Klarenbeek SE, Weekenstroo HHA, Sedelaar JPM, Futterer JJ, Prokop M, Tummers M. The Effect of Higher Level Computerized Clinical Decision Support Systems on Oncology Care: A Systematic Review. Cancers (Basel) 2020;12.



PART II

Clinical decision support systems
for multidisciplinary teams



CHAPTER 2

Clinical decision support systems for multidisciplinary team decision-making in patients with solid cancer: Composition of an implementation model based on a scoping review

Mathijs P. Hendriks, Agnes Jager, Kees C.W.J. Ebben, Janine A. van Til, Sabine Siesling

Critical Reviews in Oncology / Hematology 2024 Mar;195:104267

ABSTRACT

Generating guideline-based recommendations during multidisciplinary team (MDT) meetings in solid cancers is getting more complex due to increasing amount of information needed to follow the guidelines. Usage of clinical decision support systems (CDSSs) can simplify and optimize decision-making. However, CDSS implementation is lagging behind. Therefore, we aim to compose a CDSS implementation model. By performing a scoping review of the currently reported CDSSs for MDT decision-making we determined 102 barriers and 86 facilitators for CDSS implementation out of 44 papers describing 20 different CDSSs. The most frequently reported barriers and facilitators for CDSS implementation supporting MDT decision-making concerned CDSS maintenance (e.g. incorporating guideline updates), validity of recommendations and interoperability with electronic health records. Based on the identified barriers and facilitators, we composed a CDSS implementation model describing clinical utility, analytic validity and clinical validity to guide CDSS integration more successfully in the clinical workflow to support MDTs in the future.

INTRODUCTION

A personalized clinical advice for cancer patients prepared by an oncological multidisciplinary team (MDT) improves patient outcomes and patient satisfaction.[1] However, clinical decision-making by MDTs to reach a treatment advice for each unique patient is getting more complex since the amount of scientific knowledge on tumor characteristics and treatment options increase rapidly. Moreover, patients undergo more diagnostic testing and subsequent more patient and disease characteristics (data-items) have to be taken into account to generate a personalized guideline-based recommendation during the MDT for each unique patient. This complexity and the availability of all relevant information during MDT meetings is challenging. Relevant data-items are often suboptimal extracted from the patient files and reported during MDT meetings, which impedes MDTs to keep an overview of all relevant information and make optimal decisions.[2,3]

To support MDTs in reaching the challenging goal of evidence based informed decision-making, information technology and data science can be helpful to manage, register and re-use all relevant data and generate treatment recommendations. Many studies have shown that clinical decision support systems (CDSSs) can be effective tools to increase physician concordance with clinical practice guidelines.[4,5] Furthermore, CDSS usage is associated with positive clinical outcomes in two systematic reviews.[6,7] One systematic review evaluating clinically relevant outcomes related to CDSS usage for the diagnosis, treatment and supportive care revealed that 23 out of 24 included studies suggested a positive impact on the quality of care by the use of CDSSs for clinical decision making.[6] Another systematic review focusing on CDSSs impact on process outcomes (e.g. percentage change MDT treatment decision after using CDSS), guideline adherence and clinical outcomes included nine studies and found that CDSS implementation did significantly improve process outcomes and guideline adherence but no improvement

in clinical outcomes.[7] Importantly, these two reviews did not focus on implementation of CDSS in MDT settings and both included only two articles that focused on CDSS for decision-making in the MDT. Moreover, implementation of CDSSs in the clinical workflow is challenging, which makes the implementation of CDSS in clinical practice lag behind.[8] A recent systematic review and meta-analysis described the usage and accuracy of CDSSs for multiple tumor types, but did not focus on MDT decision support.[9]

Overcoming the challenges as mentioned above implies the need for a scoping review focusing on the currently reported CDSSs for MDT decision-making in solid cancer and to identify the reported barriers and facilitators for implementation of these CDSSs. Based on these barriers and facilitators, a CDSS implementation model will be composed to support future development and implementation of CDSSs in clinical practice.

METHODS

Search strategy and selection criteria

Based on the aims of our study, a scoping review was chosen as study design.[10,11] To provide an overview of the currently existing CDSSs for multidisciplinary decision-making in solid cancer, a search strategy was determined with the support of two health information specialists. The conducted search syntax is reported in supplemental table A. The syntax combined synonyms for 'multidisciplinary', 'decision support', 'cancer' and 'human'. The Cochrane Library (https://www.cochranelibrary.com/cdsr/reviews/topics, MEDLINE (accessed through PubMed) and Scopus were systematically searched up to November 20th, 2023.

A CDSS is defined as a system intended to improve healthcare delivery by enhancing medical decisions with targeted clinical knowledge, patient information, and other health information.[12] A CDSS can be any software in which individual patient characteristics (data-items) are matched to a computerized knowledge data-base (e.g. rule-based, using IF-THEN statements) or a data-base leveraging artificial intelligence, machine learning or statistical pattern recognition. Based on this match patient-specific recommendations are generated.[13] Studies concerning CDSSs for multidisciplinary decision-making in solid cancer were included if they met the following inclusion criteria. The CDSS should: 1) be data-driven, making usage of information technology and/or data science. Preferably, a description of the CDSS explaining the CDSS methodology should be available; 2) the CDSS should go beyond fixed decision rules (i.e. the system should be able to support decision-making for multiple possible combinations of patient and/or tumor characteristics by using a computerized knowledge data-base or a data-base leveraging artificial intelligence, machine learning or statistical pattern recognition); 3) support multidisciplinary decision-making by MDTs. CDSSs focusing on only one discipline were not eligible; 4) focus on medical professionals, not patients; 5) focus on solid cancer; 6) should be reported in a peer-reviewed journal in English. Articles reporting on the design and implementation of CDSSs for MDT in solid cancer were also eligible for inclusion.

Screening, data abstraction & statistics

Two reviewers (MH & KE) independently screened the title and abstract of all identified articles for compatibility with the research topic. In case of non-uniform assessment, discrepancies were resolved by discussions between the two reviewers. The references listed in studies that were selected for full-text review were screened for potentially useful studies. EndNote X9 was used for reference management. The result of the selection process was visualized according to the PRISMA 2009 flow diagram (http://www.prisma-statement.org/documents/PRISMA%20 2009%20flow%20diagram.pdf).

To summarize the reported CDSSs and to identify barriers and facilitators for implementation of CDSSs in daily clinical practice, the following data were extracted for each included study: study aim (including reporting main findings of the most frequent aims), study design, CDSS characteristics, CDSS knowledge base, main study outcome, barriers and facilitators for implementation of the CDSS. For descriptive statistics, Microsoft Excel was used. Data were presented by CDSS, in order of frequency. Numbers were indicated as absolute numbers with or without percentages, or as a median with range. The scoping review included, by design, no meta-analysis of the included studies.[10] The identified CDSSs were not scored for risk of bias, as there is no available tool for systematically assessment, such as QUADAS-2 for assessment of diagnostic test accuracy or the prediction model risk of bias assessment tool (PROBAST).[14,15]

Composition of a CDSS implementation model

The basic principle of a CDSS is that the appropriate clinical data is processed in such way that these data can be adequately matched to the database of the CDSS in order to reach a valid recommendation. Subsequently, this recommendation should be applicable to decision-making at the point of care. All identified barriers and facilitators were categorized and ranked in order of reported frequency. The five most frequently reported categories of both barriers and facilitators qualified for a detailed report. Based on the identified categories, a model was composed highlighting all important aspects that need to be covered by the CDSS for implementation in daily practice. This imposes requirements on the validity of a CDSS respectively. The model had to cover both the input level of the CDSS with accurate clinical data (i.e. analytic validity) and the output level with valid recommendations (i.e. clinical validity), resulting in a balanced weighing favoring clinical utility of the CDSS.

RESULTS

Study selection

The search strategy in the following database Cochrane Database, MEDLINE (accessed through PubMed) and Scopus resulted in 27, 881 and 326 hits respectively. After removal of duplicates, 1083 abstracts were screened based on title and abstract. Of these, 81 studies fulfilled the inclusion criteria and were considered eligible for full text review. After reading the full text, 44 articles describing twenty CDSS were included in this scoping review (Fig. 1).[16-59] A meta-analysis of Watson for Oncology's (WFO) clinical performance was excluded because two of the included studies were in Chinese, for

one study there was no full paper available and all other studies were already included in our scoping review.[60]

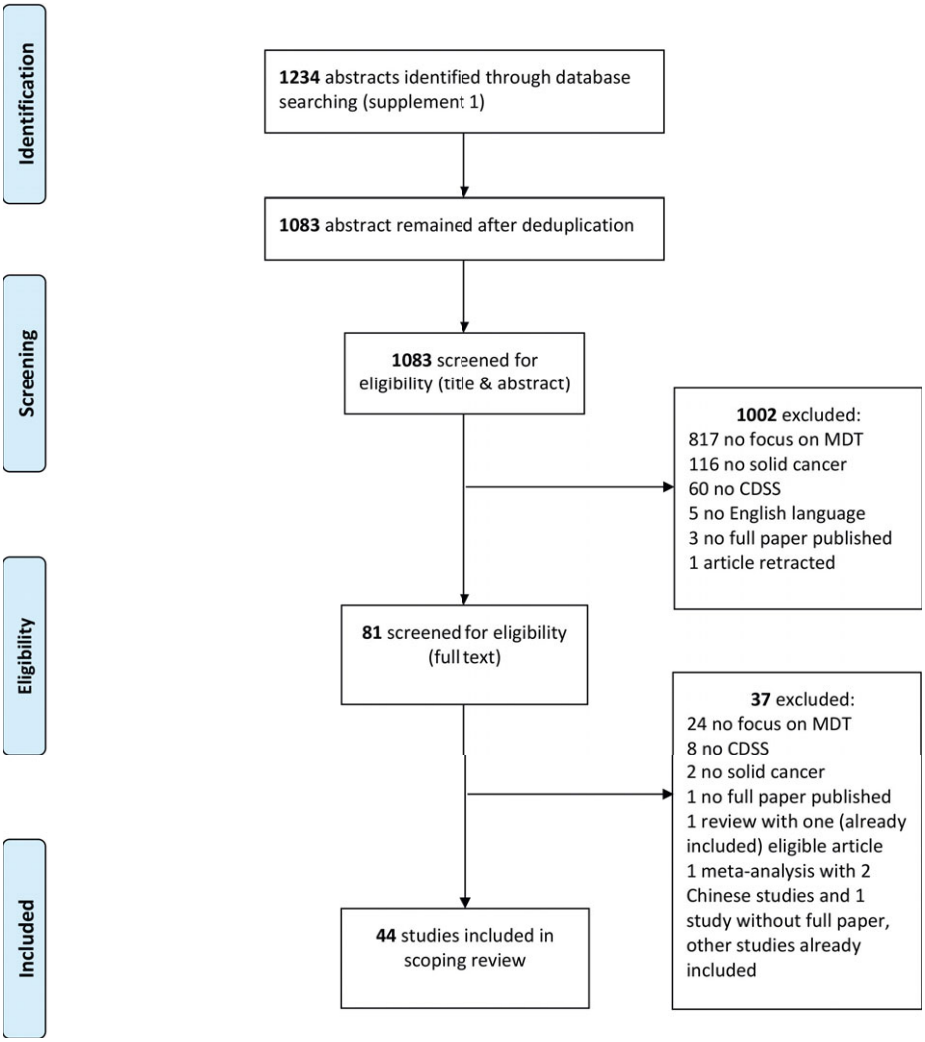


Fig. 1. Flow diagram.

Existing CDSSs for multidisciplinary decision-making in solid cancer

Table 1 depicts a detailed summary of all included articles. Most articles originated from European (n = 26) and Asian study groups (n = 12). Twenty-three papers (52%) focused on breast cancer exclusively. Most articles were single center studies (n = 28) and had a retrospective design (n = 22). Decision support was investigated in the non-metastatic setting in 22 studies (50%), the metastatic setting in two studies (5%), and 19 studies (43%) in both settings. One study did not report the disease setting.

Table 1. Characteristics of 44 included articles

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
Aikemu, 2021	2017 - 2018	colorectal cancer	China	M- & M+	prospective, single center, observational study	WFO	cognitive computing system	NA $		250
Choi, 2019	2017 - 2017	gastric cancer	Korea	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		65
Kim, 2019	2016 - 2017	colorectal cancer	Korea	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		69
Kim, 2020	2018	lung cancer	Korea	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		405
Lee, 2020	2018	breast, colorectal, gastric, lung, thyroid cancer	Korea	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		285
Lee, 2018	2009 - 2016	colon cancer	Korea	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		656
Liu, 2018	2017	lung cancer	China	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		149
Somashekhar, 2018	2014 - 2016	breast cancer	India, USA, UK	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		638

Table 1. Characteristics of 44 included articles (continued)

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
Tian, 2020	2016 - 2018	gastric cancer	China	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		235
Zhao, 2020	2016 - 2018	breast cancer	China	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		302
Zhou, 2019	2017	lung, breast, gastrointestinal, gynaecological cancer	China	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		362
Zou, 2020	2016 - 2018	cervical cancer	China	M- & M+	retrospective, single center, observational study	WFO	cognitive computing system	NA $		246
Bouaud, 2014	2009 - 2010	breast cancer	France	M-	prospective, multicenter cluster RCT	OncoDoc2	decision tree	local CancerEst CPG	557	
Bouaud, 2012	2007 - 2009	breast cancer	France	M-	prospective, multicenter cluster RCT, subanalysis	OncoDoc2	decision tree	local CancerEst CPG	199	
Bouaud, 2011	2007 - 2009	breast cancer	France	M-	prospective, multicenter cluster RCT, subanalysis	OncoDoc2	decision tree	local CancerEst CPG	169	

Table 1. Characteristics of 44 included articles (continued)

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
Bouaud, 2015	2009 - 2010	breast cancer	France	M-	prospective, multicenter cluster RCT, subanalysis	OncoDoc2	decision tree	local CancerEst CPG	394	
Séroussi, 2007	2005 - 2006	breast cancer	France	M-	prospective, single center, uncontrolled before/after intervention study	OncoDoc2	decision tree	local CancerEst CPG	467	316
Séroussi, 2013	2007 - 2009	breast cancer	France	M-	prospective, single center, observational cohort	OncoDoc2	decision tree	local CancerEst CPG	1624	
Séroussi, 2012	2007 - 2009	breast cancer	France	M-	prospective, single center, observational cohort	OncoDoc2	decision tree	local CancerEst CPG	1624	
Séroussi, 2013	2009 - 2010	breast cancer	France	M-	prospective, multicenter cluster RCT, subanalysis	OncoDoc2	decision tree	local CancerEst CPG	825	
Redjdal, 2020	NA	breast cancer	France	M-	retrospective study	GL-DSS; OncoDoc	rule-based & subsumption-based; decision tree	local CancerEst CPG	1861	
Redjdal, 2021	NA	breast cancer	France	M-	retrospective study	GL-DSS; OncoDoc	rule-based & subsumption-based; decision tree	local CancerEst CPG	1861	

Table 1. Characteristics of 44 included articles (continued)

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
Séroussi, 2017	NA	breast cancer	France	M-	original report with a case study	GL-DSS	rule-based & subsumption-based	eight (inter) national CPGs		
Ebben. 2022	2019	breast, colorectal, prostate cancer	Netherlands	M- & M+	prospective, multicenter, observational study	Oncoguide	decision tree	Dutch guideline for breast, colo-rectal and prostate cancer	296	
Hendriks, 2019	NA	breast cancer	Netherlands	M-	original report	Oncoguide	decision tree	Dutch guideline for breast cancer		
Hendriks, 2020	2012 - 2015	breast cancer	Netherlands	M-	retrospective, single center, observational study	Oncoguide	decision tree	Dutch guideline for breast cancer		394
Keikes, 2021	2016 - 2017	colorectal cancer	Netherlands	M- & M+	original report	Oncoguide	decision tree	Dutch guideline for colorectal cancer	158	
Alcorn, 2022	2007 - 2013	lung, breast, prostate cancer, other	USA	M+	retrospective, single center, observational study	BMETS-DSP	machine-learning model	institutional database		397
Cypko, 2017	not reported	laryngeal cancer	Germany, Poland, USA	M- & M+	retrospective, validation workflow	Kernal for Workflow, Knowledge, and Decision	Bayesian network model	not reported		
Eccher, 2014	2009 and 2012	breast cancer	Italy	M-	prospective, single center, observational cohort	OncoCure	Asbru-based	(inter) national guidelines		61

Table 1. Characteristics of 44 included articles (continued)

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
Epstein, 2006	not reported	breast cancer	Hong Kong	M-	prospective, single center, observational cohort	Adjuvant!	Bayesian network model	SEER database		102
Gaudioso, 2017	NA	breast cancer	USA	not reported	prospective, single center, observational	not reported	not reported	not reported		
Griewing	2023	breast cancer	Germany	M- & M+	prospective, single center, observational	ChatGPT 3.5	AI-based large language model	German breast cancer guideline		20
Heiden, 2015	NA	breast, colon, prostate cancer	Germany	M- & M+	original report	Health Care Management Platform	meta-model	existing clinical practice guidelines		
Lin, 2016	2007-2015	breast cancer	Australia	M-	retrospective, single center, original report		supervised machine learning	ESMO & NCCN		1065
Lukac, 2023	2023	breast cancer	Germany	M-	retrospective, single center, observational study	ChatGPT 3.5	AI-based large language model	German breast cancer guideline		10
Macchia, 2022	2015 - 2018	cervical cancr	Italy	M-	retrospective, single center, observational study	MTB virtual assistant	natural language processing & supervised learning technique	medical guidelines and machine learning		96
Ng, 2023	NA	liver cancer	Germany	M- & M+	prospective, single center RCT	ADBoard	natural language processing & machine learning	current guidelines		

Table 1. Characteristics of 44 included articles (continued)

Paper	study period	cancer type	country	setting	study design	CDSS	knowledge base	reference guideline	decisions (n)	patients (n)
O'Reilly, 2008	2004	colorectal cancer	UK	M+	retrospective, single center, external validation study	Oncosurge	RAND/UCLA Appropriateness Method (RAM)	NA		98
Prebet, 2018	NA	breast cancer	France	M-	original report		decision tree	ESMO & NCCN		
Rossille, 2005	NA	breast cancer	France, Canada	M-	original report		multi-model reasoning (rule-based & case-based)	SOR guidelines & case series		
Sesen, 2014	2006 - 2010	lung cancer	UK	M- & M+	original report	Lung Cancer Assistant	rule-based & probalistic interference	four (inter) national CPGs		4020
Shekarriz, 2020	2008 - 2017	pancreatic cancer	Germany	M-	retrospective, single center, observational study	MEBDAS®	quantitative calculation	NA		126
Thavanesan, 2023	2010 - 2020	oesophageal cancer	UK	M-	retrospective, single center, observational study	not reported	machine-learning model	NA		399

Abbreviations: BMETS-DSP, bone metastases ensemble trees for survival decision support platform; CDSS, clinical decision support system; CPG, clinical practice guideline; EHR, electronic health record; EP, emerging pattern; ISPM, IntelliSpace Precision Medicine; Multidisciplinary Team Orchestrator; MSM, multidisciplinary staff meeting; MDT, multidisciplinary team; MTB, multidisciplinary Tumor Board; RCT, randomized clinical trial; WFO, Watson for Oncology. $ Watson for Oncology is based on relevant studies, expert recommendations by doctors of Memorial Sloan-Kettering Cancer Center and American guidelines

In the 44 included articles, twenty unique CDSSs were described. The most frequently described CDSSs were WFO (n = 12), OncoDoc 2 (n = 8), the guideline-based decision support system (GL-DSS) (n = 3), and Oncoguide (n = 4). WFO used a cognitive computing system (which refers to the use of reasoning, language processing, machine learning and human capabilities that help regular computing better solve problems and analyze data) as knowledgebase. OncoDoc2, GL-DSS and Oncoguide used decision trees as knowledgebase. Of all included studies, 27 studies (61%) reported reference guideline(s) or databases (in case of survival prediction CDSSs) used as knowledgebase for the studied CDSS. In all included studies, a median of 250 (range 10 – 420) patients were described and a median of 512 (range 158 – 1861) decisions were reported.

Study aims of the 44 included studies

There were differences in main aims per study (supplemental table B). Most studies (n = 25) investigated the concordance rate between the CDSS and MDT generated recommendations and searched patient patterns associated with disconcordance. Nine studies focused on the development or methods to design a CDSS. Two studies described the development of a machine learning model to predict MDT decisions. Two studies investigated the integration of complementarity of different guidelines in the CDSS. Two studies evaluated the impact of CDSS based survival prediction on MDT decision-making. The remaining four studies all had different goals (supplemental table B).

The main findings of the defined aims of 44 included studies

Of the 25 studies that focused on concordance rate between the CDSS and MDT generated recommendations, four studies compared concordance rates in both situations, where the CDSS was used and was not used (control arm): three studies with OncoDoc2 and one study with WFO. These four studies considered a MDT recommendation concordant if the recommendation corresponded to the 'to be recommended' or 'for consideration' category of the CDSS. The studies concluded that CDSS usage improved the concordance rate.[18,47,51,54] In the other 21 studies, there was no control arm. Five studies focused on reasons for non-concordance between CDSS and MDT recommendations.[19,20,49-51] The study of Bouaud et al. proposed four reasons for non-concordance: (1) practice evolution; (2) particular cases not covered by current guideline; (3) MDT judgment that an alternative treatment is better suited for the patient than the CDSS recommendation; (4) specific patient preference.[20]

Nine studies described the development and/or validation of a CDSS[23,27,31,32,40,52] or method to design a CDSS[29,45,46] to support treatment decisions. Two studies developed machine learning models to predict MDT decisions. In a breast cancer study, machine learning did more accurately predict adjuvant chemotherapy recommendation by the MDT compared to simple application of guidelines. The authors concluded that some non-clinicopathologic variables such as patient preference and resource availability are weighted by the MDT, but these factors are not captured by guidelines.[37] Another study showed that machine learning-based models trained on pretreatment clinicopathological variables of patients with esophageal cancer can predict curative MDT treatment decisions with good accuracy.[55] Two studies demonstrated that CDSSs

can use multiple reference guidelines as knowledgebase to generate recommendations and this complementarity improves and enriches coverage of more specific clinical situations.[43,48]

One study with survival prediction model Adjuvant! found that MDT initial treatment recommendations for breast cancer were modified after showing the impact of adjuvant systemic therapy on survival in 12.7% of cases.[26] A pilot study with BMETS-DSP, a CDSS for multidisciplinary management of bone metastases, showed significantly improvement of survival estimation accuracy by physicians and selection of prognosis-appropriate palliative radiotherapy regimens.[17] A study investigating MDT attitude towards CDSS usage found that a guideline-based CDSS, when wrongly used, could deliver non guideline-based recommendations (automation bias).[21] Lee and Lee found that WFO usage during MDT meetings positively changed patient satisfaction and leads to a positive patient perception after treatment.[35] Redjdal et al. investigated the interoperability between two CDSSs for breast cancer. The authors of that study had to solve semantic and structural interoperability issues to make OncoDoc data reusable by the GL-DSS of DESIREE 2.[44] And finally, one retrospective study found a low data availability in patient records for adequate application of a CDSS in breast cancer.[30]

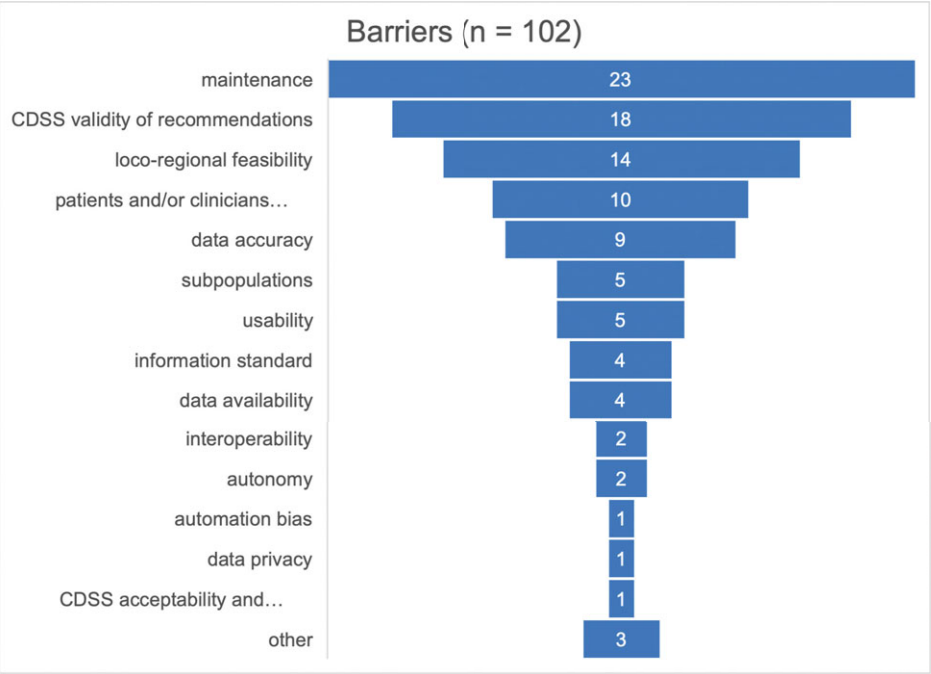
Barriers for CDSS implementation

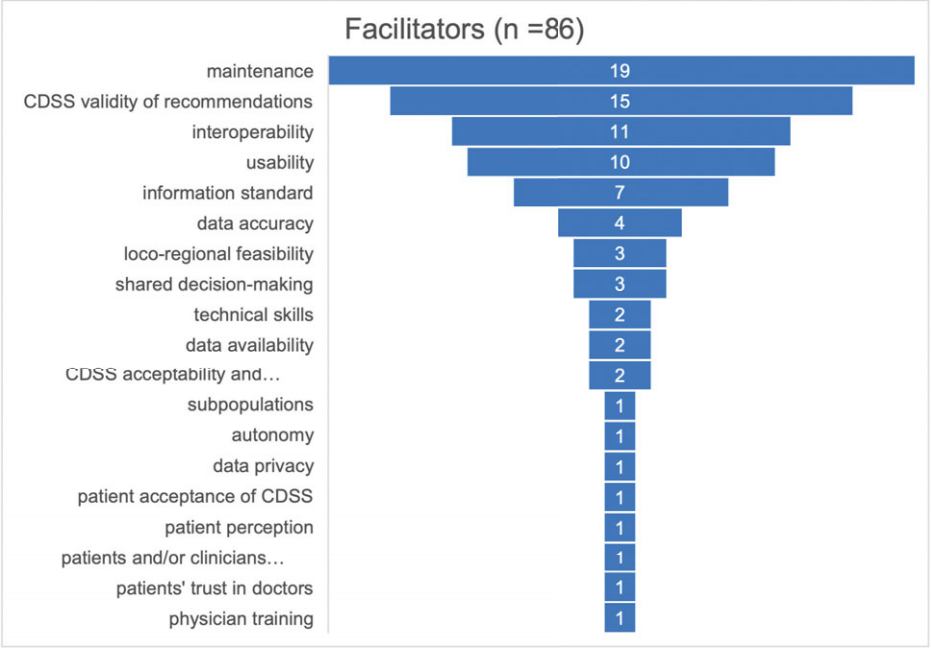
Specific information on barriers for CDSS implementation was reported in 35 studies (supplemental table C & Fig. 2). All mentioned barriers (n = 102, supplemental table C) were categorized in groups and reported in order of frequency (Fig. 2). Definitions of all categories are included in supplemental table E.

The first most frequently reported barrier concerns CDSS maintenance. For example, guideline-outdated recommendations should be updated.[19,20,22,30,56-59] Another example: some patient cases are not supported by CDSSs due to recommendation gaps in the guideline.[25,32,45,47] Further, identified discrepancies between different guidelines (NCCN & ESMO) should be addressed by guideline working parties to update the CDSS.[43]

A second largest barrier is the lack of internal and external validation of CDSSs. A potential risk of converting text-based guideline recommendations and considerations into computer interpretable decision trees is losing nuance.[32] This is an example of potential loss of internal validity. Most CDSSs have been tested by the developers of the CDSS, without sufficient external validation.

The third most often mentioned barrier reflects loco-regional feasibility of the recommendations, pinpointing the importance of CDSSs to deal with context specific requirements or limitations: e.g. CDSSs can recommend certain treatments that are not available (or tolerated) locally or lack reimbursement.[22,33,34,36,38,54,56-59]


Barriers (n = 102)
maintenance 23
CDSS validity of recommendations 18
loco-regional feasibility 14
patients and/or clinicians… 10
data accuracy 9
subpopulations 5
usability 5
information standard 4
data availability 4
interoperability 2
autonomy 2
automation bias 1
data privacy 1
CDSS acceptability and… 1
other 3


Facilitators (n =86)
maintenance 19
CDSS validity of recommendations 15
interoperability 11
usability 10
information standard 7
data accuracy 4
loco-regional feasibility 3
shared decision-making 3
technical skills 2
data availability 2
CDSS acceptability and… 2
subpopulations 1
autonomy 1
data privacy 1
patient acceptance of CDSS 1
patient perception 1
patients and/or clinicians… 1
patients' trust in doctors 1
physician training 1

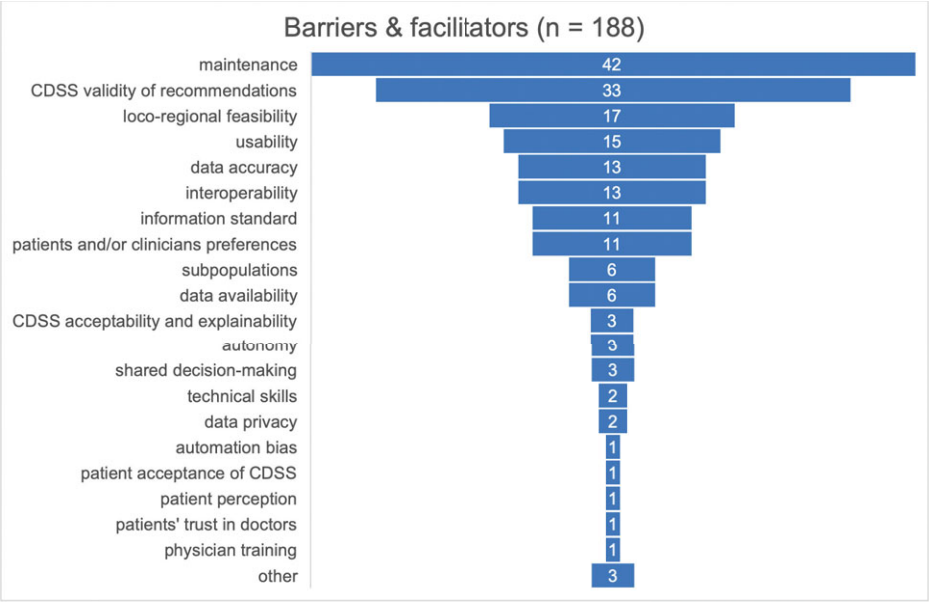


Fig. 2. Barriers and facilitators mentioned in the 44 included studies.
For details, see supplementary tables C, D & E. For each included study the number of reported barriers (B) and facilitators (F) are scored for each category. Note: in total there were 188 barriers and facilitators, however this table only reflects the 15 most common categories, reflecting 98 barriers and 82 facilitators.

Fourth, CDSS do not include clinicians' and patients' preferences in their recommendations. This means that that CDSS include not all factors that are relevant to the clinician and/or patient in their recommendation.[20,22,39,55] Clinicians' treatment decisions can be influenced by additional covariables that are not included in the guideline (and therefore not in de CDSS).[26] Two studies reported that clinicians have a holistic view on the disease which can alter parameter thresholds in patient subpopulations based on comorbidity, patient preferences and level of social support systems, which is not supported by the CDSS.[25,54]

Another barrier reflects data accuracy. Manual input of patient data in the CDSS is sensitive to errors.[32] Moreover, the lack of interoperability between CDSSs and other sources like electronic health records is challenging and threatening the availability of accurate data.[25,40]

Other barriers that were identified more frequently were: the fact that certain subpopulations are treated differently based on age and/or medical history;[20,22,26] ambiguous guideline terminology usage for guideline rule-based CDSSs reflecting the need for an information standard,[31,52] and the usability of the CDSS in daily practice. Manual input of data in a CDSS is time consuming.[18,31,32,41,52] If a CDSS is being used, it is important to use it well. A study with OncoDoc2 found that MDT compliance with

clinical practice guidelines was better when the CDSS was not used than navigating through the system improperly.[18,21]

Facilitators for CDSS implementation

Facilitators for CDSS implementation were reported in 37 studies (supplemental table D + Fig. 2). All mentioned facilitators (n = 86, supplemental table D) were categorized in groups and reported in order of frequency (Fig. 2).

The first most frequently reported facilitator concerns CDSS maintenance. This included the usage of up-to-date guidelines,[20,33] taking into account the loco-regional characteristics of patients,[22,38] the possibility for modular updating of the CDSS,[30,31] enlarging the coverage of CDSSs and enriching recommendations by making use of complementarity of clinical practice guidelines.[43,48]

Secondly, evaluating CDSS validity can facilitate CDSS implementation. CDSSs can by their systematically design elucidate information gaps, inconclusive treatment recommendations and guideline considerations which should be described in the CDSS and can be addressed in guideline updates.[31,32] Further, it is recommended to check the validity of non-concordance between MDT decisions and CDSS recommendations by (guideline updating) experts.[19,23,32,37,42,47,49,53,56]

A third facilitator involves CDSS interoperability. Important other conditions for implementing decision tree-based knowledge bases in CDSSs and interoperability with electronic health records are usage of unequivocal and unambiguous definitions of data (i.e. patient and tumor characteristics) on the basis of internationally acknowledged classification and coding system. Reaching consensus internationally on these data definitions is recommended by three included studies, it can pave the way for reconciliation of guidelines, covering and enriching more clinical patient situations with CDSSs by complementarity.[31,43,48]

The fourth most mentioned facilitator concerns CDSS usability. Gaudioso reported two important factors when starting to use a CDSS: (1) users prefer relevant clinical information to be displayed on a single screen as human cognitive load is limited and (2) users need to trust the system. However, one article states that medical oncologists want to read pathology reports fully, as they do not trust somebody else's interpretation.[27]

The fifth most reported facilitator concerns the importance of using an information standard. One study reports the importance of addressing vagueness and uncertainty in rule eligibility criteria by explicating the implicit expert knowledge.[52] Further, usage of information standards can solve the problem of limited interchangeability of data between various CDSSs and the electronic health record.[18,24,25,31,32,40,44,46,52]

Table 2 Overview of the most frequently reported categories of barriers and facilitators.

			maintenance		CDSS validity		loco-regional feasibility		usability		data accuracy		interoperability		information standard		patient & clinician preferences		patient sub-populations		data availability		CDSS acceptability and explainability		autonomy		shared decision-making		techniqual skills		data privacy	
CDSS	**first author**		**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**
WFO	Aikemu	2021	1	1	1	1	1	1											1	1												
WFO	Choi	2019	1		1		1	2									1		1													
WFO	Kim	2019		1	2		1																									
WFO	Kim	2020			1		1																									
WFO	Lee	2020			1																											
WFO	Lee	2018			2		1																									
WFO	Liu	2018	4	1			1																									
WFO	Somashekhar	2018					1										1															
WFO	Tian	2020	1	1		1	1																									
WFO	Zhao	2020	1				2										1															
WFO	Zhou	2019	2	1		1	2																	1								1
WFO	Zou	2020	2	1			2										1															
OncoDoc2	Bouaud	2014							1	1	1	1							1		1											
OncoDoc2	Bouaud	2012	1	1																												
OncoDoc2	Bouaud	2011	1	1													1		1			1										
OncoDoc2	Bouaud	2015							1	1	1	1													1	1						
OncoDoc2	Séroussi	2007	1	1						1																						

Table 2 Overview of the most frequently reported categories of barriers and facilitators. (continued)

			maintenance		CDSS validity		loco-regional feasibility		usability		data accuracy		interoperability		information standard		patient & clinician preferences		patient sub-populations		data availability		CDSS acceptability and explainability		autonomy		shared decision-making		techniqual skills		data privacy	
CDSS	**first author**		**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**
OncoDoc2	Séroussi	2013		1																												
OncoDoc2	Séroussi	2012																														
OncoDoc2	Séroussi	2013																														
GL-DSS	Redjdal	2020											1																		1	
GL-DSS	Redjdal	2021	1	1																												
GL-DSS	Séroussi	2017		2										1		1																
Oncoguide	Ebben	2022								1				1		1					1	1			1							
Oncoguide	Hendriks	2019		1		1			1					1	1	1					1							1				
Oncoguide	Hendriks	2020	1	1										2	1	1																
Oncoguide	Keikes	2021	1	1	2	2			1	1	1	1		2		1																
BMETS-DSP	Alcorn	2022			1	1																										
Kernal for Workflow, Know-	Cypko	2017			2	1					2																		1			
ledge & Decision Management																																
OncoCure	Eccher	2014	1							1	1		1				1	1														
Adjuvant!	Epstein	2006															1		1								1					

Table 2 Overview of the most frequently reported categories of barriers and facilitators. (continued)

			maintenance		CDSS validity		loco-regional feasibility		usability		data accuracy		interoperability		information standard		patient & clinician preferences		patient sub-populations		data availability		CDSS acceptability and explainability		autonomy		shared decision-making		techniqual skills		data privacy	
CDSS	**first author**		**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**
NR	Gaudioso	2017								2																						
ChatGPT 3.5	Griewing	2023	1		2																								1			
Health Care Management	Heiden	2015																														
Platform																																
NR	Lin	2016	2	1		2									1																	
ChatGPT 3.5	Lukac	2023				2				1							1															
MTB virtual assistant	Macchia	2022			1						1			1		1																
ADBoard	Ng	2023			1					1	1										1											
Oncosurge	O'Reilly	2008				1																										
NR	Prebet	2018	1	1																												
NR	Rossille	2005				1								1																		
Lung Cancer Assistant	Sesen	2014		1	1				1		1			1	1	1	1															
MEBDAS®	Shekarriz	2020				1																							1			
NR	Thavanesan	2023										1		1			1						1		1							

Table 2 Overview of the most frequently reported categories of barriers and facilitators. (continued)

			maintenance		CDSS validity		loco-regional feasibility		usability		data accuracy		interoperability		information standard		patient & clinician preferences		patient sub-populations		data availability		CDSS acceptability and explainability		autonomy		shared decision-making		techniqual skills		data privacy	
CDSS	**first author**		**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**	**B**	**F**
Barriers (n)		98	#		#		#		5		9		2		4		#		5		4		1		2		0		0		1	
Facilitators (n)		82		#		#		3		#		4		#		7		1		1		2		2		1		3		2		1

For each included study the number of reported barriers (B) and facilitators (F) are scored for each category. Note: in total there were 188 barriers and facilitators, however this table only reflects the 15 most common categories, reflecting 98 barriers and 82 facilitators.

Barriers and facilitators per CDSS

Based on the most frequently reported categories of barriers and facilitators for CDSS implementation, we evaluated for each CDSS which of those categories have been explicitly addressed or not by the authors (Table 2). WFO is not addressing the categories usability, information standard and interoperability. Further, WFO is not solely based on guidelines, but also on expert opinion of one tertiary hospital in the USA, impeding localized use of WFO in other countries. OncoDoc2 has been extensively studied but has never been validated outside the hospital group of Paris. Oncoguide is a more recent developed CDSS requiring manual data entry and interoperability of the system with the electronic health record to facilitate implementation. For all CDSSs, patient privacy is an issue that needs to be addressed. This point was mentioned both as a barrier and a facilitator.[44,58]

A CDSS implementation model

Based on all barriers and facilitators identified (Fig. 2; supplemental tables C and D), we composed an implementation model that captures the balance of most important factors to consider for implementing a CDSS for real-time MDT decision support (Fig. 3 and Table 2). Although some factors were mentioned more often than other ones in the included studies, all of them are important and need to be addressed.

The input of a CDSS (i.e. analytic validity) is clinical data (patient and tumor characteristics), that need to be real-time available and accurate. These data (originating from radiology reports, pathology reports, standardized / synoptic reporting in electronic health records) should be interoperable with the CDSS and lead to a valid recommendation. On the output level (i.e. clinical validity), CDSS usability and transparency is essential key for clinicians to use the system and trust the generated recommendations. As CDSSs cannot take into account clinicians' and patients' preferences, it is important that the theoretical treatment options generated by the CDSS can be explainable tailored to each specific patient during MDT meetings. The CDSS should generate recommendations that are locally available and feasible. Ultimately, the MDT must determine which recommendations are in the best interest of the patient and, if applicable justify when deliberate guideline deviations are made.

To warrant a balance between CDSS input and output, three factors are important: (1) CDSS maintenance (e.g. timely updating the CDSS when new guidelines / evidence becomes available); (2) using an information standard to prevent vagueness and to facilitate usage of the complementarity of guidelines; (3) to secure data privacy (CDSSs are medical devices for which CE certification is mandatory).

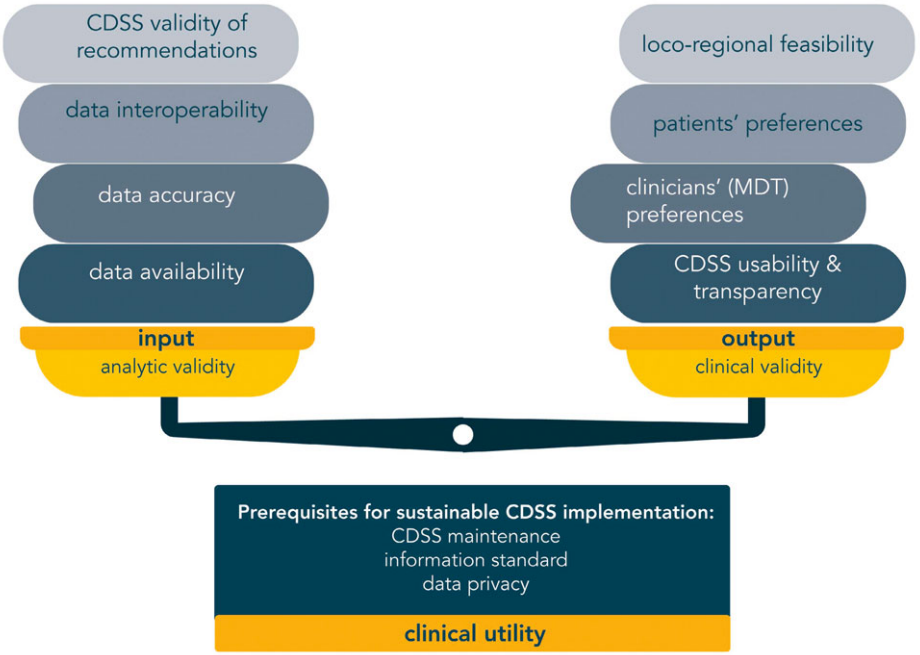


Fig. 3. A CDSS implementation model.

The left side of the scale reflects the analytic validity of the input of the CDSS: necessary data for the CDSS need to be available, accurate and interoperable between data sources (e.g. electronic health records) and the CDSS. The generated recommendations by the CDSS need to be valid (e.g. they should adequately adhere to the reference database of the CDSS such as a guideline). The right part of the scale represents the clinical validity of the CDSS: is the CDSS usable and transparent? Can preferences of the MDT and the patient be integrated? Are the generated recommendations of CDSS locally feasible in the clinic? The bottom of the scale shows the prerequisites for sustainable CDSS implementation: the maintenance (i.e. governance, regular updating the CDSS), an information standard (to preserve that the right data are processed at the input level of the CDSS) and data privacy (to comply with international standards like the General Data Protection Regulation). And "clinical utility" at the very bottom reflects the validity of the CDSS as a whole.

DISCUSSION

This is the first review focusing explicitly on CDSSs for multidisciplinary team decision-making in solid cancer. In the 44 included studies in our scoping review, only four CDDSs have been studied more intensely with three or more publications on the same CDSS: WFO, OncoDoc2, GL-DSS and Oncoguide. Importantly, these CDSSs are not implemented yet in a broad sense in the clinical workflow. Based on the many barriers and facilitators for CDSS implementation identified in this review, a compact theoretical model has been composed aiming to promote and support CDSS implementation. This model visualizes the balance between analytic and clinical validity with a solid basis of utility and may guide further development and implementation of CDSSs in the clinical

workflow at the MDT level. Further studies are warranted to evaluate the usability of this CDSS implementation model.

Factors undermining implementation of CDSS use during MDT meetings are missing data, not easily reusable data (lack of interoperability of a CDSS and the electronic health record) and data of which a standardized definition (information standard) is lacking. Many CDSSs use manual data-entry which is error prone. Moreover, data collection should not be time consuming, trustworthy and the CDSS should be able to deliver real-time support.[61] Software solutions are needed for incorporation of real-time decision support in clinical workflow.[62] Ideally, a CDSS should import relevant (standardized) data from the electronic health record automatically and uses these error-free copied source data for decision-support. This also contributes to the transparency of a CDSS, which is important for clinicians to trust the system. In this context, rule-based CDSSs are more intuitive for clinicians to understand compared to systems using machine learning techniques.[63] For each CDSS counts that the system should be safe to use in terms of patient privacy and data security.[58]

Besides the more technical issues, a major concern is the maintenance process of a CDSS to ensure the CDSS uses the most recent guideline update. Most CDSSs refer to local and/or (inter)national clinical practice guidelines regarding the generated recommendations. Guideline committees can validate a CDSS when a system is referring to their (updated) guideline. The rule-based CDSS Oncoguide is an example of this.[31] More challenging are CDSSs that use more knowledge bases, like WFO. The latter is based on database training with patients treated in a tertiary hospital in the USA and WFO does for instance recommend systemic therapy options that are not reimbursed or available in other countries or recommend treatment options that are not feasible locally.[22,33,34,36,37,54,56-59] Further, it is important to assess the clinical utility of a CDSS, preferably by adequate multicenter validation studies and using both an intervention arm where the CDSS is used and a control arm where the CDSS is not used. Importantly, development of internationally accepted criteria is needed to assess the analytic and clinical validity, the clinical utility and the risk of bias of a CDSS.

The chosen focus on CDSSs for multidisciplinary team decision-making in solid cancer is clinically relevant and reviews on this particular topic were lacking. A limitation of our review is that included studies were not systematically scored for methodological quality because internationally accepted criteria to assess the risk of bias for CDSSs are lacking. Regarding the design of included studies in this review, many suffered from drawbacks such as a retrospective and/or single center design and the lack of a control arm. Furthermore, most studies evaluating a CDSS were led by the developers of the particular CDSS. It turns out that CDSSs were more likely to improve practitioner performance in studies where the authors also developed the CDSS compared to studies in which the authors were not the developers.[4] Of all included studies in our review, only WFO has been studied by authors that were not the developers of the CDSS.

Practice implications and recommendations on the model

To improve CDSS implementation in the clinical workflow to support MDT clinical decision-making in daily clinical practice, more guidance CDSS development, implementation and evaluation is needed. Based on the identified barriers and facilitators for implementation of CDSSs to guide MDTs in solid cancer we recommend clinicians of MDTs, CDSS developers, guideline working party members and electronic health record suppliers to collaborate and focus on the essential prerequisites of a CDSS as shown in the proposed CDSS implementation model. The usability of this theoretical model should be explored in future studies.

With a joint effort, it should be possible to successfully overcome the most important outstanding challenges: 1) to make necessary data-items for guideline-based decision making available during MDT meeting; 2) to promote data accuracy by reusing data from source documents which prerequisites; 3) data-interoperability with the electronic health record; 4) to assess the CDSS validity of recommendations; 5) to improve CDSS usability and transparency in such a way that the CDSS is easily real-time usable during MDT meetings; 6) to include clinicians' and 7) patients' preferences in the MDT decision reporting; 8) to include the loco-regional feasibility in the MDT decision reporting; 9) to warrant CDSS maintenance procedures; 10) to reach an internationally accepted information standard that supports unambiguously guideline development; 11) to comply with data privacy regulations; 12) to assess the clinical utility of the CDSS. Once these challenges are overcome, the data-driven CDSSs can potentially boost electronic health records into learning health systems, and potentially leading to growth of real-world population-based "big data" that can be analyzed systematically using both regular techniques and more modern data analysis techniques such as machine-learning. A huge opportunity to bring personalized medicine a step further.[64]

The next step involves performing multicenter studies to evaluate the effectiveness of CDSS application in daily practice patient care.[9] As MDT workload is expanding due to increasing number of patients and more recommendations in the guideline related to more treatment options, implementation of CDSS can help to structure, reuse, organize and present data in MDTs to support decision-making and to make this process more efficiently.[24,65] MDTs are also challenged to apply increasing knowledge regarding treatment data to their patients, and artificial intelligence is ideally suitable to deal with large amounts of data.[28,39] With a view to broader implementation of CDSS in the clinical workflow, it is important that the CDSS to be investigated have sufficient clinical utility, analytic validity and clinical validity. Future research will elucidate whether such CDSS meet the outlined expectations in terms of optimizing recommendation quality, alleviating MDT burden, and eventually enhancing care.

CONCLUSION

We have shown that only a few CDSSs have been externally validated and implemented in daily care. CDSS maintenance, validity of recommendations and interoperability are important facilitators for CDSS implementation. Internationally accepted criteria are needed to assess the analytic and clinical validity, the clinical utility and the risk of bias of a CDSS. Our novel implementation model for CDSS development and implementation in the clinical workflow can hopefully fulfill the challenging aim of supporting oncological MDTs, providing an overview of the increasing amount of available knowledge to further generate personalized state-of-the-art recommendations for our patients.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment
We thank the health information specialists of the University of Twente, dr. ir. J. Brands and dr. ir. J.G.M. Becht, for their contribution to the design of the search syntax. We acknowledge dr. Xander A.A.M. Verbeek, head of Research and Development at the Netherlands Comprehensive Cancer Organisation (IKNL), for his contribution to the study design.

REFERENCES

1. Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Policy 2015;119:464-74.
2. Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. Ann Surg Oncol 2011;18:2116-25.
3. Ebben K, Sieswerda MS, Luiten EJT, et al. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. JCO Clin Cancer Inform 2020;4:346-56.
4. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293:1223-38.
5. Roshanov PS, Fernandes N, Wilczynski JM, et al. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. BMJ 2013;346:f657.
6. Pawloski PA, Brooks GA, Nielsen ME, Olson-Bullis BA. A Systematic Review of Clinical Decision Support Systems for Clinical Oncology Practice. J Natl Compr Canc Netw 2019;17:331-8.
7. Klarenbeek SE, Weekenstroo HHA, Sedelaar JPM, Futterer JJ, Prokop M, Tummers M. The Effect of Higher Level Computerized Clinical Decision Support Systems on Oncology Care: A Systematic Review. Cancers (Basel) 2020;12.
8. Chua IS, Gaziel-Yablowitz M, Korach ZT, et al. Artificial intelligence in oncology: Path to implementation. Cancer Med 2021;10:4138-49.
9. Oehring R, Ramasetti N, Ng S, et al. Use and accuracy of decision support systems using artificial intelligence for tumor diseases: a systematic review and meta-analysis. Front Oncol 2023;13.
10. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18:143.
11. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13:141-6.
12. Osheroff JA, Teich JM, Levick D, et al. Improving outcomes with clinical decision support: an implementer's guide: Himss Publishing; 2012.
13. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med 2020;3:17.
14. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
15. Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med 2019;170:51-8.
16. Aikemu B, Xue P, Hong H, et al. Artificial Intelligence in Decision-Making for Colorectal Cancer Treatment Strategy: An Observational Study of Implementing Watson for Oncology in a 250-Case Cohort. Front Oncol 2021;10.
17. Alcorn SR, LaVigne AW, Elledge CR, et al. Evaluation of the Clinical Utility of the Bone Metastases Ensemble Trees for Survival Decision Support Platform (BMETS-DSP): A Case-Based Pilot Assessment. JCO Clin Cancer Inform 2022;6:e2200082.

18. Bouaud J, Blaszka-Jaulerry B, Zelek L, et al. Health information technology: use it well, or don't! Findings from the use of a decision support system for breast cancer management. AMIA Annu Symp Proc 2014;2014:315-24.
19. Bouaud J, Messai N, Laouénan C, Mentré F, Séroussi B. Elicitating patient patterns of physician non-compliance with breast cancer guidelines using formal concept analysis. Stud Health Technol Inform 2012;180:477-81.
20. Bouaud J, Séroussi B. Revisiting the EBM decision model to formalize non-compliance with computerized CPGs: results in the management of breast cancer with OncoDoc2. AMIA Annu Symp Proc 2011;2011:125-34.
21. Bouaud J, Spano JP, Lefranc JP, et al. Physicians' Attitudes Towards the Advice of a Guideline-Based Decision Support System: A Case Study With OncoDoc2 in the Management of Breast Cancer Patients. Stud Health Technol Inform 2015;216:264-9.
22. Choi YI, Chung JW, Kim KO, et al. Concordance Rate between Clinicians and Watson for Oncology among Patients with Advanced Gastric Cancer: Early, Real-World Experience in Korea. Can J Gastroenterol Hepatol 2019;2019:8072928.
23. Cypko MA, Stoehr M, Kozniewski M, et al. Validation workflow for a clinical Bayesian network model in multidisciplinary decision making in head and neck oncology treatment. Int J Comput Assist Radiol Surg 2017;12:1959-70.
24. Ebben K, Hendriks MP, Markus L, et al. Using guideline-based clinical decision support in oncological multidisciplinary team meetings: A prospective, multicenter concordance study. Int J Qual Health Care 2022;34.
25. Eccher C, Seyfang A, Ferro A. Implementation and evaluation of an Asbru-based decision support system for adjuvant treatment in breast cancer. Comput Methods Programs Biomed 2014;117:308-21.
26. Epstein RJ, Leung TW, Mak J, Cheung PS. Utility of a web-based breast cancer predictive algorithm for adjuvant chemotherapeutic decision making in a multidisciplinary oncology center. Cancer Invest 2006;24:367-73.
27. Gaudioso C, Elkin P. Considerations of Human Factors in the Design and Implementation of Clinical Decision Support Systems for Tumor Boards. Stud Health Technol Inform 2017;245:1324.
28. Griewing S, Gremke N, Wagner U, Lingenfelder M, Kuhn S, Boekhoff J. Challenging ChatGPT 3.5 in Senology—An Assessment of Concordance with Breast Cancer Tumor Board Decision Making. J Pers Med 2023;13.
29. Heiden K, Sinha M, Böckmann B. Virtual Oncological Networks--IT Support for an Evidence-based, Oncological Health Care Management. Stud Health Technol Inform 2015;216:953.
30. Hendriks MP, Verbeek X, van Manen JG, et al. Clinical decision trees support systematic evaluation of multidisciplinary team recommendations. Breast Cancer Res Treat 2020;183:355-63.
31. Hendriks MP, Verbeek X, van Vegchel T, et al. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. JCO Clin Cancer Inform 2019;3:1-14.
32. Keikes L, Kos M, Verbeek X, et al. Conversion of a colorectal cancer guideline into clinical decision trees with assessment of validity. Int J Qual Health Care 2021;33.
33. Kim EJ, Woo HS, Cho JH, et al. Early experience with Watson for oncology in Korean patients with colorectal cancer. PLoS One 2019;14:e0213640.
34. Kim MS, Park HY, Kho BG, et al. Artificial intelligence and lung cancer treatment decision: Agreement with recommendation of multidisciplinary tumor board. Transl Lung Cancer Res 2020;9:507-14.

35. Lee K, Lee SH. Artificial Intelligence-Driven Oncology Clinical Decision Support System for Multidisciplinary Teams. Sensors (Basel) 2020;20.
36. Lee WS, Ahn SM, Chung JW, et al. Assessing Concordance With Watson for Oncology, a Cognitive Computing Decision Support System for Colon Cancer Treatment in Korea. JCO Clin Cancer Inform 2018;2:1-8.
37. Lin FP, Pokorny A, Teng C, Dear R, Epstein RJ. Computational prediction of multidisciplinary team decision-making for adjuvant breast cancer drug therapies: a machine learning approach. BMC Cancer 2016;16:929.
38. Liu C, Liu X, Wu F, Xie M, Feng Y, Hu C. Using Artificial Intelligence (Watson for Oncology) for Treatment Recommendations Amongst Chinese Patients with Lung Cancer: Feasibility Study. J Med Internet Res 2018;20:e11087.
39. Lukac S, Dayan D, Fink V, et al. Evaluating ChatGPT as an adjunct for the multidisciplinary tumor board decision-making in primary breast cancer cases. Arch Gynecol Obstet 2023;308:1831-44.
40. Macchia G, Ferrandina G, Patarnello S, et al. Multidisciplinary Tumor Board Smart Virtual Assistant in Locally Advanced Cervical Cancer: A Proof of Concept. Front Oncol 2022;11.
41. Ng SST, Oehring R, Ramasetti N, et al. Concordance of a decision algorithm and multidisciplinary team meetings for patients with liver cancer-a study protocol for a randomized controlled trial. Trials 2023;24:577.
42. O'Reilly DA, Chaudhari M, Ballal M, Ghaneh P, Wu A, Poston GJ. The Oncosurge strategy for the management of colorectal liver metastases - an external validation study. Eur J Surg Oncol 2008;34:538-40.
43. Prebet C, Bouaud J, Guézennec G, Seroussi B. Taking into Account the Complementarity of Contemporary Breast Cancer Guidelines to Leverage Decision Support in the DESIREE Project. Stud Health Technol Inform 2018;247:755-9.
44. Redjdal A, Bouaud J, Guézennec G, Gligorov J, Seroussi B. Creating Synthetic Patients to Address Interoperability Issues: A Case Study with the Management of Breast Cancer Patients. Stud Health Technol Inform 2020;275:177-81.
45. Redjdal A, Bouaud J, Guézennec G, Gligorov J, Seroussi B. Reusing Decisions Made with One Decision Support System to Assess a Second Decision Support System: Introducing the Notion of Complex Cases. Stud Health Technol Inform 2021;281:649-53.
46. Rossille D, Laurent JF, Burgun A. Modelling a decision-support system for oncology using rule-based and case-based reasoning methodologies. Int J Med Inform 2005;74:299-306.
47. Séroussi B, Bouaud J, Gligorov J, Uzan S. Supporting multidisciplinary staff meetings for guideline-based breast cancer management: a study with OncoDoc2. AMIA Annu Symp Proc 2007;2007:656-60.
48. Séroussi B, Guézennec G, Lamy JB, et al. Reconciliation of multiple guidelines for decision support: a case study on the multidisciplinary management of breast cancer within the DESIREE project. AMIA Annu Symp Proc 2017;2017:1527-36.
49. Séroussi B, Laouénan C, Gligorov J, Uzan S, Mentré F, Bouaud J. Which breast cancer decisions remain non-compliant with guidelines despite the use of computerised decision support? Br J Cancer 2013;109:1147-56.
50. Séroussi B, Soulet A, Messai N, Laouénan C, Mentré F, Bouaud J. Patient clinical profiles associated with physician non-compliance despite the use of a guideline-based decision support system: a case study with OncoDoc2 using data mining techniques. AMIA Annu Symp Proc 2012;2012:828-37.

51. Séroussi B, Soulet A, Spano JP, et al. Which patients may benefit from the use of a decision support system to improve compliance of physician decisions with clinical practice guidelines: a case study with breast cancer involving data mining. Stud Health Technol Inform 2013;192:534-8.
52. Sesen MB, Peake MD, Banares-Alcantara R, et al. Lung Cancer Assistant: a hybrid clinical decision support application for lung cancer care. J R Soc Interface 2014;11:20140534.
53. Shekarriz J, Keck T, Shekarriz H. Computerized Medical Evidence-Based Decision Assistance System "MEBDAS®" improves in-hospital outcome after pancreatoduodenectomy for pancreatic cancer. Pancreatology 2020;20:746-50.
54. Somashekhar SP, Sepúlveda MJ, Puglielli S, et al. Watson for Oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. Ann Oncol 2018;29:418-23.
55. Thavanesan N, Bodala I, Walters Z, Ramchurn S, Underwood TJ, Vigneswaran G. Machine learning to predict curative multidisciplinary team treatment decisions in oesophageal cancer. Eur J Surg Oncol 2023;49:106986.
56. Tian Y, Liu X, Wang Z, et al. Concordance Between Watson for Oncology and a Multidisciplinary Clinical Decision-Making Team for Gastric Cancer and the Prognostic Implications: Retrospective Study. J Med Internet Res 2020;22:e14122.
57. Zhao X, Zhang Y, Ma X, et al. Concordance between treatment recommendations provided by IBM Watson for Oncology and a multidisciplinary tumor board for breast cancer in China. Jpn J Clin Oncol 2020;50:852-8.
58. Zhou N, Zhang CT, Lv HY, et al. Concordance Study Between IBM Watson for Oncology and Clinical Practice for Patients with Cancer in China. Oncologist 2019;24:812-9.
59. Zou FW, Tang YF, Liu CY, Ma JA, Hu CH. Concordance Study Between IBM Watson for Oncology and Real Clinical Practice for Cervical Cancer Patients in China: A Retrospective Analysis. Front Genet 2020;11.
60. Jie Z, Zhiying Z, Li L. A meta-analysis of Watson for Oncology in clinical application. Sci Rep 2021;11:5792.
61. Janssen A, Robinson T, Brunner M, Harnett P, Museth KE, Shaw T. Multidisciplinary teams and ICT: a qualitative study exploring the use of technology and its impact on multidisciplinary team meetings. BMC Health Serv Res 2018;18:444.
62. Nabhan C, Feinberg BA. Clinical Pathways in Oncology: Software Solutions. JCO Clin Cancer Inform 2017;1:1-5.
63. Bradley A, van der Meer R, McKay C. Personalized Pancreatic Cancer Management: A Systematic Review of How Machine Learning Is Supporting Decision-making. Pancreas 2019;48:598-604.
64. Walsh S, de Jong EEC, van Timmeren JE, et al. Decision Support Systems in Oncology. JCO Clin Cancer Inform 2019;3:1-9.
65. Winters DA, Soukup T, Sevdalis N, Green JSA, Lamb BW. The cancer multidisciplinary team meeting: in need of change? History, challenges and future perspectives. BJU Int 2021;128:271-9.

SUPPLEMENTAL MATERIAL

Supplemental table A. Search syntax with time range up to November 20th 2023

#	database	search terms
1	Cochrane Library	(TITLE-ABS-KEY ((multidisciplinary OR interdisciplinary OR "patient care team") **AND** ("decision* support*" OR artificial AND intelligence) **AND** (cancer OR tumor OR malignant OR oncology OR neoplasm) AND human))
2	PubMed	((((multidisciplinary OR interdisciplinary OR "patient care team")) **AND** (("decision* support*" OR artificial intelligence))) **AND** (((cancer OR tumor OR malignant OR oncology))) **AND** (human) ("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "multidisciplinary"[All Fields] OR ("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "interdisciplinary"[All Fields]) OR "patient care team"[All Fields]) AND ("decision support*"[All Fields] OR ("artificial intelligence"[MeSH Terms] OR ("artificial"[All Fields] AND "intelligence"[All Fields]) OR "artificial intelligence"[All Fields])) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("malign"[All Fields] OR "malignance"[All Fields] OR "malignances"[All Fields] OR "malignant"[All Fields] OR "malignants"[All Fields] OR "malignities"[All Fields] OR "malignity"[All Fields] OR "malignization"[All Fields] OR "malignized"[All Fields] OR "maligns"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancies"[All Fields] OR "malignancy"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "oncology"[All Fields] OR "oncology s"[All Fields])) AND ("human s"[All Fields] OR "humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields])
3	Scopus	**TITLE-ABS-KEY (((multidisciplinary OR interdisciplinary OR «patient care team») AND** ("decision* support*" OR artificial AND intelligence) **AND** (cancer OR tumor OR malignant OR oncology OR neoplasm) **AND** human))

Supplemental table B. Study aims of the 44 included studies

Study aims	Frequency
to study the concordance between CDSS and MDT recommendations	25
to describe the development and/or validation of a CDSS or method	9
to develop a machine learning model to predict MDT decisions	2
to study the complementarity of different guidelines in a CDSS	2
to study the impact of CDSS based survival prediction on MDT decision making	2
to study the attitude of MDT towards CDSS recommendations	1
to study the effect of CDSS based decision-making on patient satisfaction of hospital experience	1
to study the reusage of patient data for further development of an existing CDSS	1
to study the availability of data-items during MDT meeting for CDSS application	1

Supplemental table C. Barriers for CDSS implementation

Author	barrier	category of barrier	n
Aikemu, 2021	validity of the artificial intelligence made options	CDSS validity of recommendations	4
	guideline outdated recommendation	maintenance	
	variations in the aggressiveness of treatment approaches in patient subpopulations based on age	subpopulations	
	local availability of treatments	loco-regional feasibility	
Alcorn, 2022	early efficacy of a decision support tools may not translate into measurable clinical effectiveness	other	2
	some studies indicate superiority of clinician (survival) predictions over use of predictive tools such as performance status alone	CDSS validity of recommendations	
Bouaud, 2014	quality of recorded patient data	data accuracy	4
	unavailability of data	data availability	
	recommendations based on incorrect navigations	usability	
	no corresponding navigation available in (more complex) cases	subpopulations	
Bouaud, 2012	clinical situations in which physicians do not agree with guidelines	maintenance	1
Bouaud, 2011	guideline-outdated recommendation due to constant practice evolution	maintenance	3
	impossibility to acknowledge both patients' and clinicians' preferences to describe actual decisions	patients and/or clinicians preferences	

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
	specific patient features not covered by clinical practice guidelines (e.g. breast cancer during pregnancy)	subpopulation	
Bouaud, 2015	psychological negative reactance when people feel their autonomy is threatened	autonomy	4
	automation bias, i.e. the tendency to over-trust health information technology leading to an incorrect decision in order to follow the CDSS recommendation	automation bias	
	accuracy of collected data	data accuracy	
	CDSS usability	usability	
Choi, 2019	not considering the medical history of the patient	subpopulations	5
	recommendation of agents considered outdated in Korea	maintenance	
	clinician's preferred chemotherapies, patient enrollment in clinical trials	patients and/or clinicians preferences	
	patients refusing agents not covered by insurance, MDT does therefore not recommend these agents	loco-regional feasibility	
	survival benefit of WFO recommendations in advanced gastric cancer patients has not been validated	CDSS validity of recommendations	
Cypko, 2017	incorrect data	data accuracy	4
	incomplete patient data (e.g. negative findings were missing)	data accuracy	
	outvoting relevant observations	CDSS validity of recommendations	
	incorrect model (a variable was missing)	CDSS validity of recommendations	
Ebben, 2022	physicians may tend to feel compromised in their autonomy	autonomy	3
	the evidence that clinical decision support increases MDT performance is sparce	other	
	insufficient available patient and disease characteristics	data availability	
Eccher, 2014	lack of interoperability with the electronic health record	interoperability	4
	the final decision may take into account a variety of factors that may not be directly represented in the electronic health record	data accuracy	
	the guidelines do not cover all parts of treating breast cancer equally well	maintenance	

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
	oncologists take a holistic view of the disease and the parameter thresholds	patients and/or clinicians preferences	
Epstein, 2006	limited utility of Adjuvant! perceived in certain scenarios (e.g. patients <40 yrs or >70 yrs)	subpopulations	2
	clinicians' treatment decisions continued to be strongly influenced by omitted covariables such as lymphovascular invasion, HER2 expression, and tumor mitotic rate, even though it was accepted that insufficient evidence warranted inclusion of these variables in the program	patients and/or clinicians preferences	
Gaudioso, 2017	NA		0
Griewing, 2023	ChatGPT 3,5 is limited to data published until September 2021	maintenance	3
	ChatGPT fails to successfully and consistently take individual patient information into account	CDSS validity of recommendations	
	over-recommendation tendency of ChatGPT	CDSS validity of recommendations	
Heiden, 2015	NA		0
Hendriks, 2019	missing data	data availability	3
	unclassifiable data due to lack of clear definition	information standard	
	lack of time for structured and systematically file management and for manually data entry in the CDSS	usability	
Hendriks, 2020	quick and continuous revision and subsequent implementation and evaluation of guidelines in clinical practice is challenging	maintenance	2
	impossibility to adhere to international classification and coding standards (e.g. unavailability in SNOMED CT)	information standard	
Keikes, 2021	not all patients that were run through the CDSS led to a treatment recommendation, particularly due to information gaps in the guideline	maintenance	5
	a potential risk of converting text-based guideline recommendations and considerations into decision trees is losing nuance	CDSS validity of recommendations	
	manual input of cases in the CDSS is sensitive to errors	data accuracy	

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
	manual input of cases in the CDSS is time-consuming	usability	
	CDSS is validated with MDT reports from a single tertiary center (treating more complex cases)	CDSS validity of recommendations	
Kim, 2019	WFO recommends chemotherapeutic regimens according to NCCN guidelines but has a distinct prioritizing algorithm (based on training with cases from a tertiary medical center in the USA) that is different from that of the MDT in Korea	CDSS validity of recommendations	3
	it seems that WFO does not recommend chemotherapy regimens with reported lower efficacies	CDSS validity of recommendations	
	no reimbursement by the national health insurance system for particular treatment regimen	loco-regional feasibility	
Kim, 2020	WFO could not reflect patient statuses in detail (co-morbidity or preference)	CDSS validity of recommendations	2
	differences across countries regarding guidelines, national licensing of recommended drugs or treatments, compliance with insurance coverage	loco-regional feasibility	
Lee, 2020	inability of WFO to consider insurance coverage, medical guidelines, race and geographical region	CDSS validity of recommendations	1
Lee, 2018	loco-regional no reimbursement for certain treatments	loco-regional feasibility	3
	WFO recommendation not up to date (e.g. not recommending biologic agents)	CDSS validity of recommendations	
	following WFO recommendations may contribute to undertreatment in older patients (e.g. WFO generally does not recommend doublet chemotherapy in these patients)	CDSS validity of recommendations	
Lin, 2016	poor agreement between guidelines (e.g. different thresholds for patients with 'oligonodal' disease)	information standard & maintenance	2
	several factors (e.g. treatment toxicity, performance status, quality of life) can strongly influence the MDT treatment decision but such nuances are poorly captured by practice guidelines	maintenance	
Liu, 2018	not all cases were supported by WFO	maintenance	5

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
	WFO treatment option 'concurrent chemoradiation' is not tolerated in Chinese patients due to usually weaker physique than that of Western patients	maintenance	
	China uses other drugs that are equally effective but not reported by WFO as to be 'recommended' or 'for consideration'	maintenance	
	some recommended drugs by WFO are not available in the Chinese market	loco-regional feasibility	
	WFO does not take co-morbidity, patient preferences, medical insurance etc. into consideration	maintenance	
Lukac, 2023	studies analyzing AI in lung cancer treatment decisions showed that the agreement of MDT and AI was strong in a metastatic situation, but not in the early stages where the shared decision process plays an important role	patients and/or clinicians preferences	1
Macchia, 2022	information overload with unstructured data that are nor organized	data accuracy	2
	point of views may be various and sometimes conflicting, especially if there are conflicting data	CDSS validity of recommendations	
Ng, 2023	incomplete data due to failure of clinicians to submit adequate information	data availability	3
	finding information in the hospital information system and determining its relevance is time-consuming time-consuming	data accuracy	
	the inability of the algorithm to consider decision-making factors that may not be included in the hospital information system, such as subjective physical assessments or psychosocial factors	CDSS validity of recommendations	
O'Reilly, 2008	NA		0
Prebet, 2018	discrepancy between different guidelines (NCCN & ESMO)	maintenance	1
Redjdal, 2020	the authors had to solve semantic and structural interoperability issues to make OncoDoc data re-usable by the GL-DSS of DESIREE	interoperability	2

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
	lack of clinical data in health information technology hinders innovation and raises the barrier of entry into the industry. The main reason comes from data privacy and relies on the problem of re-identification	data privacy	
Redjdal, 2021	not all patients that were run through the CDSS led to a treatment recommendation	maintenance	1
Rossille, 2005	NA		0
Séroussi, 2007	many organizational and technical barriers limit the use of CDSSs in a multidimensional care process environment	other	2
	limits of CPGs to cover all clinical cases, problems of threshold in patient categorization (i.e. borderline cases)	maintenance	
Séroussi, 2017	NA		0
Séroussi, 2013	NA		0
Séroussi, 2012	NA		0
Séroussi, 2013	NA		0
Sesen, 2014	a strictly guideline rule-based approach to CDSSs is imprecise in quantifying the statistical or	CDSS validity of recommendations	5
	probabilistic level of support associated with different treatment options		
	elicitation and maintenance of rule-based domain representations in CDSs are expensive and	usability	
	time-consuming		
	ambiguous guideline terminology is a bottleneck in the development of guideline rule-based CDSSs	information standard	
	inability for probabilistic decision support to incorporate additional factors, other than maximizing	data accuracy	
	survival expectancy, into probabilistic queries due to lack of data on such factors		
	from a patient perspective, the MDT decisions also need to reflect on the patient's views,	patients and/or clinicians preferences	
	preferences and circumstances. Data on some of these concepts are very hard to capture, let		
	alone quantify and put in a computer model		
Shekarriz, 2020	NA		0

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
Somashekhar, 2018	local availability of therapies	loco-regional feasibility	2
	nonconcordance can result from variations in the aggressiveness of treatment approaches in	patients and/or clinicians preferences	
	patient subpopulations based on comorbidity, patient preferences and level of social support		
	systems. These factors are not captured in WFO		
Thavanesan, 2023	the explainability of deep-learning models is problematic	CDSS acceptability and explainability	2
	clinician preferences and human factors are relevant to decisions, such data is not routinely recorded	patients and/or clinicians preferences	
Tian, 2020	local guidelines and practices are not captured in WFO (e.g. China uses SOX chemotherapy and	maintenance	2
	hyperthermic intraperitoneal chemotherapy which is not available in the WFO system, the acceptance		
	of domestic radiotherapy in China is generally low)		
	the application of targeted drugs and immune therapy is limited in China because of patients'	loco-regional feasibility	
	affordability		
Zhao, 2020	patient preferences are not taking into account by WFO	patients and/or clinicians preferences	4
	local unavailability of certain drugs or no accessible drugs due to lack of reimbursement	loco-regional feasibility	
	the requirements of WFO standardized treatment differ from local clinical practice (e.g. WFO	maintenance	
	recommends single-agent chemotherapy in metastatic disease but MDT recommends		
	combination chemotherapy)		
	multi-gene detection to assess recurrence risk in early breast cancer is not enough	loco-regional feasibility	
	available in China		

Supplemental table C. Barriers for CDSS implementation (continued)

Author	barrier	category of barrier	n
Zhou, 2019	local unavailability of certain drugs or no accessible drugs due to lack of reimbursement	loco-regional feasibility	4
	certain WFO recommended treatments are not used in China (e.g. vinorelbine)	maintenance	
	multi-gene detection to assess recurrence risk in early breast cancer is not enough	loco-regional feasibility	
	available in China		
	China uses certain treatments that are not recommended by WFO (e.g. SOX chemotherapy)	maintenance	
Zou, 2020	certain drugs recommendations are not available in WFO (e.g. nedaplatin, PD-1/PD-L1 antibodies)	maintenance	5
	local inavailability of certain drugs due to lack of reimbursement	loco-regional feasibility	
	patient preferences are not taking into account by WFO	patients and/or clinicians preferences	
	some clinical settings are not yet supported by WFO (e.g. recurrent tumors)	maintenance	
	multi-gene detection is not enough available in China	loco-regional feasibility	
			101

Supplemental table D. Facilitators for CDSS implementation

Author	facilitator	category of facilitator	n
Aikemu, 2021	availability of CDSS validity (e.g. concordance between CDSS and MDT)	CDSS validity of recommendations	5
	usage of up-to-date guidelines	maintenance	
	evaluate risk and benefits of recommendations in subgroups (e.g. older age)	subpopulations	
	consideration of care setting	loco-regional feasibility	
	patient acceptance of CDSS	patient acceptance of CDSS	
Alcorn, 2022	BMETS-DSP usage improved selection of prognosis- and guideline-appropriate surgery and	CDSS validity of recommendations	1
	RT interventions		
Bouaud, 2014	initial data entry quality	data accuracy	2

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
	correct use of health information technology tools	usability	
Bouaud, 2012	insights for situations at risk of non-compliance	maintenance	1
Bouaud, 2011	usage of up-to-date guidelines	maintenance	2
	CDSS usage helps MDTs to formalize the patient case description (the "check-list effect" allows	data availability	
	for the extensive characterization of the patient clinical state)		
Bouaud, 2015	positive reactance to the CDSS (physicians demonstrates that they critically considered	autonomy	4
	inappropriate CDSS advices and that in these cases, physician's knowledge of CPGs is strongly		
	established)		
	improving CDSS user interface	usability	
	ensuring data quality	data accuracy	
	training physicians to both CDSS and CPGs while adopting a critical appraisal on CDSS output	physician training	
Choi, 2019	region-specific customization of WFO	loco-regional feasibility	2
	addition of local clinical factors would increase the level of sophistication of WFO as a CDSS	loco-regional feasibility	
Cypko, 2017	expert validation of the CDSS	CDSS validity of recommendations	2
	collaboration between clinician and computer scientist to overcome the intensive validation time	technical skills	
Ebben, 2022	application of the CDSS may stimulate more complete reporting of necessary data	data availability	4
	the CDSS should be suitable for connection with the electronic health record	interoperability	
	the importance of standardized available data and development of knowledgebases for CDS	information standard	
	integration of CDSSs into existing clinical processes	usability	
Eccher, 2014	integration of CDSS in clinical workflow	usability	2
	CDSS must allow the physician to enter subjective assessments that depend on complex implicit,	patients and/or clinicians preferences	

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
	hard to codify knowledge, but also on patient preferences (i.e. holistic parameters)		
Epstein, 2006	by providing objective estimates of minimal treatment benefit that are able to be shared with	shared decision-making	1
	patients, the option "no treatment" was offered less hesitantly in cases where significant risk		
	of disease recurrence remained		
Gaudioso, 2017	limit cognitive burden, display case relevant clinical information on a single screen	usability	2
	display radiology and pathology reports in their entirety rather than as a summary of findings	usability	
	("I want to read the report myself, I don't trust somebody else's interpretation")		
Griewing, 2023	exponential increase in oncology treatment data calls for the application of automated data	technical skills	1
	computing		
Heiden, 2015	NA		0
Hendriks, 2019	completeness of data-items in the electronic health record can be improved if free text reporting	information standard	5
	is replaced by clearly defined standardized reporting of data-items		
	if MDT report multiple alternatives explicitly, this can facilitate shared decision-making	shared decision-making	
	CDTs can be used to explicate the decision-making process, provided that all data-items are	maintenance	
	unambiguously present. In this way, CDTs can act as a learning health system facilitating		
	tightening and updating guidelines		
	needed data should be registered in a standardized way, be exchangeable and reusable with	interoperability	
	MDT reporting forms and the CDTs		
	situations were identified for which the guideline represents no recommendation yet	CDSS validity of recommendations	
Hendriks, 2020	systematic construction of CDTs	interoperability	4

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
	use of unequivocal and unambiguous definition of data-items on the basis of internationally	information standard	
	acknowledged classification and coding systems (e.g. SNOMED CT)		
	the modular character of CDTs provides a means for quick and clear implementation and	maintenance	
	accessibility of dynamic guidelines		
	connection of CDSS to the electronic health record	interoperability	
Keikes, 2021	describe information gaps, inconclusive treatment recommendations and guideline	CDSS validity of recommendations	8
	considerations specifically in the CDSS to prevent losing nuance		
	integrate CDSS with patient data derived from the electronic health records, this requires	information standard & interoperabi-	
	standardized terminology and synoptic reporting	lity & data accuracy & usability	
	validation of CDSS using MDT reports of different hospitals	CDSS validity of recommendations	
	the Oncoguide platform may facilitate data collection for cancer registries if a link between	interoperability	
	the decision tree and registries is generated.		
	the inherent modular character of decision trees fits the current modular revision process for	maintenance	
	an increasing number of guidelines in Dutch oncology		
Kim, 2019	usage of up-to-date versions of WFO and NCCN guidelines	maintenance	1
Kim, 2020	NA		0
Lee, 2020	the use of WFO has a positive effect on patient satisfaction and perception of the hospital	patient perception	1
Lee, 2018	NA		0
Lin, 2016	identification of additional non-clinicopathological variables, not captured in guidelines, that	maintenance & CDSS validity	3
	impact expert advice		

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
	further studies at an external center would clarify the clinical utility of the CDSS	CDSS validity of recommendations	
Liu, 2018	WFO needs to learn the regional characteristics of patients to improve its assistive ability	maintenance	1
Lukac, 2023	AI is capable to work with huge amount of information and can support a more precise medicine	CDSS validity of recommendations	3
	One of the strengths of Chat- GPT is to engage in a conversation about a topic. Here the AI shows	usability	
	remarkable results implementing previous answers and improving the outcome.		
	reflecting possible comorbidities and performance status of the patient as a relevant factor	CDSS validity of recommendations	
Macchia, 2022	integrating different sources and information	interoperability	2
	reducing potential inconsistencies by developing data-driven methods and standardized language	information standard	
	and interpretation		
Ng, 2023	using a decision algorithm that improves the efficiency of multidisciplinary team meetings	usability	1
Liu, 2018	WFO needs to learn the regional characteristics of patients to improve its assistive ability	maintenance	1
O'Reilly, 2008	conduct further studies in a prospective setting	CDSS validity of recommendations	1
Prebet, 2018	complementarity of CPGs enlarges the coverage of CDSSs and enrich recommendations	maintenance	1
Redjdal, 2020	NA		0
Redjdal, 2021	improvement of CPGs increases compliance of MTD decisions and the CDSS	maintenance	1
Rossille, 2005	for the future system to become entirely automated, patient's data should be automatically	interoperability	2
	acquired from the patient records		
	case-based retrieval can support therapeutic decisions in cases that do not or cannot	CDSS validity of recommendations	
	comply with recommended guidelines. A multi-model reasoning CDSS based on both guideline		

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
	and case series, which will automatically compare the patient's case to the corresponding		
	guideline, then to the other cases, and retrieve similar cases.		
Séroussi, 2007	check validity of noncompliance between MDT decision and CDSS recommendation by	maintenance	2
	guideline updating experts		
	CDSS usage decreases the number of missing steps and increases compliance	usability	
Séroussi, 2017	reconcile CPGs on the basis of complementarity to extend clinical coverage	maintenance	4
	usage of authoritative terminologies such as the NCI thesaurus, LOINC, and SNOMED CT,	information standard & interoperability	
	to further warranty semantic interoperability with potential hospital information systems or		
	electronic medical records		
	when running a CDSS based on different guidelines, this may lead to intra and inter-CPG	maintenance	
	conflicting recommendations.		
Séroussi, 2013	the systematic use of CDSSs should help identify situations supported by low evidence as	maintenance	1
	candidate profiles for prospective studies, besides repeated noncompliance should trigger		
	the revision of guidelines to follow the evolution of practices		
Séroussi, 2012	NA		0
Séroussi, 2013	NA		0
Sesen, 2014	address vagueness and uncertainty in rule eligibility criteria by explicating the implicit expert	maintenance	3
	knowledge		
	usage of open-source language for implementing guidelines would facilitate the dissemination	information standard & interoperability	
	and re-use of information between different computer interpretable guideline formalisms		

Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
Shekarriz, 220	the quantitative calculation method of MEBDAS® allows patients to be involved in the therapeutic	shared decision-making	2
	decision-making process (e.g. based on the prediction of life expectancy and quality of life		
	the patient can intervene in the decision-making process)		
	controlled prospective studies can provide more valid results	CDSS validity of recommendations	
Somashekhar, 2018	NA		0
Thavanesan, 2023	accurate predictive models would provide for consistent clinical assistive decision tools capable of	data accuracy	3
	standardizing such decisions, improving efficiency, and positively impacting healthcare equality		
	any clinical assistive decision tool needs to operate within current electronic healthcare infrastructure	interoperability	
	acceptability and explainability of CADTs is a major consideration in the integration AI-based tools	CDSS acceptability and explainability	
	within healthcare		
Tian, 2020	larger sample size required for further validation of concordance in early versus advanced	CDSS validity of recommendations	2
	stage disease		
	local guidelines should be incorporated into WFO for better application in China	maintenance	
Zhao, 2020	WFO can improve the problem of doctor-patient trust (patients in China often suspect doctors	patients' trust in doctors	1
	of overtreatment and a crisis of trust is growing)		
Zhou, 2019	the CDSS must be sufficiently accepted by users and integrated into the physician's workflow	CDSS acceptability and explainability	4
	determine the accuracy of the CDSS for diagnostic and treatment recommendations	CDSS validity of recommendations	
	patient privacy and security	data privacy	
	accelerate the localization of WFO so it can be comprehensively and rapidly applied in China	maintenance	

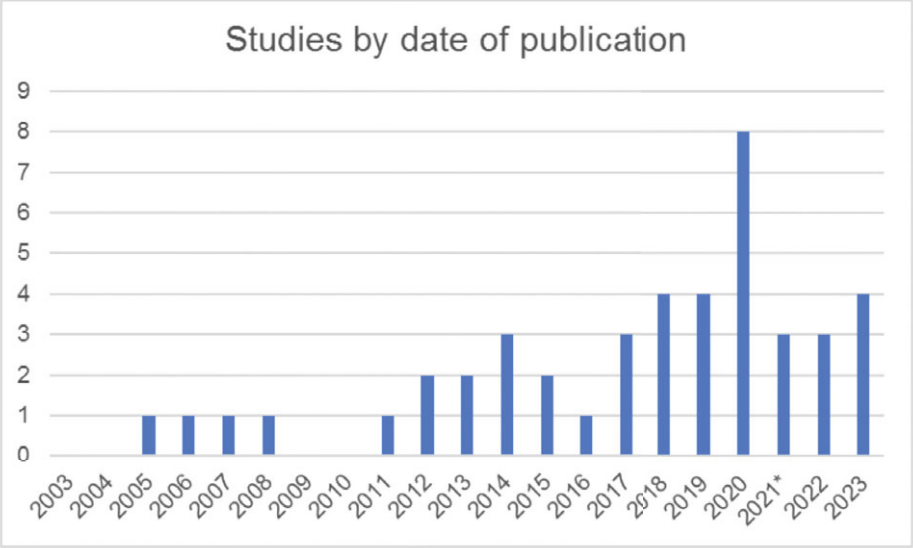
Supplemental table D. Facilitators for CDSS implementation (continued)

Author	facilitator	category of facilitator	n
Zou, 2020	improve WFO to adept the real clinical practice in different countries. Patients' physical and	maintenance	1
	mental state, economic situation, complications, patients' treatment preference and medical		
	reimbursement plan in different countries should be taken into account and not just provide advice		
	based on existing knowledge.		
			87

Supplemental table E. Definitions of all categories of barriers and facilitators

Barrier category	definition of category
maintenance	all shortcomings of a CDSS that can be attributed to the CDSS not being up to date
CDSS validity of recommendations	the CDSS is not taking into account or judging certain data-items leading to less valid recommendations
loco-regional feasibility	the CDSS recommendation is not taking into account the local feasibility
patients and/ or clinicians preferences	the CDSS recommendation does not include preferences of patients and clinicians
data accuracy	all barriers that hamper the input of the correct data
subpopulations	implies patient categories for which the CDSS can not be properly used
usability	all barriers which reduce the ease of use of the CDSS
information standard	involves barriers structuring and coding patient data according to guidelines and international standards
data availability	unavailability of data
interoperability	barriers caused by the inability of the CDSS to connect with the data in the electronic health record
autonomy	inability of clinicians to use the CDSS because CDSS recommendations might undermine their autonomy
automation bias	the tendency to over-trust health information technology leading a physician to make an incorrect decision
	in order to follow the CDSS recommendation
data privacy	inability to apply the CDSS in clinical practice due to privacy legislation
CDSS acceptability and explainability	clinicians can not see and understand how the CDSS reaches its recommendations

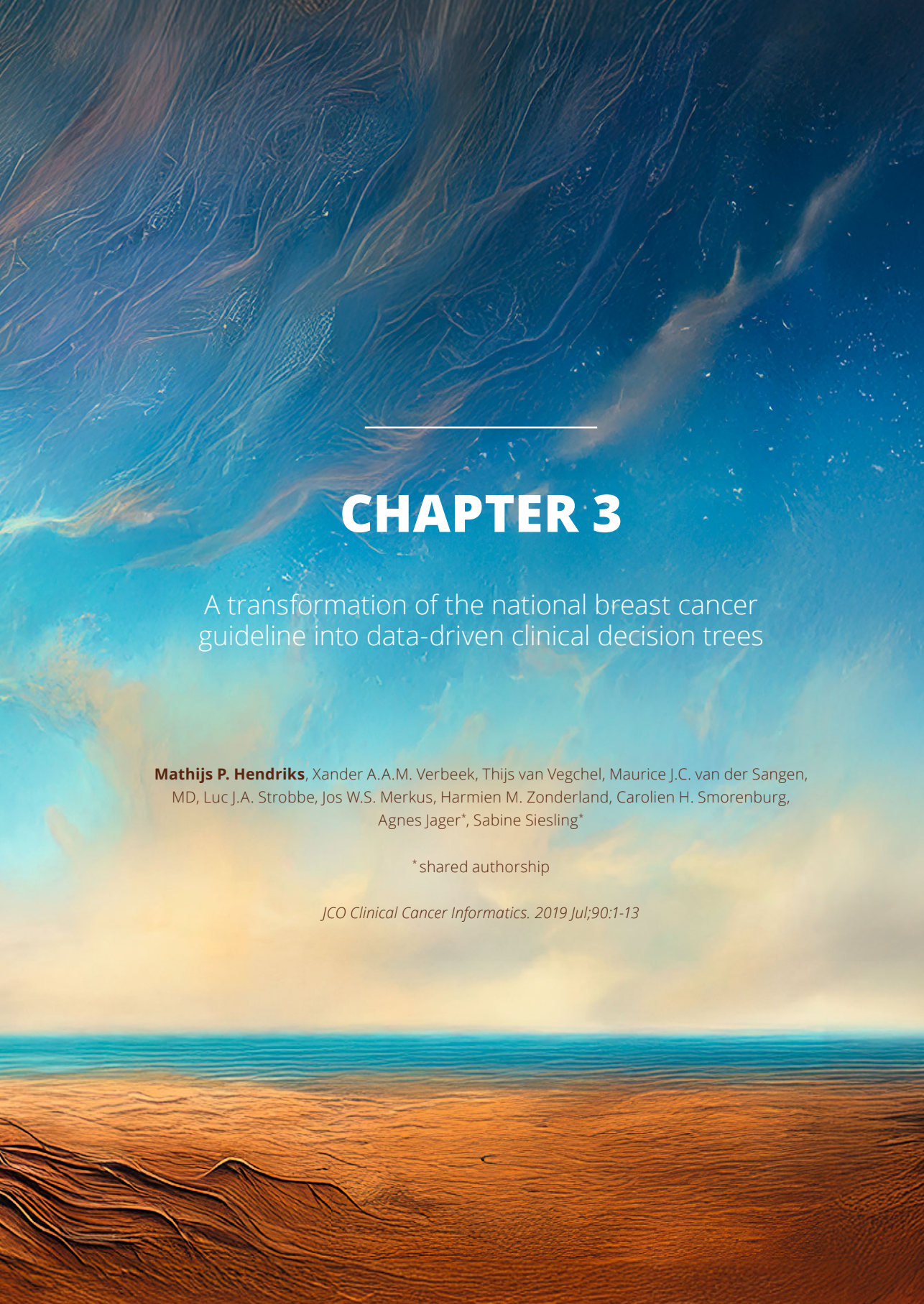
Facilitator category	definition of category
maintenance	all benefits of a CDSS that can be attributed to the CDSS being up to date
CDSS validity of recommendations	the CDSS is taking into account or judging certain data-items leading to more valid recommendations
interoperability	facilitators caused by the ability of the CDSS to connect with the data in the electronic health record
usability	all facilitators which improve the ease of use of the CDSS
information standard	involves facilitators structuring and coding patient data according to guidelines and international standards
data accuracy	all facilitators that improve the input of the correct data
loco-regional feasibility	the CDSS recommendation is taking into account the local feasibility
shared decision-making	the CDSS mentions alternative diagnostic or treatment options facilitating shared decision-making
technical skills	the CDSS performance is improved by making use of expertise of clinical data science
data availability	properties of the CDSS that promote availability of data needed for the CDSS to deliver a recommendation
CDSS acceptability and explainability	the extent to which clinicians understand the CDSS, how the CDSS generates the recommendations
subpopulations	implies that the CDSS also can be used in certain specific patient categories
autonomy	ability of clinicians to use the CDSS because they believe the CDSS support their autonomy to optimize decisions
data privacy	the ability to apply the CDSS in clinical practice in accordance with privacy legislation
patient acceptance of CDSS	the extent to which a patient has trust in the CDSS guided recommendation
patient perception	attitude of patients towards CDSS usage of CDSS for MDT support
patients and/ or clinicians preferences	the CDSS recommendation does include preferences of patients and clinicians
patients' trust in doctors	attitude of patients towards doctors who use CDSSs for guiding treatment recommendations
physician training	reflects skills of the physician that improve the technical usage of the CDSS in clinical practice



Supplemental figure F. Graphic showing the number of included studies by date of publication.

PART III

Clinical decision support using
clinical decision trees



CHAPTER 3

A transformation of the national breast cancer guideline into data-driven clinical decision trees

Mathijs P. Hendriks, Xander A.A.M. Verbeek, Thijs van Vegchel, Maurice J.C. van der Sangen, MD, Luc J.A. Strobbe, Jos W.S. Merkus, Harmien M. Zonderland, Carolien H. Smorenburg, Agnes Jager*, Sabine Siesling*

*shared authorship

JCO Clinical Cancer Informatics. 2019 Jul;90:1-13

ABSTRACT

PURPOSE The essence of guideline recommendations often is intertwined in large texts. This impedes clinical implementation and evaluation and delays timely modular revisions needed to deal with an ever-growing amount of knowledge and application of personalized medicine. The aim of this project was to model guideline recommendations as data-driven clinical decision trees (CDTs) that are clinically interpretable and suitable for implementation in decision support systems.

METHODS All recommendations of the Dutch national breast cancer guideline for nonmetastatic breast cancer were translated into CDTs. CDTs were constructed by nodes, branches, and leaves that represent data items (patient and tumor characteristics [e.g., T stage]), data item values (e.g. T2 or less), and recommendations (e.g. chemotherapy), respectively. For all data items, source of origin was identified (e.g. pathology), and where applicable, data item values were defined on the basis of existing classification and coding systems (e.g. TNM, Breast Imaging Reporting and Data System, Systematized Nomenclature of Medicine). All unique routes through all CDTs were counted to measure the degree of data-based personalization of recommendations.

RESULTS In total, 60 CDTs were necessary to cover the whole guideline and were driven by 114 data items. Data items originated from pathology (49%), radiology (27%), clinical (12%), and multidisciplinary team (12%) reports. Of all data items, 101 (89%) could be classified by existing classification and coding systems. All 60 CDTs could be integrated in an interactive decision support app that contained 376 unique patient subpopulations.

CONCLUSION By defining data items unambiguously and unequivocally and coding them to an international coding system, it was possible to present a complex guideline as systematically constructed modular data-driven CDTs that are clinically interpretable and accessible in a decision support app.

CONTEXT SUMMARY

Key Objective

To develop a scalable method for representing textual guideline recommendations as systematically designed, modular, data-driven clinical decision trees (CDTs) and to apply this method on a complex guideline. We tested this method using the Dutch national breast cancer guideline.

Knowledge Generated

The rules that comprise CDTs can be systematically derived from guideline recommendations. At each point in the care path, the CDT describes the most appropriate new interventions on the basis of the accumulating patient data available up to that point. We demonstrate the feasibility of applying the CDT method on a complex guideline. Data items that comprise the CDT were defined unequivocally and

unambiguously on the basis of international classification and coding systems. In this way, interoperability with electronic health records and implementation of CDTs in decision support systems can be facilitated.

Relevance

The modular character of CDTs could provide a means for quick and clear implementation and accessibility of dynamic guidelines. Moreover, fast-growing knowledge could be taken into account more rapidly and easily by modular updating of CDTs, which supports implementation of data-driven personalized health care.

INTRODUCTION

The National Academy of Medicine defines clinical practice guidelines as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1] It has been shown that their implementation reduces unwanted variability in clinical practice and improves outcome, therefore im- proving the quality of care.[2]

Quick and continuous revision and subsequent implementation and evaluation of guidelines in clinical practice are essential but challenging for several reasons.[3] First, guideline development is time consuming and modular revision (meant to accelerate the revision process) cumbersome because modules often are intertwined in the entire guideline text. Second, as cancer treatment is getting more personalized and based on (biomarker) data, guideline recommendations need to be defined for ever-smaller and more-specific patient populations, which makes them more complex. Finally, routine, explicit guideline utilization for each patient is cumbersome because of ambiguity in guideline texts attributable to the use of equivocal terms.

Methods for transforming guidelines into computer- interpretable formats are well studied and have been successfully used for relatively simple guidelines, such as medication alerts to warn for potential contraindications.[4-6] However, these methods often are aimed at how to describe guidelines in formal computer languages and not as much at the actual translation of free-text guidelines into such formats. Moreover, such descriptions are difficult to grasp and interpret by physicians involved in guideline commit- tees. Therefore, the application of such an approach to complex multidisciplinary (oncology) guidelines has remained challenging. Occasionally, guidelines, such as those of the National Comprehensive Cancer Network (NCCN), are presented in widely used, compact flowcharts. However, these flowcharts are not fully data modulated, and a strict relationship between all possible (combinations of) patient/disease characteristics and guideline recommendations is not always present.

To anticipate these challenges and complement the NCCN flowcharts, we hypothesized that the transformation of guideline text into data-driven clinical decision trees (CDTs) can facilitate the continuous cycle of guideline development, implementation,

evaluation, revision, and maintenance.[7] We therefore set up a project that transformed the Dutch national breast cancer guideline into CDTs.[8] Our aim was to model systematically all national breast cancer guideline recommendations for non- metastatic breast cancer as data-driven CDTs on the basis of existing classification systems. When we succeed, we will try to develop an app that clinicians can use directly in daily practice, that complies with prerequisites for integration into the electronic health record (EHR), and that facilitates continuous learning from real-time data.

METHODS

To represent text-based guideline recommendations in CDTs, we used a repetitive data collection approach for each step in a nominal patient-centric care pathway (Fig 1). Our method is based on a generic model for patient disease state that regresses, remains stable, or progresses either spontaneously or as a result of care interventions. During care, data that describe the disease state accumulate. The care pathway is decomposed into interventions for measuring the disease state (e.g. diagnoses) that result in new data, which add to prior knowledge, and into interventions that influence the disease state. At each point, the CDTs describe the most appropriate new intervention on the basis of data available up to that point. The rules that comprise the CDT are derived from guideline recommendations. All CDTs can be used independently from one another (e.g. a CDT for postoperative treatment can be used independently from a CDT for preoperative treatment and its outcome). By connecting CDTs head to tail, the actual care pathway can be reconstructed. The model is scalable across diseases because at no point are assumptions made on care process or type of data.

Guideline text recommendations were mapped according to this approach and subsequently for each step modeled into data-driven CDTs. The method was applied to the 2012 version of the Dutch national breast cancer guideline. CDTs were developed together with researchers of the Nether- lands Comprehensive Cancer Organization assisted by a multidisciplinary panel of breast cancer specialists (including surgeons, medical and radiation oncologists, radiologists, and pathologists) and supervised by the members of the Dutch national guideline working group to ensure accuracy and clinical interpretability.

CDTs

CDTs consist of nodes, branches, and leaves. For modeling and visualization of a CDT, the following concepts were used: The trunk of the tree represents the step in the care pathway to which the recommendation applies (e.g. post- operative treatment tree). The nodes represent patient or tumor characteristics (e.g. T stage) formulated as data items (e.g. T2 or less). Data items are derived from medical history, physical examination, or diagnostic tests and can be independent (e.g. tumor diameter) or dependent (e.g. a data item that is classified as a category on the basis of another data item, such as T stage derived from tumor diameter). The branches represent cutoff points. The leaves represent patient-specific recommendations (e.g. treatment recommendations, advice

to perform a diagnostic test). It is optional to present the level of evidence that underlies a specific recommendation.

In each CDT, the patient or population, intervention, com- parison, and outcome (PICO) system is represented. Leaves represent recommended interventions, and the collection of nodes and cutoff points that lead to a leaf represent the patient or population to whom the recommendation applies. Information such as background literature, studies that compare outcomes of various diagnostic or treatment strategies, and level of evidence is provided as meta- information that underlies the leaves (recommendations).[9] This PICO strategy is supported by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to judge and grade the quality of scientific publications that indicate levels of evidence.[10,11] CDTs were constructed manually by systematically applying this approach to translate each guideline recommendation. All CDTs were checked and formally approved by the Dutch national guideline working group.

Implementation in Decision Support Systems and Interoperability

To establish the source of data that drives guideline recommendations, we identified the source record (e.g. pathology or radiology report) for each data item. Data items analyzed included source of data origin (e.g. pathology, radiology) and relation to classification systems (e.g., TNM, Breast Imaging Reporting and Data System [BIRADS]). To quantify linguistic unity (or lack thereof), we kept track of the number of different terms used in the free-text guidelines for each data item. For the purpose of linguistic unity, data items in nodes and interventions in leaves were described as much as possible using the most accepted, to our knowledge, international classification and coding systems (e.g. TNM; BIRADS; International Classification of Diseases for Oncology, Third Edition; Systematized Nomenclature of Medicine Clinical Terms [SNOMED CT (SNOMED International 2018 version 1.37.3)]). Prerequisites for implementing CDTs in decision support systems and interoperability with EHRs are the systematic construction of CDTs as described herein and the unequivocal and un- ambiguous definition of data items on the basis of internationally acknowledged classification and coding systems. The reason for using international classification or coding systems is interoperability. Technically, our method allows for associating a single data item with codes from one or more coding or classification systems (one-to-many relationship) that express the same (e.g. as can be the case in SNOMED CT and Logical Observation Identifiers Names and Codes). In this way, interoperability challenges faced during implementation can be solved pragmatically, depending on the choices made in source systems such as an EHR. Furthermore, the choice of the appropriate classification systems is included, in most cases, in the guideline itself (e.g. TNM for cancer staging, BIRADS for radiology outcomes, New York Heart Association classification for heart failure, Eastern Cooperative Oncology Group or WHO for performance score).

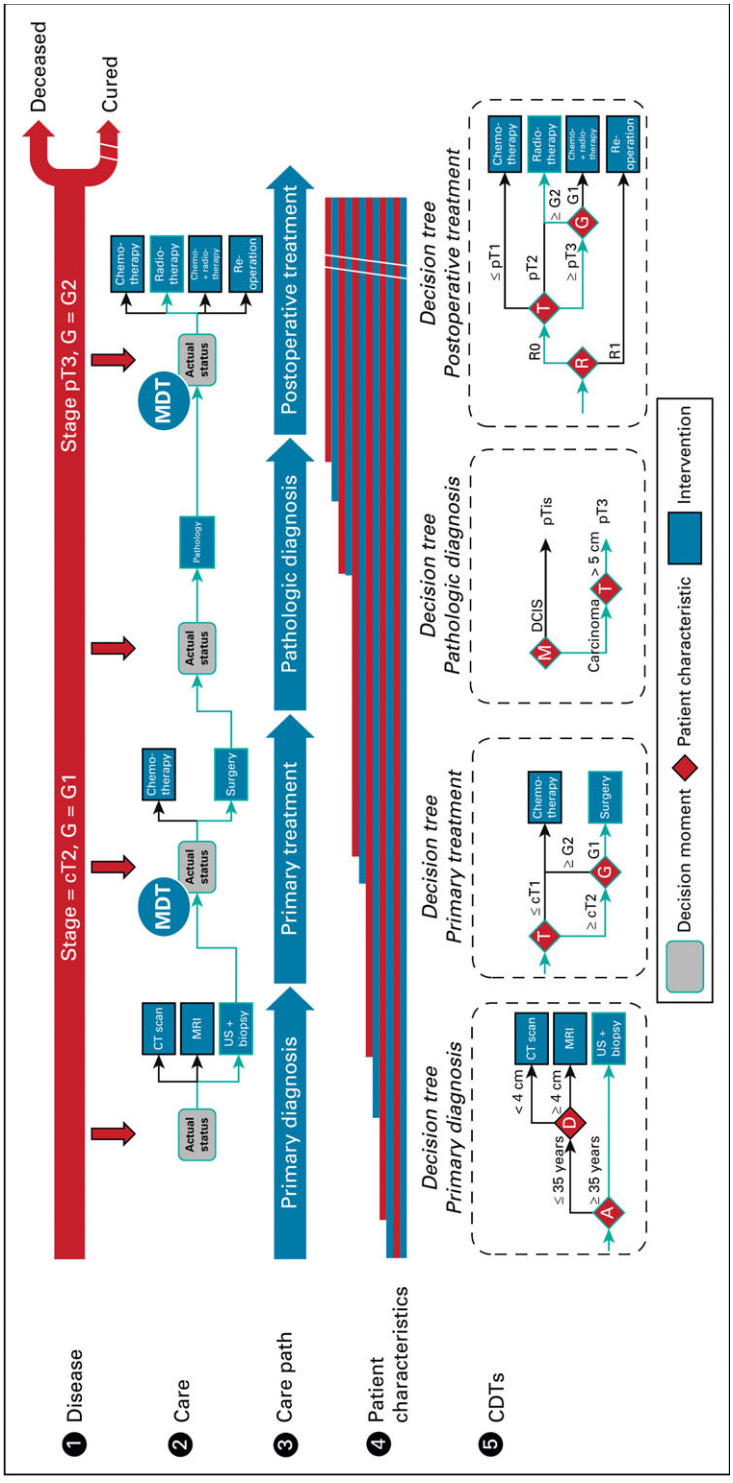


FIG 1. Conceptual and simplified reflection of the breast cancer care pathway and related clinical decision trees (CDTs). See the Methods section for a detailed description. A, age; CT, computed tomography; D, tumor diameter; DCIS, ductal carcinoma in situ; G, tumor grade; M, tumor morphology; MDT, multidisciplinary team; MRI, magnetic resonance imaging; R, residual tumor; T, tumor stage; US, ultrasound.

Personalization

To express the complexity and degree to which guideline recommendations are personalized, all unique patient routes through all CDTs, which reflect patient sub-populations, were counted.

Decision Support

The CDTs were developed using Gaston (Medical Decision Support Systems BV, Eindhoven, the Netherlands).[12] CDTs were created by simple drag-and-drop actions, using the data items as building blocks. Data items themselves were defined and coded (e.g. SNOMED CT) in ART-DECOR (Advanced Tooling Requirements-Data Elements Codes, Object Identifiers and Rules), which is an international open source tool used by the Dutch National Institute for Information and Communication Technology (https://www.nictiz.nl/standaardisatie/art-decor) for development, maintenance, and publication of information standards for interoperability. Accordingly, the CDTs are interoperable per design, and a direct relation between information de- rived from different sources (e.g. pathology or radiology reports) is modeled in such a way to enable (digital) in- formation exchange and interoperability among the various actors in the care pathway.

CDTs were implemented in an interactive decision support application, Oncoguide (www.oncoguide.nl), which is also available for tablet computers. The application is designed to be used as a stand-alone app for manual data entry and to connect to EHRs for automatic electronic data exchange. For the latter, Oncoguide is accessible through RESTful Web Services (an application programming interface) and thereby follows the latest development on the Fast Health Interoperability Resources infrastructure of the international HL7 community (http://www.hl7.org/Special/ committees/fiwg/index.cfm).

RESULTS

CDTs

We translated the recommendations of the Dutch national breast cancer guideline (199 pages, A4 text format, 9,920 line numbers, 100,564 words, 13 chapters, and seven appendices) into 60 CDTs driven by 98 independent and 16 dependent data items. Figure 2 shows an example of a CDT. Table 1 lists a classification of data items with respect to their record source. Most objective data items originated from pathology reports (56 of 114; 49%), followed by radiology reports (30 of 114; 27%), clinical patient characteristics (14 of 114; 12%), and multidisciplinary team interpretation/validation (14 of 114; 12%). A list of all data items can be found in Appendix Table A1.

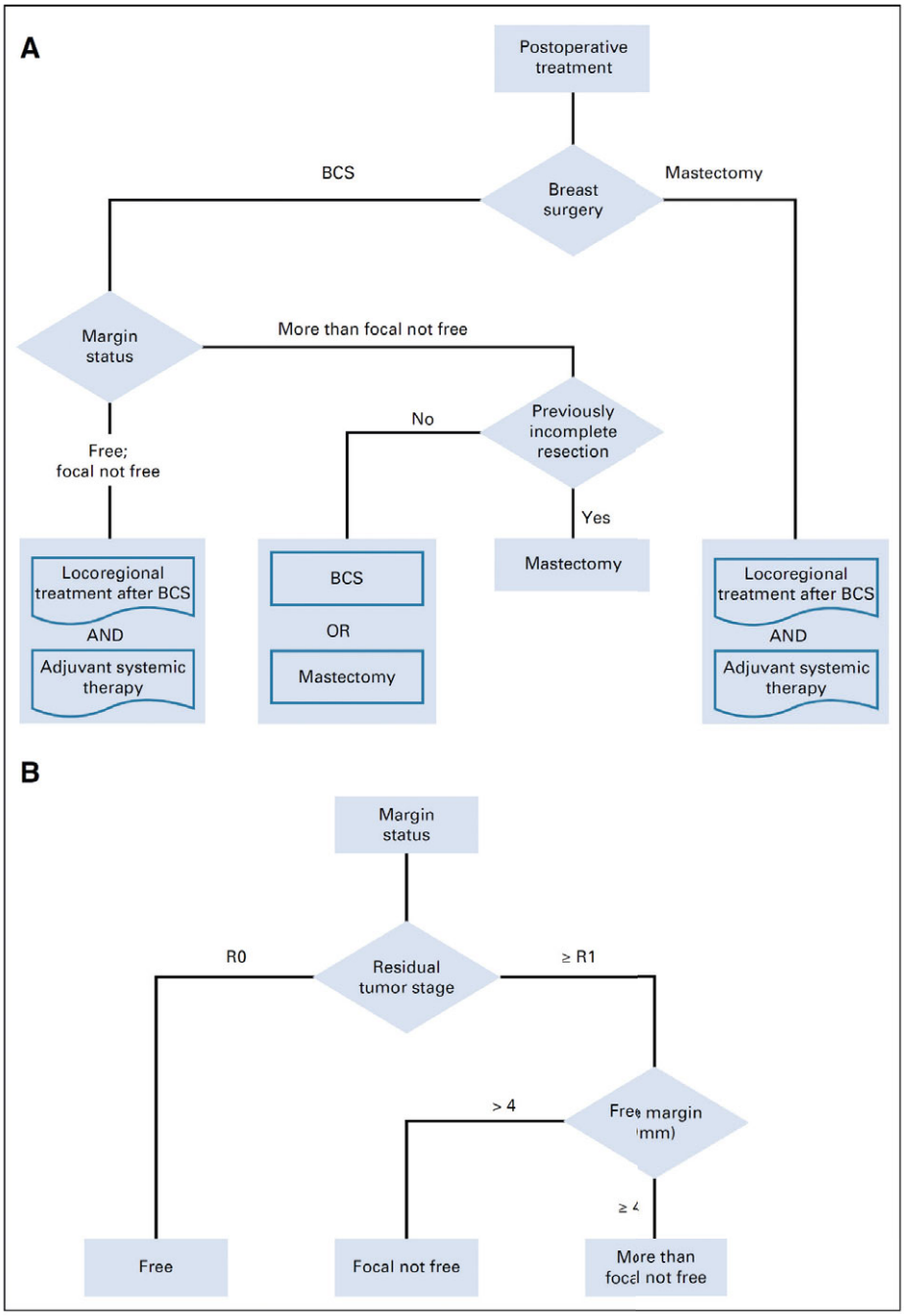


FIG 2. Example of a clinical decision tree (CDT).

(A) The top rectangle reflects the trunk of the CDT postoperative treatment. The rhombuses reflect the nodes and represent the data items. The branches define the cutoff values, which lead to additional nodes (rhombuses) or guideline recommendations (bottom rectangles; a delineated recommendation [rectangle with a curly bottom] means referral to another CDT, such as locoregional treatment after breast-conserving surgery[BCS]). (B) Note the double-delineated rhombus margin status, which can be unfolded to define the value of margin status. In contrast to other countries, the Dutch national breast cancer guideline does not recommend re-excision for focally positive margins after BCS in invasive tumor and recommends whole-breast irradiation, including boost.13

TABLE 1. Sources of 114 Data Items That Appear in All Clinical Decision Trees

	Pathology	Radiology	Clinical	MDT	Total
Subjective data item	0	3	1	7	11
Objective data item	56	27	13	7	103
Number (%)	56 (49)	30 (27)	14 (12)	14 (12)	114 (100)

NOTE. Data items can be classified objectively (e.g. tumor diameter) or subjectively (e.g. size of ductal carcinoma in situ compared with breast volume). Clinical refers to data items that are classified by clinical judgment (e.g. inflammatory breast), and MDT reflects data items classified by the MDT (e.g. discrepancy between clinical findings and imaging). A full list of all data items can be found in Appendix Table A1. Abbreviation: MDT, multidisciplinary team.

Implementation in Decision Support and Interoperability

Of all data items, 89% could be classified by existing classification and/or coding systems. On the basis of existing classification systems only, 75 (65%) of 114 data items were classified (66 to TNM, eight to BIRADS, and one to Response Evaluation Criteria in Solid Tumors [RECIST]). On the basis of the coding system SNOMED CT, only 90 (79%) of 114 data items could be classified. Ten data items could be qualified as too ambiguous to quantify (e.g. size of ductal carcinoma in situ compared with breast volume; Appendix Table A1).

Twenty-two of 60 CDTs concerned recommendations for diagnostics, whereas 33 of 60 CDTs involved treatment recommendations. Five (8%) of 60 CDTs lacked recommendations because guideline recommendations were not available (e.g. evaluation of surgical margin after treatment, recurrent disease).

By constructing CDTs systematically, all possible outcome values of each data item should lead to a recommendation. Four situations were identified for which the guideline represents no recommendation (as yet). For example, when a left ventricular ejection fraction of less than 50% is found in human epidermal growth factor receptor 2– positive breast cancer, the guideline lacks recommendations. As an example of ambiguity of data items within the guideline, Table 2 lists the many definitions of the data item margin status used in different classification systems.

Personalization

In each CDT, there were one or more possible routes to reach one of the available recommendations, each of them defining a specific patient subpopulation. The total

possible number of unique patient routes through all CDTs that led to one or more recommendations was 376 (see Appendix Fig A1). The mean number of possible patient routes per CDT was equal for CDTs that lead to treatment recommendations (6.4; median, four; range, one to 24) compared with CDTs that lead to diagnostic recommendations (6.3; median, three; range, one to 18).

TABLE 2. Definitions of Margin Status Used in the Dutch National Breast Cancer Guideline and Other National and International Scientific Authoritative Sources

Authority	Definition
Dutch breast cancer guideline 2012	free, focal not free*, more than focal not free
	tumor positive margin status vs tumor negative margin status
	radical margin status vs not radical
	tumor growth into a surgical margin
PALGA[1]	Free
	Focal not free (tumormargin <= 4mm)
	More than focal not free
TNM[2] atlas (resection margin)	R0: no residual tumor
	R1: microscopic residual tumor
	R2: macroscopic residual tumor
NBCA[3]	Radical
	Focal not radical
	More than focal not radical
	Unknown / not judgeable
Dutch cancer registry	Radical or not apparent and DCIS radical or not apparent
	Radical or not apparent and DCIS focal not radical
	Radical or not apparent and DCIS not radical
	Focal not radical and DCIS radical or not apparent
	Focal not radical and DCIS focal not radical
	Focal not radical and DCIS not radical
	Not radical and not important
	Unclear mention of radicality of invasive and/or DCIS component

[1] PALGA = Dutch nationwide network and registry of histo- and cytopathology. [2] TNM = cancerclassification
system developed by the International Union Against Cancer. [3] NBCA = NABON Breast Cancer Audit.
* tumor reaching an inked surface in a limited surface (≤ 4mm)
Abbreviations: DCIS, ductal carcinoma in situ; NBCA, NABON Breast Cancer Audit; PALGA, Dutch nationwide network and registry of histo- and cytopathology.
*Tumor reaching an inked surface in a limited surface (≤ 4 mm).

Decision Support

All CDTs were successfully integrated in the interactive decision support app Oncoguide and are accessible free of charge (see Methods section). In the app, patient data are projected on the CDTs and show the path to the automatically generated patient-specific recommendation.

DISCUSSION

We show that it is feasible to transform a complex text- based guideline, such as the Dutch national breast cancer guideline, into data-driven CDTs. Although the concept of decision trees is not new, the clinical application of data- driven, moderated CDTs on a complex medical multidisciplinary guideline in such a way that they are both clinically interpretable and suitable for implementation in decision support systems has not been described earlier.[14] By de- fining the data items needed for the CDTs, it was mostly possible to adhere to international classification and coding standards, although 21% of the data items needed to cover the complete guideline was not available in SNOMED CT.

Although this does not limit the possibility to model recommendations as CDTs, closing this gap is important because different international guidelines (NCCN, Euro- pean Society of Medical Oncology) can only give complementary recommendations if there is consensus about the definitions of all data items that determine diagnostic or treatment recommendations. For items currently not covered in SNOMED CT, we have put forward change requests for their inclusion at SNOMED International.

Because of the vagueness of recommendations, guidelines are sometimes criticized for not being helpful in practice.[15,16] Different definitions of certain data values (Table 2) were encountered in the different chapters of the guideline, which automatically show up while designing CDTs. In this way, the CDT method is also a quality control instrument because it needs consequent and equivocal definitions. In contrast with text-based guidelines, our method can help the guideline updating process because it is based on compact guideline modules, and one can focus on the modules that need revision.

Clinical decision making is more and more personalized, and this is reflected in 376 unique subpopulations already described in the Dutch national breast cancer guideline. It is likely that this number will increase substantially because available pathology and genomic data will affect guideline recommendations soon. Moreover, in 2016, ASCO recommended the integration of higher-quality genomic data into clinical practice.[17] These data can be modularly incorporated in CDTs.

In contrast to NCCN guidelines and flowcharts, our method of systematically constructed CDTs is fully data driven and delivers unambiguously and unequivocally defined and coded data items that relate all possible (combinations of) patient/ disease characteristics to subpopulation-specific guideline recommendations. To our knowledge, only a few guideline-based clinical decision support systems have been

routinely used for breast cancer management in the hospital setting.[18-21] However, these local initiatives use decision rules and do not cover full national guidelines.

In 2012, ASCO started with the development of Cancer- LinQ, a rapid learning system to improve the quality and efficiency of cancer care by generating new knowledge on the basis of aggregated real-world patient data extracted from EHRs.[22,23] Decision support systems, such as the Oncoguide app, can help to bring this goal a step closer because this tool is able to register patient subpopulation treatment choices and reasons for guideline deviations. The application of Oncoguide for decision support has been evaluated in comparison with Watson (IBM, Armonk, NY) on the basis of synthetic patient cases.[24] However, additional research is needed to evaluate the value of guidelines-based decision support in daily clinical practice.

All CDTs together cover the whole care pathway for non- metastatic breast cancer and follow all diagnostic and therapeutic options on the basis of the guideline. From our systematic method of constructing CDTs emerged five CDTs that lack recommendations, which pinpoints guideline gaps or, in other words, patient subpopulations that are not fully discussed in the guideline. These gaps can be addressed in future guideline updates.

Protocols, standardized reporting, and decision trees are sometimes put aside as cookbook medicine that ignores the fundamentally uncertain nature of medicine.[25] How- ever, the method described in this article does not reduce the level of evidence and secondary strength of recommendations in CDTs where evidence is weak or lacking. Although CDTs lack large text documents, no information is lost. Classification of recommendations by international grading systems, such as GRADE, is maintained.[11] Like- wise, as with text-based guidelines, it is up to the physicians to adhere to or deviate from the recommendations mentioned in the CDTs.[7]

A strength of this study is that we tested the method of CDTs by applying it to a highly complex multidisciplinary guideline while strictly adhering to international classification and coding systems. Moreover, our method is generalizable for guidelines in other disease areas where recommendations are based on the PICO system. The method already has been applied successfully to guidelines for other types of cancer, including to NCCN guidelines and Dutch nursing guidelines for pain management and wound care (all accessible online in Oncoguide).[26] Furthermore, because no assumptions are needed for how the care process is organized, this model is scalable toward the future when more data become available. Similarly, this model is scalable across diseases, provided that CDTs are constructed systematically as described in the Methods section.

In this study, we tested the feasibility of modeling a complex textual guideline into systematically designed, modular, data-driven CDTs as the basis for a decision support system that can be used as a stand-alone application and has the ability to connect to EHRs through modern Web interfaces using international standards for electronic patient data exchange. Data on the practical application of CDTs in clinical practice is needed, however. Therefore, we are currently working with Dutch hospitals and EHR

vendors to implement and evaluate the application of CDT-based decision support in routine clinical practice. Application of CDTs in practice and compliance of EHR documentation with the associated information standard offer to facilitate decision making and continuously evaluate and improve guidelines by comparison with real-live data. In addition to guideline recommendations, other types of knowledge can be represented as CDTs, such as clinical trial or genomic testing (MammaPrint [Agendia, Amsterdam, the Nether- lands] and Oncotype DX [Genomic Health, Redwood City, CA]) indications. As an example of the latter, Figure 3 shows a CDT with recommendations for genomic testing in the Oncoguide application.

In conclusion, it is possible to present the complex Dutch national breast cancer guideline as clinically interpretable, modular, data-driven CDTs by using a set of 114 data items, 89% of which are defined by existing international classification and coding systems. The modular character of CDTs could provide a means for quick and clear implementation and accessibility of dynamic guidelines. More- over, fast-growing knowledge could more rapidly and easily be taken into account by modularly updating CDTs, which supports implementation of data-driven personalized health care.

To demonstrate the potential application of CDTs as decision support, all CDTs were successfully implemented in an interactive decision support app, Oncoguide. Onco-guide provides a framework to register unique patient subpopulations and has the potency to report on physician, and potentially patient, motivation for guideline adherence or nonadherence in daily practice, which facilitates collaborative learning and improves the quality of care.[27] Connection of Oncoguide to the EHR will be an essential next step to enable routine use of decision support in daily practice. The unequivocal and unambiguous definition of data items is an essential prerequisite for implementation of CDTs in decision support systems, and reaching consensus internationally on these definitions is a challenge for all national and international guideline working groups.

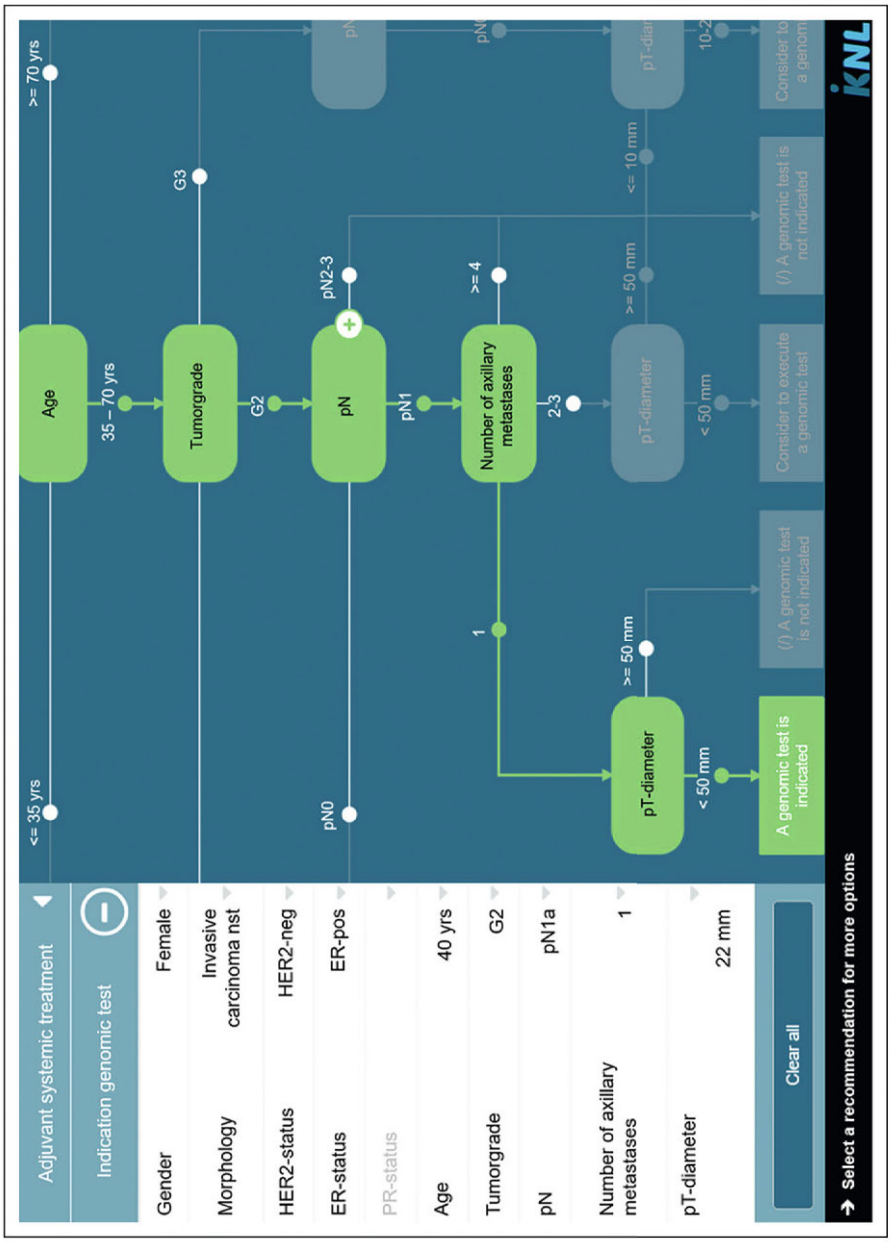


FIG 3. Screenshot that shows a part of the clinical decision tree (CDT) for indication genomic testing in Oncoguide (translated into English).

The green path through the CDT highlights the data provided in the data panel on the left side projected onto the CDT, which in this case leads to the recommendation that genomic testing is indicated. The full tree (in Dutch) is also accessible in an interactive format through https://oncoguide.nl/#!/projects/7/guideline/17/tree/153/10494. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; neg, negative; pos, positive.

REFERENCES

1. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.
2. Panella M, Marchisio S, Di Stanislao F. Reducing clinical variations with clinical pathways: do pathways work? Int J Qual Health Care 2003;15:509-21.
3. Martinez Garcia L, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. CMAJ 2014;186:1211-9.
4. de Clercq P, Kaiser K, Hasman A. Computer-Interpretable Guideline formalisms. Stud Health Technol Inform 2008;139:22-43.
5. Peleg M. Computer-interpretable clinical guidelines: a methodological review. J Biomed Inform 2013;46:744-63.
6. Robertson J, Walkom E, Pearson SA, Hains I, Williamsone M, Newby D. The impact of pharmacy computerised clinical decision support on prescribing, clinical and patient outcomes: a systematic review of the literature. Int J Pharm Pract 2010;18:69-87.
7. Quality of Care Directorate: Directive for Guidelines: 20 Criteria for Developing and Implementing a Clinical Guideline [in Dutch]. The Hague, the Netherlands, Quality of Care Directorate. 2012.
8. NABON: Breast Cancer: Dutch Guideline, Version 2.0. 2012.
9. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc 2006;2006:359-63.
10. Burgers JS, van Everdingen JJ. Evidence-based guideline development in the Netherlands: the EBRO platform. Ned Tijdschr Geneeskd 2004;148:2057-9.
11. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol 2017;87:4-13.
12. de Clercq PA, Hasman A, Blom JA, Korsten HH. Design and implementation of a framework to support the development of clinical guidelines. Int J Med Inform 2001;64:285-318.
13. Vos EL, Siesling S, Baaijens MHA, et al. Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival. Breast Cancer Res Treat 2017;164:157-67.
14. Shiffman RN, Greenes RA. Improving clinical guidelines with logic and decision-table techniques: application to hepatitis immunization recommendations. Med Decis Making 1994;14:245-54.
15. Merkow RP, Korenstein D, Yeahia R, Bach PB, Baxi SS. Quality of Cancer Surveillance Clinical Practice Guidelines: Specificity and Consistency of Recommendations. JAMA Intern Med 2017;177:701-9.
16. Codish S, Shiffman RN. A model of ambiguity and vagueness in clinical practice guideline recommendations. AMIA Annu Symp Proc 2005;2005:146-50.
17. Hughes KS, Ambinder EP, Hess GP, et al. Identifying Health Information Technology Needs of Oncologists to Facilitate the Adoption of Genomic Medicine: Recommendations From the 2016 American Society of Clinical Oncology Omics and Precision Oncology Workshop. J Clin Oncol 2017;35:3153-9.
18. Patkar V, Acosta D, Davidson T, Jones A, Fox J, Keshtgar M. Using computerised decision support to improve compliance of cancer multidisciplinary meetings with evidence-based guidance. BMJ Open 2012;2.

19. Eccher C, Seyfang A, Ferro A. Implementation and evaluation of an Asbru-based decision support system for adjuvant treatment in breast cancer. Comput Methods Programs Biomed 2014;117:308-21.
20. Bouaud J, Spano JP, Lefranc JP, et al. Physicians' Attitudes Towards the Advice of a Guideline-Based Decision Support System: A Case Study With OncoDoc2 in the Management of Breast Cancer Patients. Stud Health Technol Inform 2015;216:264-9.
21. Seroussi B, Guezennec G, Lamy JB, et al. Reconciliation of multiple guidelines for decision support: a case study on the multidisciplinary management of breast cancer within the DESIREE project. AMIA Annu Symp Proc 2017;2017:1527-36.
22. Sledge GW, Jr., Miller RS, Hauser R. CancerLinQ and the future of cancer care. Am Soc Clin Oncol Educ Book 2013:430-4.
23. Schilsky RL, Michels DL, Kearbey AH, Yu PP, Hudis CA. Building a rapid learning health care system for oncology: the regulatory framework of CancerLinQ. J Clin Oncol 2014;32:2373-9.
24. Keikes L, Medlock S, van de Berg DJ, et al. The first steps in the evaluation of a "black-box" decision support tool: a protocol and feasibility study for the evaluation of Watson for Oncology. J Clin Transl Res 2018;3:411-23.
25. Morris AH. Computerized protocols and bedside decision support. Crit Care Clin 1999;15:523-45, vi.
26. Ebben K L, van der Werf J, et al: . A method for structured comparison of oncologic clinical practice guidelines. National Comprehensive Cancer Network Annual Conference, Orlando, FL, March 22-24, 2018.
27. Abernethy AP, Etheredge LM, Ganz PA, et al. Rapid-learning system for cancer care. J Clin Oncol 2010;28:4268-74.

APPENDICES

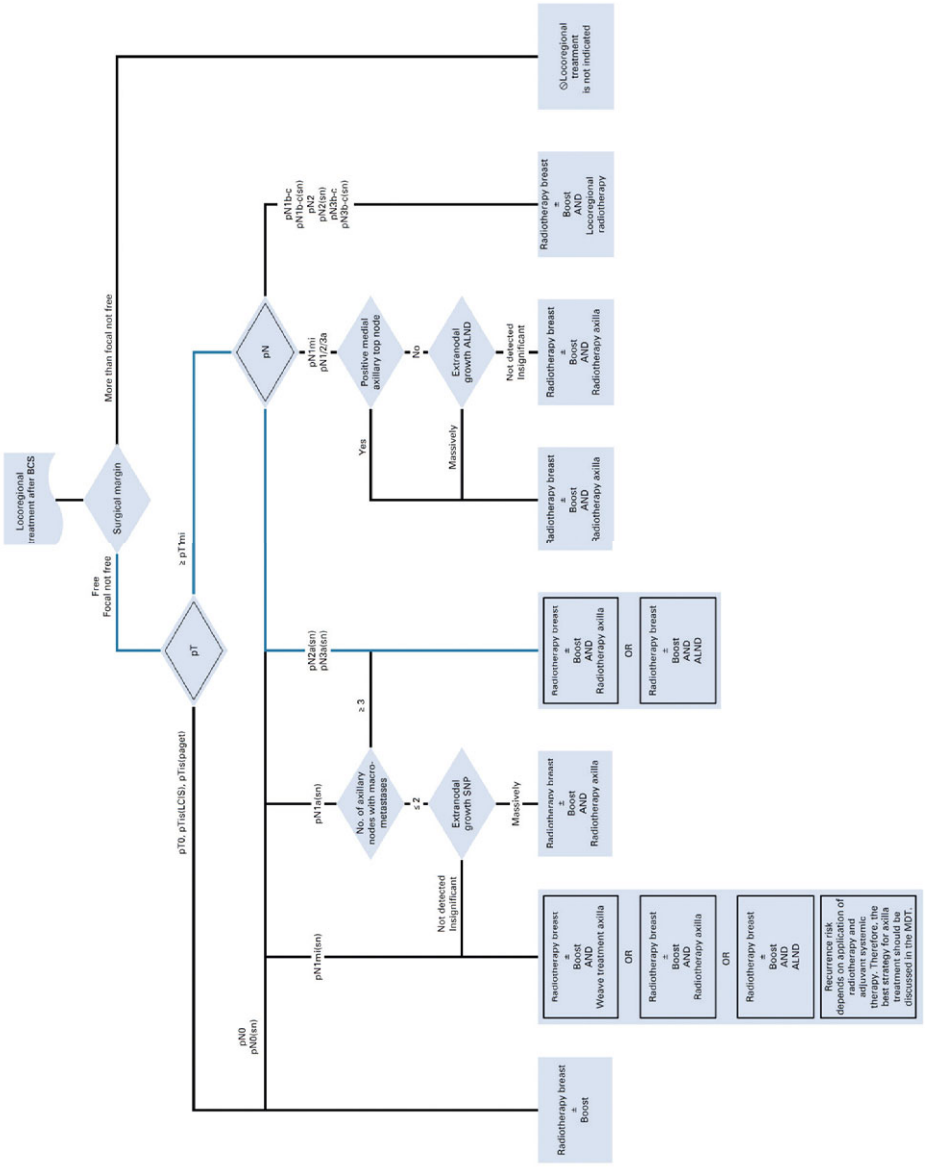


FIG A1. A unique patient route within a clinical decision tree that is based on the Dutch breast cancer guideline 2012.

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; LCIS, lobular carcinoma in situ; mi, micrometastasis; MDT, multidisciplinary team; paget, Paget's disease; sn, sentinel node; SNP, sentinel node procedure.

TABLE A1. All 114 Unique Data Items

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
1	Discrepancy between clinical findings and imaging	discrepancy (finding)	no	MDT
2	Systemic treatment administered	chemotherapy, endocrine therapy	no	MDT
3	Size DCIS compared to breast volume	NA	yes	MDT
4	Cycle systemic therapy ended	post-chemotherapy	no	MDT
5	Treatment line endocrine therapy	endocrine therapy	no	MDT
6	Representative cytology specimen	NA	yes	MDT
7	Representative histology specimen	NA	yes	MDT
8	Lymph node surgery	lymph node operation	no	MDT
9	Breast tumor surgery	breast operation	no	MDT
10	History of regional radiotherapy	radiotherapy to breast	no	MDT
11	Resectability relapse	NA	yes	MDT
12	History of chest wall radiotherapy	radiotherapy to thorax	no	MDT
13	Time expired since incidence date	NA	no	MDT
14	Extension in adjacent structures	tumor extension	no	MDT
15	Breastfeeding	breast feeding	no	Clinical
16	Fixed axillary lymph nodes	N2 metastases to ipsilateral axillary lymph node(s) fixed to one another or to other structures	no	Clinical
17	Sex	Sex	no	Clinical
18	Inflammatory breast	inflammatory breast disease	no	Clinical
19	Clinically positive axillary lymph nodes	axillary lymphadenopathy	no	Clinical
20	Clinically positive infraclavicular lymph nodes	infraclavicular lymphadenopathy	no	Clinical
21	Clinically positive parasternal lymph nodes	parasternal lymphadenopathy	no	Clinical
22	Clinically positive supraclavicular lymph nodes	supraclavicular lymphadenopathy	no	Clinical

TABLE A1. All 114 Unique Data Items (continued)

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
23	Clinical suspicion on gynecomastia	on examination gynaecomastia	no	Clinical
24	Age	age	no	Clinical
25	Menopausal status	menopausal state	no	Clinical
26	Painful retromamillary mass	breast pain, breast mass	no	Clinical
27	Gynecomastia presentation (symmetric/asymmetric)	NA	no	Clinical
28	Pregnant	pregnant	no	Clinical
29	BI-RADS	NA	no	Radiology
30	Breast calcifications	breast calcification	no	Radiology
31	cM status	clinical M category	no	Radiology
32	cN status	clinical N category	no	Radiology
33	cT status	clinical T category	no	Radiology
34	cT-diameter status	tumor size	no	Radiology
35	Decrease left ventricular ejection fractions	Left ventricular ejection (qualifier value)	no	Radiology
36	Cortical thickness of ultrasonographic suspicious axillary lymph node	NA	no	Radiology
37	Distribution of calcifications	diffuse nodular calcifications of breast	no	Radiology
38	Well assessable mammography	mammography assessment - needs additional imaging evaluation	yes	Radiology
39	Clinical suspicion on distant metastases	NA	yes	Radiology
40	Clinical suspicion on a Phyllodes tumor	Phyllodes tumor of the breast	no	Radiology
41	Relapse location	local recurrence of malignant tumor of breast	no	Radiology
42	Metastatic site(s)	tumor metastatic to bone, cancer metastatic to liver	no	Radiology
43	Left ventricular ejection fraction	left ventricular ejection fraction	no	Radiology
44	Occult breast mass	occult carcinoma	no	Radiology
45	Response metastasis/ metastases	medication response	no	Radiology
46	Response primary tumor	medication response	no	Radiology
47	rM	NA	no	Radiology

TABLE A1. All 114 Unique Data Items (continued)

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
48	rN	NA	no	Radiology
49	Solid component on imaging	NA	no	Radiology
50	Solid mass in the breast	breast mass	no	Radiology
51	Suspicious axillary lymph node on ultrasound imaging	ultrasound of left axilla, ultrasound of right axilla, suspected lymphoma	no	Radiology
52	Symmetric cortex suspicious axillary lymph node on ultrasound imaging	NA	no	Radiology
53	Tumor distribution on mammography	NA	no	Radiology
54	Suspicious invasive component	invasive tumor border	yes	Radiology
55	DCIS with suspicious invasive component	NA	yes	Radiology
56	ycN status	NA	no	Radiology
57	ycT status	NA	no	Radiology
58	ycT-diameter status	NA	no	Radiology
59	Breast cytology result	cytology	no	Pathology
60	Number of axillary sentinel lymph nodes with macrometastases	axillary lymph nodes, number of lymph nodes with macrometastases, sentinel node	no	Pathology
61	Number of axillary sentinel lymph nodes with micro- and/or macrometastases	axillary lymph nodes, number of lymph nodes with macrometastases, number of lymph nodes with micrometastases, sentinel node	no	Pathology
62	Number of axillary sentinel lymph nodes with micrometastases	axillary lymph nodes, number of lymph nodes with micrometastases, sentinel node	no	Pathology
63	Number of sentinel lymph nodes with isolated tumor cells	number of sentinel lymph nodes examined, tumor cell	no	Pathology
64	Number of sentinel lymph nodes with macrometastases	number of lymph nodes with macrometastases	no	Pathology
65	Angioinvasion	vascular invasion	no	Pathology
66	Previous incomplete surgical excision	surgical margin finding	no	Pathology
67	Estrogen receptor status	status of estrogen receptors of neoplasm	no	Pathology

TABLE A1. All 114 Unique Data Items (continued)

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
68	Estrogen receptor status metastasis	status of estrogen receptors of neoplasm, metastases status	no	Pathology
69	Estrogen receptor status recurrence	status of estrogen receptors of neoplasm, recurrence of tumor	no	Pathology
70	Extra nodal growth axillary lymph node dissection	extra capsular extension of nodal tumor, axillary lymph node	no	Pathology
71	Extra nodal growth sentinel node	extra capsular extension of nodal tumor, sentinel node	no	Pathology
72	Extra nodal growth axillary top lymph node	NA	no	Pathology
73	Gene mutation	genetic mutation	no	Pathology
74	Tumor grade (postoperatively)	tumor grade, postoperative diagnosis	no	Pathology
75	Tumor grade (preoperatively)	tumor grade, preoperative diagnosis	no	Pathology
76	HER2-status	human epidermal growth factor 2	no	Pathology
77	HER2-status (metastasis)	human epidermal growth factor 2, metastases status	no	Pathology
78	HER2-status (postoperatively)	human epidermal growth factor 2, postoperative diagnosis	no	Pathology
79	Lymphangitis cutis	lymphangitis of breast	no	Pathology
80	Morphology	morphology	no	Pathology
81	Morphology (postoperatively after neoadjuvant chemotherapy)	morphology, postoperative diagnosis, neo-adjuvant - intent	no	Pathology
82	Morphology (preoperatively after neoadjuvant chemotherapy)	morphology, preoperative diagnosis, neo-adjuvant - intent	no	Pathology
83	Morphology (preoperatively)	morphology, preoperative diagnosis	no	Pathology
84	N0 risk status	NA	no	Pathology
85	Pathological tumor response	pathological staging	no	Pathology
86	pM status	pathological staging, metastases diagnosis	no	Pathology
87	pN status	pathological staging, cancer metastatic to lymph nodes	no	Pathology

TABLE A1. All 114 Unique Data Items (continued)

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
88	positive axillary lymph nodes	neoplasm of axillary lymph nodes	no	Pathology
89	positive infraclavicular lymph nodes	neoplasm of infraclavicular lymph nodes	no	Pathology
90	positive axillary top lymph node	NA	no	Pathology
91	positive parasternal lymph nodes	neoplasm of parasternal lymph nodes	no	Pathology
92	positive parasternal lymph nodes sentinel node	operation on sentinel lymph node, neoplasm of parasternal lymph nodes	no	Pathology
93	Positive supraclavicular lymph nodes	neoplasm of supraclavicular lymph nodes	no	Pathology
94	Positive supraclavicular lymph nodes sentinel node	operation on sentinel lymph node, neoplasm of supraclavicular lymph nodes	no	Pathology
95	pT	pathological staging	no	Pathology
96	pT-diameter	tumor size	no	Pathology
97	surgical margin status	surgical margin status	yes	Pathology
98	Relapse surgical margin status	surgical margins, local recurrence of malignant tumor	no	Pathology
99	Total number of axillary lymph nodes with macrometastases	number of lymph nodes with macrometastases	no	Pathology
100	Total number of axillary lymph nodes with micro- and/or macrometastases	number of lymph nodes with macrometastases, number of lymph nodes with micrometastases	no	Pathology
101	Total number of axillary lymph nodes with micrometastases	number of lymph nodes with micrometastases	no	Pathology
102	Total number of lymph nodes with isolated tumor cells	number of lymph nodes examined, tumor cells	no	Pathology
103	Residual tumor	residual tumor	no	Pathology
104	Result cytology breast abnormality	cytology diagnosis, breast tumor	no	Pathology
105	Result cytology lymph node	cytology diagnosis, lymph node	no	Pathology
106	Result histology breast abnormality	histology test, breast mass	no	Pathology

TABLE A1. All 114 Unique Data Items (continued)

	Data-item	SNOMED-CT description	Ambiguity data-item present?	Data source
107	Result axillary lymph node dissection	axillary lymph node dissection, pN	no	Pathology
108	Result sentinel node biopsy	sentinel node biopsy	no	Pathology
109	Result sentinel node	specimen from sentinel lymph node	no	Pathology
110	Result frozen section sentinel node	frozen section lymph node sample	no	Pathology
111	Free surgical margin	surgical margin(s) free of tumor	yes	Pathology
112	ypN status	NA	no	Pathology
113	ypT status	NA	no	Pathology
114	ypT-diameter status	NA	no	Pathology

NOTE. Data items are presented with the SNOMED CT description, if available; the qualification if a data item is ambiguous; and the source of data item origin (e.g. MDT). Abbreviations: BIRADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; MDT, multidisciplinary team; NA, not available; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms.

CHAPTER 4

Clinical decision trees support systematic evaluation of multidisciplinary team recommendations

Mathijs P. Hendriks, Xander A. A. M. Verbeek, Jeannette G. van Manen, Sannah E. van der Heijden, Shirley H. L. Go, Gea A. Gooiker, Thijs van Vegchel, Sabine Siesling, Agnes Jager

Breast Cancer Research and Treatment. 2020 Sep;183(2):355-363

ABSTRACT

Purpose

EUSOMA's recommendation that "each patient has to be fully informed about each step in the diagnostic and therapeutic pathway" could be supported by guideline-based clinical decision trees (CDTs). The Dutch breast cancer guideline has been modeled into CDTs (www.oncoguide.nl). Prerequisites for adequate CDT usage are availability of necessary patient data at the time of decision-making and to consider all possible treatment alternatives provided in the CDT.

Methods

This retrospective single-center study evaluated 394 randomly selected female patients with non-metastatic breast cancer between 2012 and 2015. Four pivotal CDTs were selected. Two researchers analyzed patient records to determine to which degree patient data required per CDT were available at the time of multidisciplinary team (MDT) meeting and how often multiple alternatives were actually reported.

Results

The four selected CDTs were indication for magnetic resonance imaging (MRI) scan, preoperative and adjuvant systemic treatment, and immediate breast reconstruction. For 70%, 13%, 97% and 13% of patients, respectively, all necessary data were available. The two most frequent underreported data-items were "clinical M-stage" (87%) and "assessable mammography" (28%). Treatment alternatives were reported by MDTs in 32% of patients regarding primary treatment and in 28% regarding breast reconstruction.

Conclusion

Both the availability of data in patient records essential for guideline-based recommendations and the reporting of possible treatment alternatives of the investigated CDTs were low. To meet EUSOMA's requirements, information that is supposed to be implicitly known must be explicated by MDTs. Moreover, MDTs have to adhere to clear definitions of data-items in their reporting.

INTRODUCTION

Background

The European Society of Breast Cancer Specialists (EUSOMA) recommends that "each patient has to be fully informed about each step in the diagnostic and therapeutic pathway and must be given adequate time to consider the alternatives and make an informed decision".[1] As diagnostic and treatment modalities in breast cancer are increasing rapidly, clinicians are challenged to apply a growing amount of knowledge during clinical decision-making for optimal patient care. The multidisciplinary team (MDT) is supported by clinical practice guidelines, consolidating knowledge in evidence- or consensus-based recommendations aiming to improve the quality of care.[2] However, as guidelines are increasingly complex and dynamic, it is challenging to overview and consider all relevant recommendations for each clinical decision.

Guideline-based clinical decision trees (CDTs) could be of great value to comply to EUSOMA's recommendations. To apply CDTs, all relevant data-items for a guideline-based recommendation should be available during MDT meetings and should be reported explicitly. In case the guideline recommendation consists of more than one alternative (e.g., breast surgery vs. preoperative systemic treatment), the MDT should report which alternatives will be proposed to the patient or should be waived substantiated.

In the Netherlands, the Breast Cancer guideline has been set up by a multidisciplinary group of specialists and patients advocates under the auspices of the National Breast Cancer Organization (NABON).[3] In previous work, we have shown that the Dutch NABON guideline was success- fully transformed into 60 clinical decision trees (CDTs) driven by 114 unique data-items, resulting in recommendations for in total 376 unique patient and tumor features combinations.[4] A path through a CDT follows "nodes" that represent patient- and/or disease characteristics (i.e., data-items) and results in "a leaf" representing a guideline recommendation. A CDT therefore defines explicitly which data-items should be minimally available for a guideline- based recommendation.

The main objective of this study is to evaluate the avail- ability of the required data-items during MDT meetings—as verifiable in the electronic health records—for four pivotal CDTs: indication for (1) performing an MRI scan, (2) pre- operative systemic treatment (PST), (3) adjuvant systemic treatment (AST) and (4) immediate breast reconstruction (IBR). Our second objectives are (i) to evaluate whether the MDT reports mention multiple alternatives for those cases in which the guideline recommendation consist of more than one alternative; (ii) to evaluate the concordance of recommendations generated by the MDT and the CDTs.

METHODS

Population

This retrospective single-center study was performed in Northwest Clinics, a teaching hospital and oncology center in the province North Holland. All malignancies in Dutch hospitals are registered in the Netherlands Cancer registry (NCR). For this study, all patients aged 18 years or older and diagnosed with breast cancer in Northwest Clinics were selected from the NCR between February 2012 and February 2015 (N = 1239). Exclusion criteria were male sex, patients with recurrent breast tumors or advanced breast cancer at diagnosis, patients being treated for other cancer(s) in the past, patients receiving treatment in another hospital and patients who were not at least discussed once in a MDT meeting. A required sample size was calculated to estimate proportions with a 5% accuracy ($n = z2^{*}p(1 - p)d2$, where n = sample size, $z = z$ value for 95% CI 1.96, p = largest possible proportion = 0.5 and d = accuracy of 5% = 0.05). We expected a dropout rate of 25% based on the exclusion criteria. The required sample size calculated to estimate proportions was 385 patients. Considering the expected dropout rate, 504 patients were randomly selected from the original cohort.

Guideline-based decision-making using CDTs

CDTs based on the Dutch breast cancer guideline of 2012 were used, which was valid during the study period.[4] For each decision point in the patient care pathway, all applicable guideline recommendations have been synthesized into CDTs. CDT nodes represent patient and disease characteristics (i.e., data-items, such as T-stage) and its branches represent cut-off values (e.g. cT value less than cT2). Every CDT "leaf" represents a guideline recommendation. Each recommendation has one of the following levels: "recommended for" or "recommended against" (a hard recommendation), or "recommended for consideration". This grading of recommendations to level of evidence is supported by the GRADE approach.[5] CDTs are digitally available in Dutch via a web application (www.oncoguide.nl) and for Android and iOS tablets. Oncoguide can document data output in a standardized, computable data format meeting the FAIR criteria.[6]

We focused in our study on four pivotal clinical decisions in the care pathway: indication for (1) MRI scan, (2) PST, (3) AST and (4) IBR. These CDTs contain, respectively, six, five, six and four data-items. Fifteen of these 21 data-items are unique. As example we illustrate the CDTs indication for MRI and first treatment in Figs. 1 and 2.

Data collection, analysis and availability

For included patients, all data-items needed to complete a path through CDTs in Oncoguide for the associated decision was retrieved retrospectively from the MDT, radiology and pathology reports in the electronic health record independently by two researchers (MH and SH). Data retrieval was restricted to data in the electronic health record as available at the time of the applicable MDT meeting in which each case was discussed. Data on MDT recommendations including explicit consideration of more than one treatment alternative were retrieved from de MDT reports. Concordance of recommendations reported by the MDT and the CDTs was analyzed, including

reporting motivations for disconcordance. In case a guideline recommendation was for consideration, it was verified if this was explicitly reported in the electronic health record. Data analysis was performed using Microsoft Excel for descriptive statistics. The dataset generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

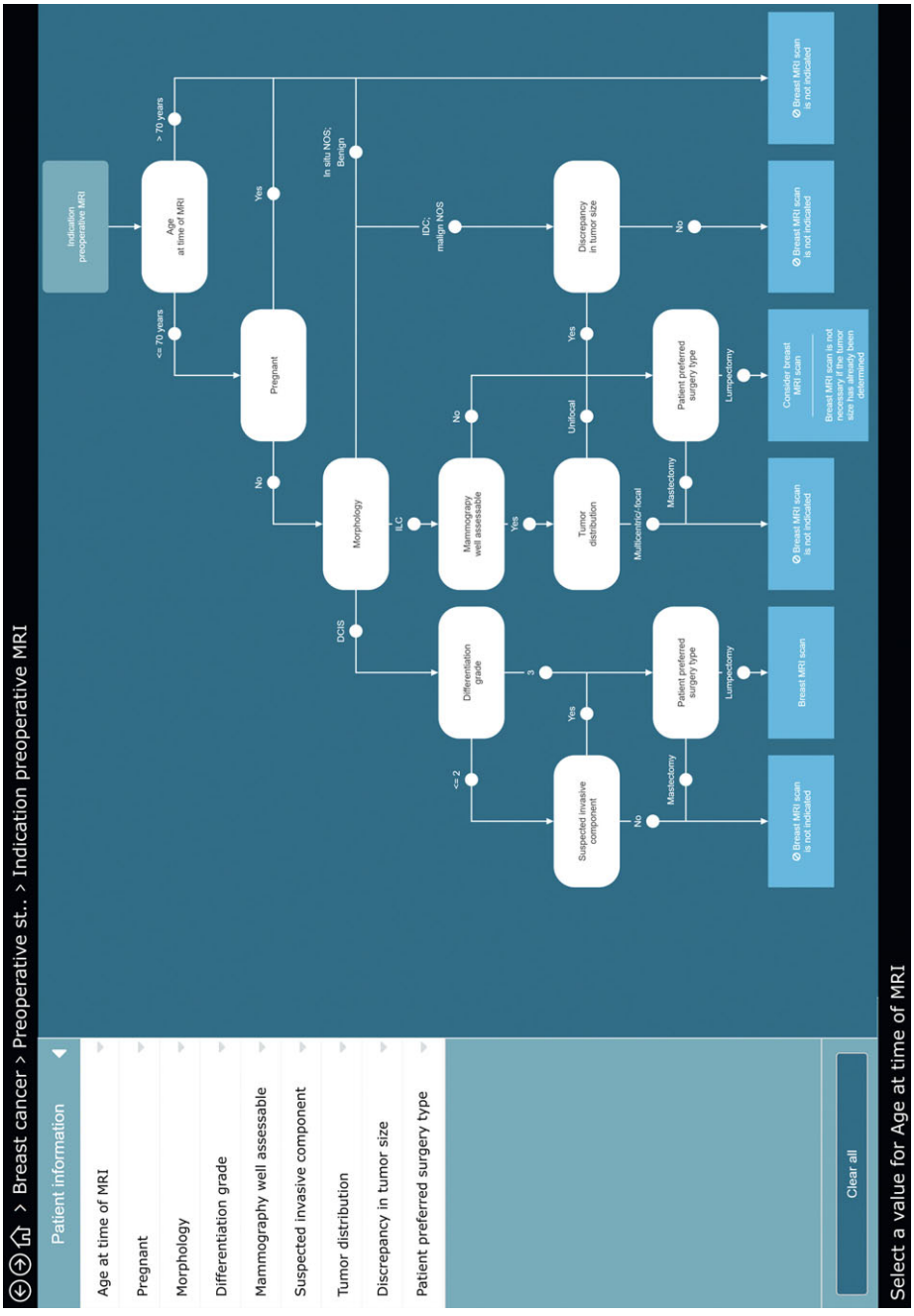


Fig. 1 Example of the clinical decision tree (CDT) of "pre-operative MRI scan" in Oncoguide.

MRI is indicated in case of (i) breast-conserving surgery, unless tumor size is already assessed; (ii) discrepancy between tumor size assessed by clinical examination, mammography and/or ultrasound; (iii) lobular carcinoma unless unifocal mass on well assessable mammography. **PST = preoperative systemic treatment

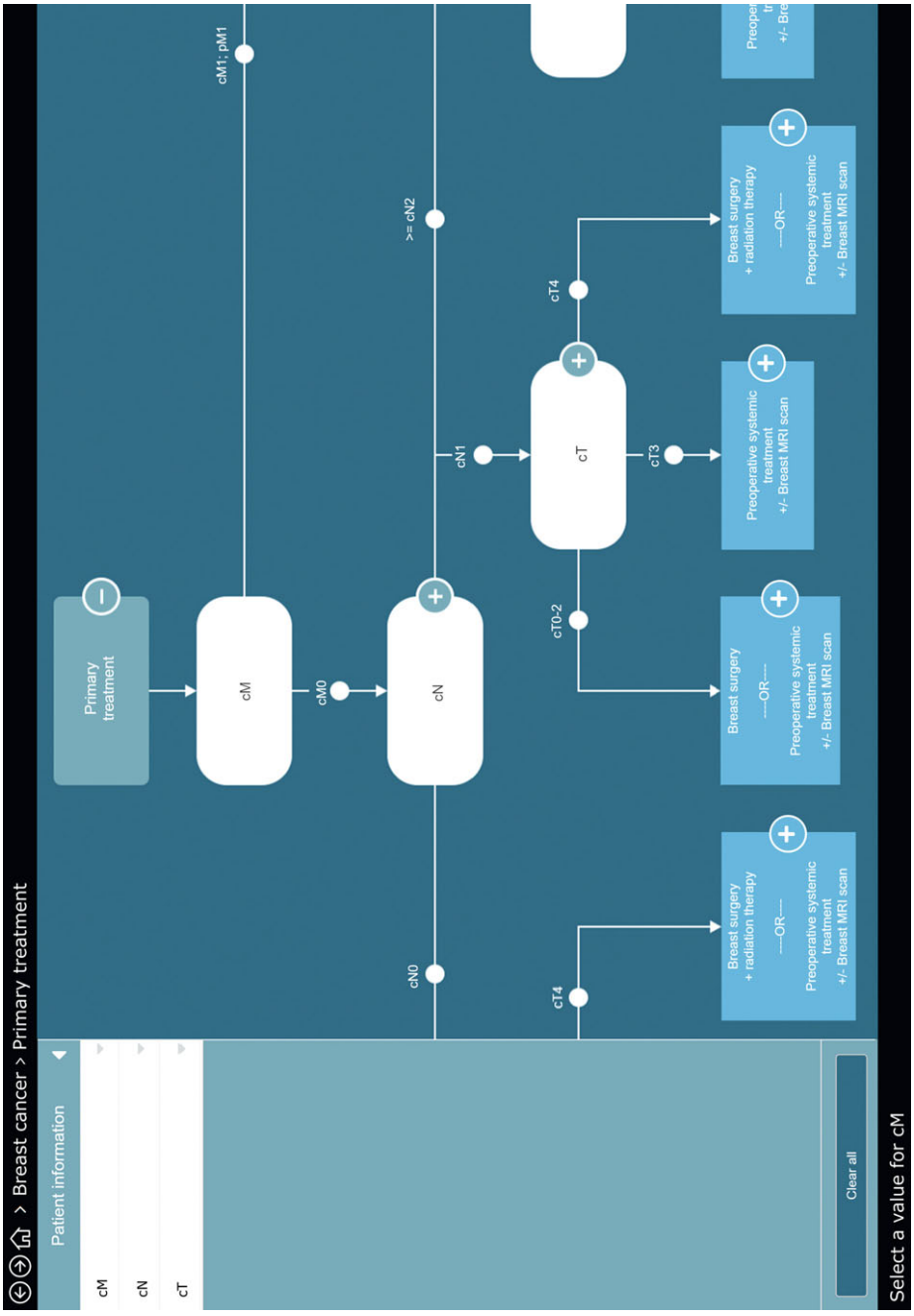


Fig. 2 Example of the clinical decision tree regarding first treatment.

Note that some "leaves" (i.e., the rectangles at the bottom of the CDT) result in a guideline-based recommendation with more than one alternative.

RESULTS

Of the 504 randomly selected patients, 110 patients were excluded for the reasons of no invasive breast cancer (*n* = 4), treatment for other cancer(s) in the past (*n* = 58), metastatic disease (*n* = 31), treatment received in other hospitals (*n* = 13), not discussed in at least one MDT meeting (*n* = 3) and not being diagnosed within the research period (*n* = 1). The residual included patients (*n* = 384) were equally divided over the 3 years of study duration (Table 1).

Availability of data during MDT meetings

Of all required 8004 data-items necessary for the four pivotal CDTs, 808 (10.1%) data-items were missing. Unverifiable data-items were "clinical M-stage" 81.6% (*n* = 659), "assessable mammography" 13.9% (*n* = 112) and 4.6% (*n* = 37) due to missing data on three other items (tumor distribution, ER status and tumor grade).

Data-items as required in the CDT for MRI scan, PST, AST and IBR were complete in 70%, 13%, 97% and 13% of the patients, respectively (Table 2). At maximum, two data-items were missing for each CDT, and this occurred in 1%, 1%, 0% and 2% of patients, respectively. Assuming the most frequent missing data-items "clinical M-stage" and "assessable mammography" as known would result in complete data-item availability in 97%, 99%, 97% and 97%, respectively.

Table 1 Patient characteristics of 394 randomly selected patients.

	number	percentage
Total number	394	
Age (years)		
Median	62	
Range	31 - 93	
>70 years	104	26
Period		
February 2012 till February 2013	127	32
February 2013 till February 2014	134	34
February 2014 till February 2015	133	34
Tumor type		
invasive ductal carcinoma	331	84
invasive lobular carcinoma	49	12
other	14	4
Receptor status		
ER+/HER2-	308	78
ER+/HER2+	13	3
ER-/HER2+	3	1

Table 1 Patient characteristics of 394 randomly (continued)

	number	percentage
ER-/HER2-	46	12
Receptor status not available	24	6
Clinical tumor stage		
stage I	215	55
stage II	156	40
stage III	23	6
Pathological tumor stage		
pCR	11	3
stage I	172	44
stage II	149	38
stage III	35	9
no surgery	27	7

Percentages may not equal 100% due to rounding
pCR pathologic complete response

Table 2 Availability of data-items during MDT meetings: an analysis using CDTs for four domains in the care path

Indication	Data-item name (values)	Data-item verifiable in EHR	
		No of patients	Percentage
MRI (n= 394)			
	Pregnant	394	100
	Age at time MRI (years)	394	100
	Morphology (i.e. lobular carcinoma, ductal carcinoma, other)	394	100
	Mammography well assessable (yes or no)	282	72
	Tumor distribution (not registered, unifocal, multicentric)	383	97
	Discrepancy tumor size: clinical vs. on imaging (no or yes)	394	100
	All data items available	276	70
Preoperative systemic treatment (n = 394)			
	Clinical M stage* (not registered, cM0 or cM1)	52	13
	Clinical N stage (not registered, cN0, cN1, cN2, cN3)	394	100
	Clinical T stage (not registered, cT1a, cT1b, cT1c, cT2, cT3, cT4)	394	100
	Gender (female)	394	100
	ER status (not registered, ER+, ER-)	390	99

Table 2 Availability of data-items during MDT meetings: an analysis using CDTs for four domains in the care path (continued)

Indication	Data-item name (values)	Data-item verifiable in EHR	
		No of patients	Percentage
	All data items available	52	13
Adjuvant systemic treatment (367 patients underwent surgery)			
	Pathologic N stage (not registered, pN0, pN1, pN2, pN3)	367	100
	N0 risk status		
	age (years)	367	100
	pathologic T stage (not registered, pTis, pT1a, pT1b, pT1c, pT2, pT3, pT4)	367	100
	tumor grade postoperatively** (not registered, BR gr1, BR gr2, BR gr3)	359	98
	HER2 status postoperatively (not registered, Her2+, Her2-)	367	100
	ER status*** (not registered, ER+, ER-)	364	99
	Age (years)	367	100
	All data items available	356	97
Immediate breast reconstruction (367 patients underwent surgery) #			
	Clinical M stage** (not registered, cM0 or cM1)	50	14
	Clinical N stage (not registered, cN0, cN1, cN2, cN3)	367	100
	Clinical T stage (not registered, cT1a, cT1b, cT1c, cT2, cT3, cT4)	367	100
	Tumor distribution (not registered, unifocal, multicentric)	356	97
	All data items available	46	13

BR Bloom Richardson grade
*Clinical M-stage was not explicitly reported, only when staging (PET CT) was performed
**In 7 patients, the pathologist reported that the tumor size was too small for BR grading and in one patient the BR grade was not reported
***In 367 patients, 48 were ER−, 316 ER+ and ER in 3 patients was not possible because of pTis status (no invasive tumor was found)
a In case of breast-conserving surgery (n = 264), in 0 patient reasons for direct reconstruction were reported. In case of modified radical mastectomy
(n = 103), in 29 patients reasons for immediate breast reconstruction were reported

Reporting of guideline recommendations with multiple alternatives

The CDTs for indication PST and IBR led to "leaves" recommending multiple alternatives. Regarding PST, the CDTs should have led to the alternatives "surgery first" or "PST ± MRI" in 171 (43.4%) patients. In 55 (32.2%) of these 171 patients, the MDT reported both alternatives. Regarding IBR, the CDTs should have led to the alternatives of surgery with

or without IBR in 103 (28.1%) patients with MDT recommendation for modified radical mastectomy. In these 103 patients, the MDT reported IBR to be recommended (*n* = 18), to be considered (*n* = 6) and not to be recommended explicitly because high risk for postoperative radiation therapy (n = 5). In 74 of 103 patients (71.8%), the MDT did not document any information about the (im)possibility of IBR.

Concordance of recommendations

The concordance rates between the recommendation "recommended" or "recommended for consideration" by the CDTs versus the recommendation generated by the MDT in patients of whom all data-items per CDT were available were 98%, 67%, 98% and 4% for the CDTs MRI scan, PST, AST and IBR, respectively (Table 3). In non-concordant cases, motivations for guideline deviation were not reported in 2%, 27%, 0% and 91% of cases, respectively.

Table 3 Concordance of recommendations generated by the MDT versus the CDTs in patients of which all data-items were available during MDT meetings.

Recommendation	Patients		concordant		not concordant			
					reasons not documented		reasons documented	
	N	%	N	%	N	%	N	%
MRI scan	276	70						
recommended/for consideration	49	18	48	98	1	2	NA	NA
not recommended	227	82	6	3	219	96	2*	1
PST	52	13						
recommended/for consideration	49	94	33	67	13	27	3**	6
not recommended	3	6	0	0	3	100	NA	NA
AST	356[a]	97						
recommended/for consideration	257	72	253	98	NA	NA	4[b]	2
not recommended	98	28	91	93	NA	NA	7[c]	7
IBR	46	13						
recommended	28	61	2	7	24	86	2[d]	7
for consideration	18	39	0	0	18	100	NA	NA

*Two patients received preoperative systemic treatment with preference to omit surgery in case of response to preoperative systemic therapy
**In three patients, preoperative systemic therapy was reported as an alternative in the electronic health record
a In one patient, the sentinel node procedure did not identify the sentinel node, and no pN status was available
b Three patients deliberately decided not to start adjuvant systemic treatment
c Seven patients were referred to the oncologist for the reason of "border-line" indication for adjuvant systemic treatment
d In two patients, the MDT did not recommend immediate breast reconstruction because irradiation of the thoracic wall was indicated

DISCUSSION

We found a low availability of data required for guideline- based recommendations at the time of decision-making. Complete availability and reporting of these data is important for generating verifiable guideline-based recommendations, especially when guidelines becoming more complex and patients are more involved in the decision-making process. In cases where the CDTs resulted in a guideline recommendation that consisted of multiple alternatives, these alternatives were reported by the MDT in only a minority of patients. MDT reporting of clear and motivated recommendations is valuable for internal communication between the different practitioners in the hospital and the patient. Further, we found high concordance rates between recommendations generated by the CDTs and the MDTs regarding indication for MRI scan and AST, but low rates regarding indication for PST and IBR.

In two out of four CDTs under study, we observed low percentages of data completeness in the electronic health record, mainly due to underreporting of "clinical M-stage" and "assessable mammography". One might speculate that data-items can be assumed as known by the MDT but not explicitly reported (e.g., clinical M-stage). Our observation that an absent clinical phenomenon (actually "cM0") is not reported by the MDT has been described earlier.[7,8] For adequate CDT usage, it is however essential that all data- items are explicitly available to reach a "leaf" containing a guideline-based recommendation. Another reason for not reporting a specific item might be a lack of clear definition of that data-item. For example, "assessable mammography" was not described in uniform terms making a classification according to the ACR BI-RADS® criteria impossible in 112 (28%) patients.[9] In this particular case, this illustrates the need for adherence by radiologists to an appropriate definition and subsequent high-quality file management.[10] In general, completeness of data-items in the electronic health record can be improved if free text reporting is replaced by clearly defined standardized reporting of data-items.[7,11-13] Further, standardized reporting, including clinical auditing, can be used to improve guideline compliance and to evaluate reasons for non-adherence.[14-16]

Literature about documentation of multiple treatment alternatives in MDT reports in case the guideline recommendation includes more than one alternative is limited.[17] This is remarkable because the first steps in practicing informed decision-making are being aware that you have a choice and know the appropriate alternatives.[18] Hahlweg et al. analyzed 249 cases in 11 different cancer-specific MDT meetings and found that in 10% of cases more than one treatment recommendation was reported and this is comparable with our findings.[17] Explicit reporting the prefer- able timing of systemic therapy for early breast cancer, i.e., preoperative versus adjuvant, is done in only a small number of patients.[19] For IBR, it has already been shown that patients feel significantly more involved in shared decision- making if they are informed about the treatment alternatives.[20]

There may be several reasons why MDTs do not report multiple alternatives when mentioned in the guideline recommendation. First, MDTs can guide the choices of the patients in a restrictive manner when they believe that alter- natives are not equivalent and they have a clear preference, e.g., a patient with a tumor that can evidently be treated with breast-conserving surgery is unlikely to get a MDT recommendation including the alternative of mastectomy. Further, MDT members can consider factors that are not reported, e.g., the specific wish of a patient for a certain treatment or comorbidity of a patient making one alternative much more preferable above another.[21] Third, there may be internal agreements that in certain circumstances a particular alternative is not chosen, e.g., no PST in endocrine-sensitive early-stage breast cancer or a certain alternative may not be (timely) available in the local hospital, e.g., IBR. And finally, a reason may be that not all discussed alternatives by the MDT are reported.

The concordance of recommendations generated by the CDTs and the MDTs for indication of PST and IBR was low. There may be good reasons for not concordant cases. However, we found very low reporting rates for motivated deliberately guideline deviations, possibly by the lack of (time for) structured and systematically file management facilitating explicit motivations for MDT recommendations. CDTs deliver a systematical method to assess what treatment and diagnostic modalities are recommended according to the guideline. If we want to learn from real-world data, proper patient file management of relevant data-items and reasons for deliberately chosen alternatives or guideline deviations is an essential key. CDTs can be used to explicate the decision-making process, provided that all data-items are unambiguously present. In this way, CDTs act as a learning health system facilitating tightening and updating guidelines. Integrating learning health system data with existing knowledge from the literature can help to close the evidence-to-practice gap.[22,23]

The strength of our study was that two researchers independently evaluated the availability of data during MDT meetings and that all data-items were available from the electronic health records. Moreover, the cohort was representative for the Dutch population. The retrospective use of real-world data has the advantage that MDT participants were not influenced in their reporting manner (no Hawthorne effect). The retrospective manner is also a weak point as it is not verifiable if absent data- items or treatment alternatives mean that these were not considered/discussed following the CDT or not reported only. We found a lower percentage of Her2-positive breast cancers (4%), as to be expected in the Dutch population (13%) although Her2 status was available in 95% of cases.[24] However, we do not believe that this lower percent- age biased our research objective. Further, we investigated the CDTs for only four clinical decisions in a single center, reflecting 15 unique data-items. It cannot be stated whether an availability of 13% of a data-item is exceptional or not. However, we found high availability rates of pathology data-items, and pathology data-items reflect 49% of all data-items in the guideline (56/114).[4]

CONCLUSION

The availability of data in patient electronic health records that are essential for guideline-based recommendations as well as reporting of possible treatment alternatives of the CDTs under study was low. For meeting the conditions of EUSOMA, it is warranted that MDTs explicate information that is supposed to be implicitly known and to adhere to clear definitions of data-items in their reporting. Filling in the CDTs manually is time consuming and requires dedicated support from a nurse or data manager. For real- time use of CDTs in clinical practice, it is essential key that the needed data are registered in a standardized way, are exchangeable and reusable with MDT reporting forms and the CDTs. We recommend a prospective multicenter feasibility trial to observe if the data needed for CDT application is verbally or digital available during MDT meetings, distinguishing non-availability of data due to not being discussed or not being registered only.

Funding
Not applicable.

REFERENCES

1. Wilson AR, Marotti L, Bianchi S, et al. The requirements of a specialist Breast Centre. Eur J Cancer 2013;49:3579-87.
2. Panella M, Marchisio S, Di Stanislao F. Reducing clinical variations with clinical pathways: do pathways work? International journal for quality in health care : journal of the International Society for Quality in Health Care 2003;15:509-21.
3. Dutch national breast cancer guideline 2012. (Accessed 13 Feb, 2012, at http://www.oncoline.nl/richtlijn/item/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=885.)
4. Hendriks MP, Verbeek X, van Vegchel T, et al. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. JCO Clin Cancer Inform 2019;3:1-14.
5. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. Journal of clinical epidemiology 2017;87:4-13.
6. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016;3:160018.
7. Ebben K, Sieswerda MS, Luiten EJT, et al. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. JCO Clin Cancer Inform 2020;4:346-56.
8. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:290-303.
9. Rao AA, Feneis J, Lalonde C, Ojeda-Fournier H. A Pictorial Review of Changes in the BI-RADS Fifth Edition. Radiographics 2016;36:623-39.
10. Houssami N, Boyages J, Stuart K, Brennan M. Quality of breast imaging reports falls short of recommended standards. Breast 2007;16:271-9.
11. Brown PJ, Rossington H, Taylor J, et al. Standardised reports with a template format are superior to free text reports: the case for rectal cancer reporting in clinical practice. Eur Radiol 2019;29:5121-8.
12. Patel A, Rockall A, Guthrie A, et al. Can the completeness of radiological cancer staging reports be improved using proforma reporting? A prospective multicentre non-blinded interventional study across 21 centres in the UK. BMJ Open 2018;8:e018499.
13. Aumann K, Niermann K, Asberger J, et al. Structured reporting ensures complete content and quick detection of essential data in pathology reports of oncological breast resection specimens. Breast Cancer Res Treat 2016;156:495-500.
14. Adegboyega TO, Landercasper J, Linebarger JH, et al. Institutional review of compliance with NCCN guidelines for breast cancer: lessons learned from real-time multidimensional synoptic reporting. J Natl Compr Canc Netw 2015;13:177-83.
15. Farrugia DJ, Fischer TD, Delitto D, Spiguel LR, Shaw CM. Improved Breast Cancer Care Quality Metrics After Implementation of a Standardized Tumor Board Documentation Template. J Oncol Pract 2015;11:421-3.
16. van Bommel AC, Spronk PE, Vrancken Peeters MT, et al. Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: The national NABON Breast Cancer Audit. J Surg Oncol 2017;115:243-9.
17. Hahlweg P, Didi S, Kriston L, Harter M, Nestoriuc Y, Scholl I. Process quality of decision-making in multidisciplinary cancer team meetings: a structured observational study. BMC Cancer 2017;17:772.
18. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012;27:1361-7.

19. de Ligt KM, Spronk PER, van Bommel ACM, et al. Patients' experiences with decisions on timing of chemotherapy for breast cancer. Breast 2018;37:99-106.
20. de Ligt KM, van Bommel ACM, Schreuder K, et al. The effect of being informed on receiving immediate breast reconstruction in breast cancer patients. Eur J Surg Oncol 2018;44:717-24.
21. Lin FP, Pokorny A, Teng C, Dear R, Epstein RJ. Computational prediction of multidisciplinary team decision-making for adjuvant breast cancer drug therapies: a machine learning approach. BMC Cancer 2016;16:929.
22. Guise JM, Savitz LA, Friedman CP. Mind the Gap: Putting Evidence into Practice in the Era of Learning Health Systems. J Gen Intern Med 2018;33:2237-9.
23. Leung TI, Dumontier M. Putting FAIR Evidence into Practice. J Gen Intern Med 2019.
24. Breast Cancer in the Netherlands. Trends 1989-2017 based on data of the National Cancer Registry.2018 Oct.

CHAPTER 5

Using guideline-based clinical decision support in oncological multidisciplinary team meetings: a prospective, multicenter concordance study

Kees C.W.J Ebben*, **Mathijs P. Hendriks***, Lieke Markus, Milan Kos, Ignace de Hingh, Jorg R. Oddens, Joost Rothbarth, Hans de Wilt, Luc J.A. Strobbe, Maud Bessems, Carsten T. Mellema, Sabine Siesling, Xander A.A.M. Verbeek

* Both authors contributed equally.

International Journal for Quality in Health Care. 2022 Mar 19;34(1)

ABSTRACT

Background

Multidisciplinary team meetings formulate guideline-based individual treatment plans based on patient and disease characteristics and motivate reasons for deviation. Clinical decision trees could support multidisciplinary teams to adhere more accurately to guidelines. Every clinical decision tree is tailored to a specific decision moment in a care pathway and is composed of patient and disease characteristics leading to a guideline recommendation.

Objective

This study investigated (1) the concordance between multidisciplinary team and clinical decision tree recommendations and (2) the completeness of patient and disease characteristics available during multidisciplinary team meetings to apply clinical decision trees such that it results in a guideline recommendation.

Methods

This prospective, multicenter, observational concordance study evaluated 17 selected clinical decision trees, based on the prevailing Dutch guidelines for breast, colorectal and prostate cancers. In cases with sufficient data, concordance between multidisciplinary team and clinical decision tree recommendations was classified as concordant, conditional concordant (multidisciplinary team specified a prerequisite for the recommendation) and non-concordant.

Results

Fifty-nine multidisciplinary team meetings were attended in 8 different hospitals, and 355 cases were included. For 296 cases (83.4%), all patient data were available for providing an unconditional clinical decision tree recommendation. In 59 cases (16.6%), insufficient data were available resulting in provisional clinical decision tree recommendations. From the 296 successfully generated clinical decision tree recommendations, the multidisciplinary team recommendations were concordant in 249 (84.1%) cases, conditional concordant in 24 (8.1%) cases and non-concordant in 23 (7.8%) cases of which in 7 (2.4%) cases the reason for deviation from the clinical decision tree generated guideline recommendation was not motivated.

Conclusion

The observed concordance of recommendations between multidisciplinary teams and clinical decision trees and data completeness during multidisciplinary team meetings in this study indicate a potential role for implementation of clinical decision trees to support multidisciplinary team decision-making.

Introduction

Evidence-based clinical decision-making in oncology is increasingly challenging considering the growing amount of available research knowledge, treatment options and target subpopulations characterized by molecular and genetic testing.[1-3]

Multidisciplinary teams (MDTs) are the backbone of decision-making in oncology.[4] The MDT discussion serves to obtain insight regarding the patient and disease characteristics on an aggregated level, to consider the diagnostic and treatment options and to reach a multidisciplinary recommendation. MDTs base their recommendations on clinical practice guidelines. However, MDTs can also deliberately recommend an alternative treatment option if they believe this is better suited for an individual patient. Motivations for guideline deviations have to be recorded for legal ground,[5,6] and they can provide insights in alternatives.

To manage all relevant patient and disease characteristics for making multidisciplinary guideline-based recommendations, MDTs could potentially benefit from a computerized clinical decision support system (CDSS). Evidence for complex guideline-based CDSS usage during MDT meetings is limited.[7] Also, it is unknown to what extent the complexity of a decision (i.e. the number of patient characteristics that need to be taken into consideration) is related to the usability of CDSS and concordance with MDTs.[8]

It has been shown that implementation of clinical practice guidelines (hereafter: 'guidelines') improves the quality of care.[9] However, recommendations in textual guidelines in oncology are often extensive, may be ambiguous and inconsistent,[10] spread across the full text of the guideline document, and not systematically aligned with the clinical decision process in the care path. This impedes implementation of guidelines in clinical practice. Previously, Hendriks *et al*. described a method that remodels guideline recommendations into unambiguous, data-driven decision algorithms called clinical decision trees (CDTs). CDTs were constructed by nodes, branches and leaves, representing data-items (patient and tumor characteristics, e.g. T-stage), data-item values (e.g. ≤T2) and recommendations (e.g. chemotherapy) and are identical representations of the concerning CPGs. To date, CDTs were evaluated on validity for usage in MDTs retrospectively by Hendriks *et al.*[11] for breast cancer and by Keikes *et al.*[12] for colorectal cancer.

Implementing CDTs in daily clinical practice proves to be challenging.[13-15] First of all, because physicians may tend to feel compromised in their autonomy and to not accept guidelines in a computerized manner.[16] Secondly, the evidence that clinical decision support increases MDT performance is currently sparse, because adequate techniques to measure MDT performance are challenging.[17] Finally, optimal usage of any guideline-based CDSS requires the explicit availability of relevant patient and disease characteristics during the MDT.[18] The latter implies a motivational and a technical challenge: clinicians should record the appropriate information and the CDSS should be suitable for connection with the electronic health record. However, integration of CDSS in electronic health records is currently challenging.

We performed an observational study to explore the following research questions: (i) what is the concordance between MDT and CDT recommendations for breast cancer, colorectal cancer and prostate cancer, including reporting motivations for deviation of the CDT recommendation?, (ii) to which degree required patient and disease characteristics were available during MDT meetings to apply CDTs such that it results in a guideline recommendation? and the final research question (iii) what is the influence of CDT complexity on concordance?

Methods

Design

This study was designed as a prospective, multicenter, observational, cross-sectional concordance study. The participating medical centers were academic, teaching and general hospitals [Figure 1]. The study design was exempt from approval requirement by independent medical ethics committees.

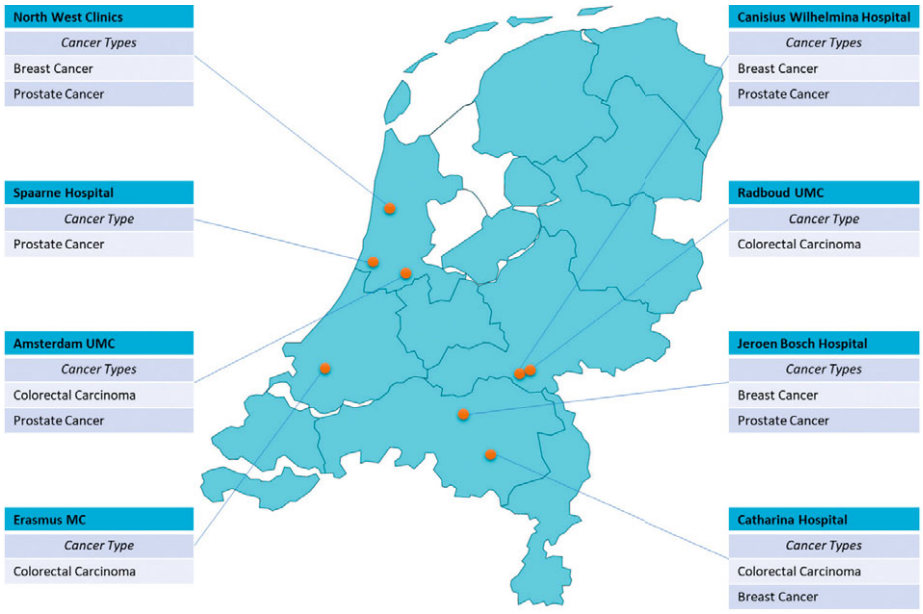
Data collection

A medical doctor with several years of (international) experience did observe, but not participate in, the MDT discussion and manually collected all available data at the time of MDT meetings (both discussed data and available reports in the electronic health records) in all participating centers. The MDT meetings were not recorded to minimize a potential Hawthorne effect. The collected data included (i) patient and disease characteristics in general (sex, age, tumor type, and tumor stage), (ii) additional data necessary for completing the relevant CDT, (iii) the individual treatment plan proposed by the MDT and (iv) the reason for deviating from the guideline (if applicable). Data were collected from August 2019 until December 2019. Case report forms are available on request.

Inclusion and exclusion criteria

Patients with suspected or pathological confirmed breast cancer (including ductal carcinoma in situ (DCIS)), colorectal cancer or prostate cancer who are discussed in an MDT meeting were eligible for inclusion, if the intended decision matched 1 of the 17 CDTs under study. The list of selected CDTs is included in Table 1. The tumor types were selected because of their high incidence and availability of guideline-based CDTs, focusing on multidisciplinary decision support. A patient was excluded when (i) the proposed decision fell outside the scope of the guideline (e.g. second relapse); (ii) the proposed decision did not match with 1 of the 17 selected CDTs under investigation (e.g. neoadjuvant therapy and patients with (loco-)regional recurrence) and (iii) the MDT preparation was insufficient and the MDT decided to postpone the decision pending further investigation results.

Figure 1 Participating hospitals and evaluated cancer types.



CDTs

The method for designing CDTs from guidelines is described elsewhere.[2] In short, CDTs are composed of nodes (data-items representing patient and disease characteristics), branches (representing the possible values of the data-items) and leaves (representing recommendations from the guideline). The CDTs are published on www.oncoguide.nl [Figure 2]. By entering patient-specific data, a single path through the CDT is generated leading to the guideline recommendation applicable for this patient. The CDTs evaluated in this study are based on the prevailing Dutch guidelines during the study period (breast cancer version 1.0, 2018 [19]; colorectal cancer version 3.0, 2014 [20] and prostate cancer version 2.1, 2016 [21]). In total, 17 CDTs were selected for evaluation in this study including primary treatment, adjuvant treatment and treatment for metastatic disease (synchronous or metachronous).

Data analysis and statistics

After each MDT meeting, the collected data were plotted onto the corresponding CDT in order to generate a guideline-based recommendation [Figure 2]. To evaluate our secondary objective, patients were assigned to one of two categories: (i) sufficient data were available during the MDT meeting to complete a single pathway through a CDT leading to a guideline recommendation [Figure 2b] or (ii) one or more parameters to fully complete a single pathway were missing [Figure 2c and d]. Consequently, multiple pathways remain open, resulting in more than one possible guideline recommendation.

Table 1 CDT complexity scores and concordance of 17 CDTs under study.

Cancer type	Phase in the clinical pathway	Clinical Decision Tree	Complexity scores per CDT				Total complexity score	# included cases per CDT
			Number of Nodes	Number of Leaves	Depth[&]	Attributes[^]		
Prostate cancer	Recurrence treatment	Treatment of metastatic castration resistant prostate carcinoma (mCRPC) post-chemotherapy	2	3	2	2	9	10
Prostate cancer	Recurrence treatment	Treatment of metastatic castration resistant prostate carcinoma (mCRPC) pre-chemotherapy	2	3	2	2	9	13
Prostate cancer	Primary treatment	Treatment of metastatic disease	2	3	2	2	9	32
Prostate cancer	Adjuvant treatment	Adjuvant treatment after prostatectomy with or without lymph node dissection	3	5	2	2	12	2
Breast cancer	Adjuvant treatment	Postoperative treatment	3	4	3	3	13	50
Breast cancer	Primary treatment	Systemic treatment in metastatic disease	3	6	3	3	15	1
Colorectal cancer	Adjuvant treatment	Adjuvant treatment rectal carcinoma	5	4	5	5	19	5
Colorectal cancer	Primary treatment	Primary treatment colon carcinoma	5	5	5	5	20	20

	# cases with complete data per CDT	Concordance per CDT				Mean concordance per CDT (%)	CDT hyperlink
		Concordant cases		Non-concordant			
		Concordant	Conditional concordant	Non-concordant, motivated	Non-concordant, non-motivated		
	8	6	1	1	0	87,5	https://oncoguide.nl/#!/projects/20/tree/38/45
	13	12	1	0	0	100	https://oncoguide.nl/#!/projects/20/tree/38/46
	30	17	4	7	2	70	https://oncoguide.nl/#!/projects/20/tree/38/407
	1	1	0	0	0	100	https://oncoguide.nl/#!/projects/20/tree/38/42
	48	38	5	1	4	79,1	https://oncoguide.nl/#!/projects/20/tree/38/406
	1	1	0	0	0	100	https://oncoguide.nl/#!/projects/7/tree/10543/168
	5	5	0	0	0	100	https://oncoguide.nl/#!/projects/27/tree/199/203
	19	17	2	0	0	100	https://oncoguide.nl/#!/projects/27/tree/199/187/189

Breast cancer	Adjuvant treatment	Locoregional treatment after breast conserving surgery	5	10	3	4	22	33*
Breast cancer	Adjuvant treatment	Regional treatment after mastectomy	6	10	4	5	25	17*
Colorectal cancer	Adjuvant treatment	Adjuvant treatment colon carcinoma	7	8	5	5	25	15
Prostate cancer	Primary treatment	Local treatment	7	9	4	5	25	69
Breast cancer	Primary treatment	Primary treatment	6	11	4	5	26	67
Colorectal cancer	Primary treatment	Treatment of metastatic disease	11	13	6	8	38	49
Colorectal cancer	Primary treatment	Primary treatment rectal carcinoma	17	16	6	11	50	22
Breast cancer	Adjuvant treatment	Local treatment after mastectomy	22	13	8	8	51	17*
Breast cancer	Adjuvant treatment	Adjuvant systemic therapy	32	48	5	7	92	51*

* > 1 CDT applies to a single case
& maximum number of nodes to get from root-node to leaf (longest path)
^ number unique data-items/attributes

	31	27	1	0	3	87,1	https://oncoguide.nl/#!/projects/7/tree/10543/182/147
	17	11	4	1	1	88,2	https://oncoguide.nl/#!/projects/7/tree/10543/182/151
	11	11	0	0	0	100	https://oncoguide.nl/#!/projects/27/tree/199/202
	52	46	4	2	0	96,2	https://oncoguide.nl/#!/projects/27/tree/199/203
	53	48	4	1	0	98,1	https://oncoguide.nl/#!/projects/7/tree/10543/101
	43	37	1	5	0	88,4	https://oncoguide.nl/#!/projects/27/tree/199/187/191
	13	10	2	0	1	92,3	https://oncoguide.nl/#!/projects/27/tree/199/187/190
	17	11	4	1	1	88,2	https://oncoguide.nl/#!/projects/7/tree/10543/182/150
	48	38	5	1	4	95,6	https://oncoguide.nl/#!/projects/7/tree/10543/182/153

For our primary objective (concordance), the cases assigned to category 1 (sufficient data) were further analyzed. The recommendation pairs (from MDT and CDT) were assigned to one of the four following groups, depending on the level of concordance: (i) concordant: the recommendation of the MDT was corresponding with (one of) the guideline recommendations; (ii) conditional concordant: the recommendation of the MDT was corresponding with (one of) the guideline recommendations; however, the MDT provides an explicit condition for the recommendation made (e.g. perform surgery after cT1-stage breast cancer based on mammography is confirmed by a MRI scan) and (iii) non-concordant: the recommendation of the MDT was not corresponding with (one of) the guideline recommendations. These are subdivided into (i) motivated cases—the MDT explicitly motivates why they deviate from the guideline—and (ii) not motivated cases— the MDT deviated from the guideline but did not provide a motivation.

Subgroup analyses regarding concordance were performed based on tumor type and tumor stage (represented by the TNM staging system: the tumor, node, metastasis classification of malignant tumors). If available, we categorized the MDT motivations for recommendations that deviated from the guideline: specific tumor characteristics, comorbidity, patient preference, age, study inclusion or obsolete guideline (= a guideline is alleged not to reflect the current status of evidence and therefore presumed to be outdated). These categories were based on prior interviews with several clinicians during the development of the Oncoguide tool. These reasons were categorized and consensus was achieved and implemented in Oncoguide.

Finally, we evaluated the presence of a potential correlation between the complexity of a CDT and the concordance. Complexity of a CDT is defined as a combination of the total number of nodes, the total number of leaves, the number of unique nodes and the tree depth (longest path) [22]. This theoretically results in scores that range from 2 to infinite. Higher scores are related to a more complex decision. The CDTs were then classified in quartiles based on their total complexity score. The first and fourth quartiles were compared for the percentage of concordant cases. The correlation for complexity and concordance was evaluated by a unifactorial analysis of variance.

Data analyses were performed using Microsoft Excel for descriptive statistics.

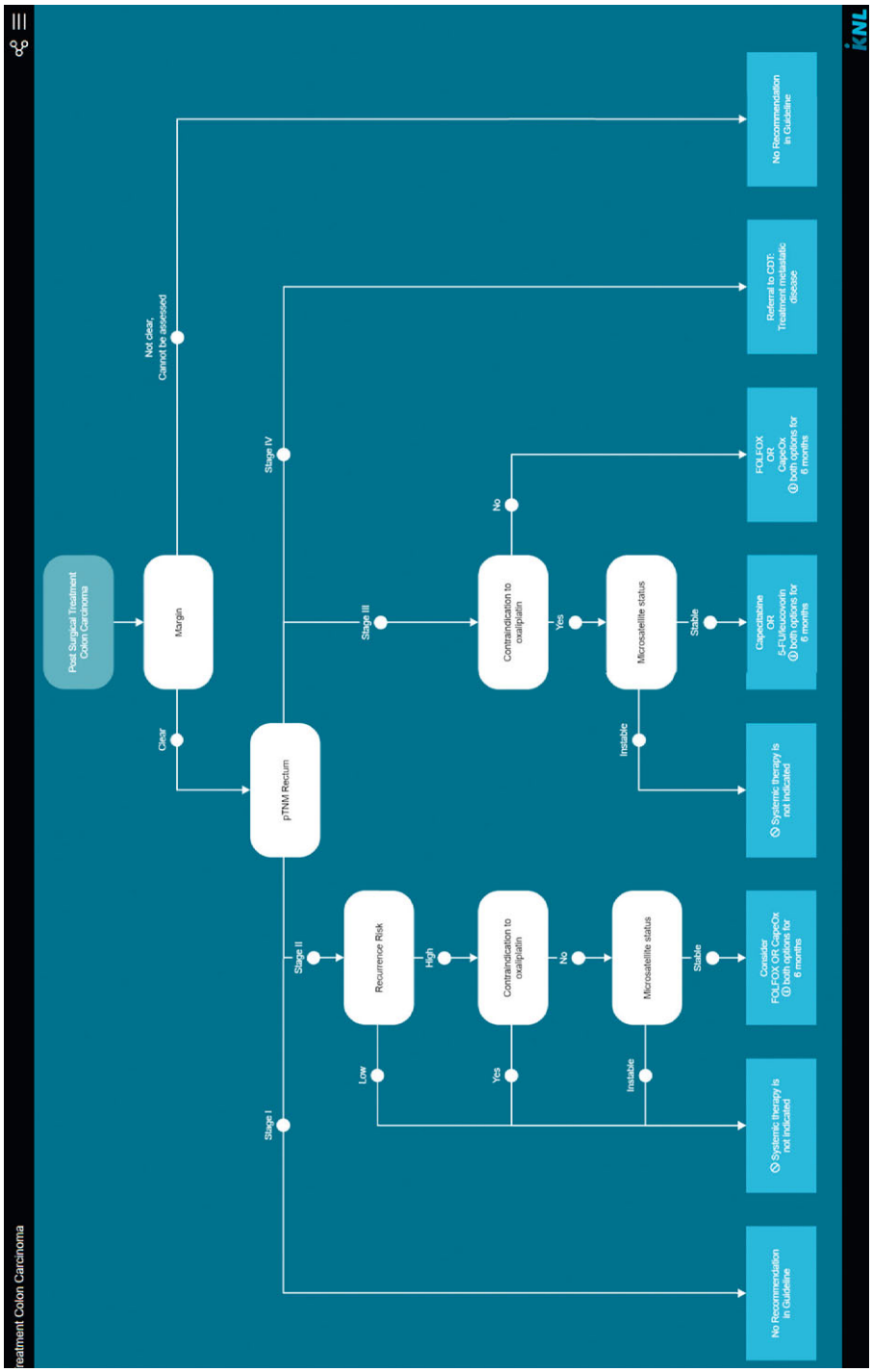


Fig. 2a Examples of clinical decision trees in Oncoguide.

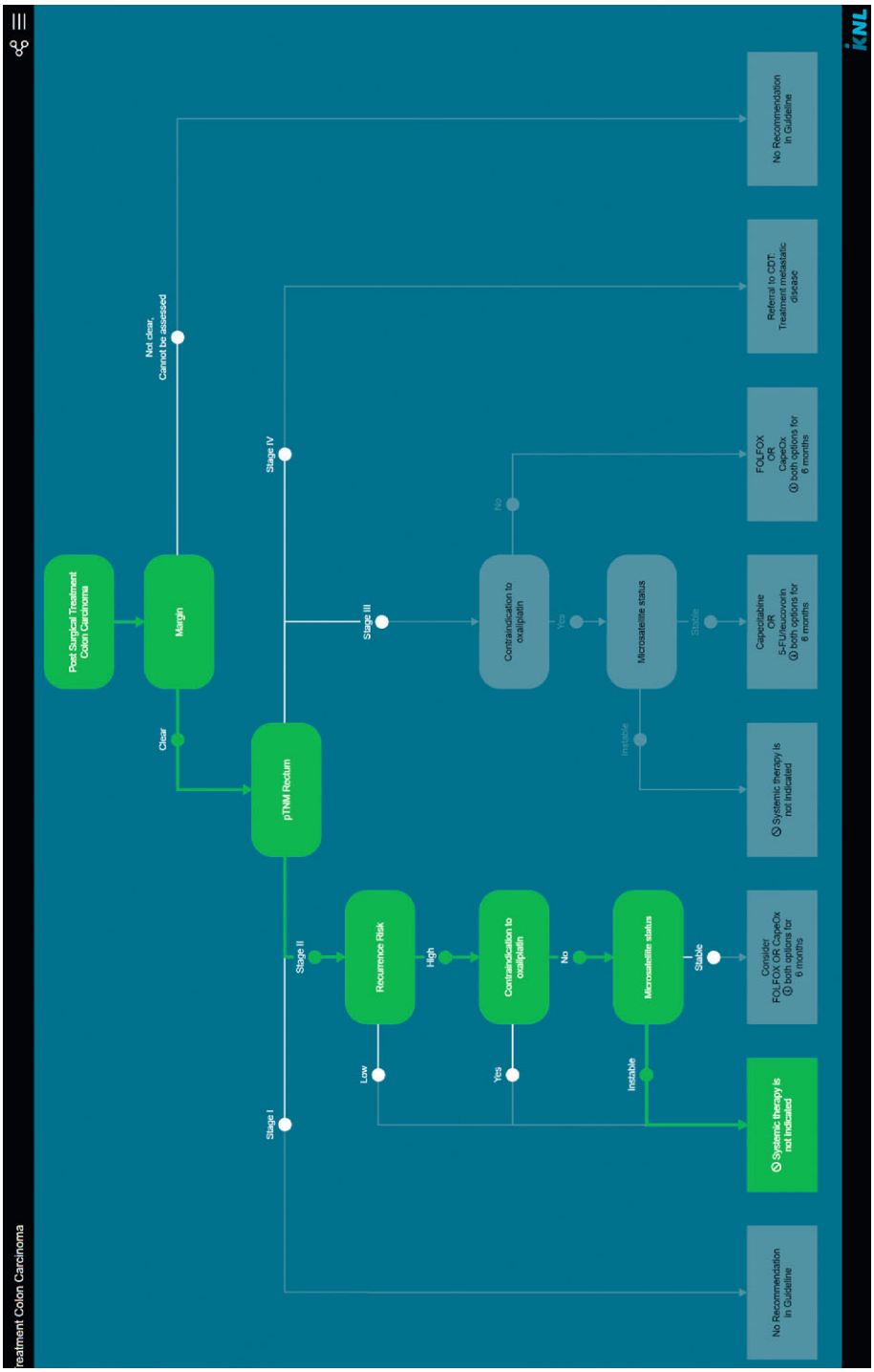


Fig. 2b Examples of clinical decision trees in Oncoguide.

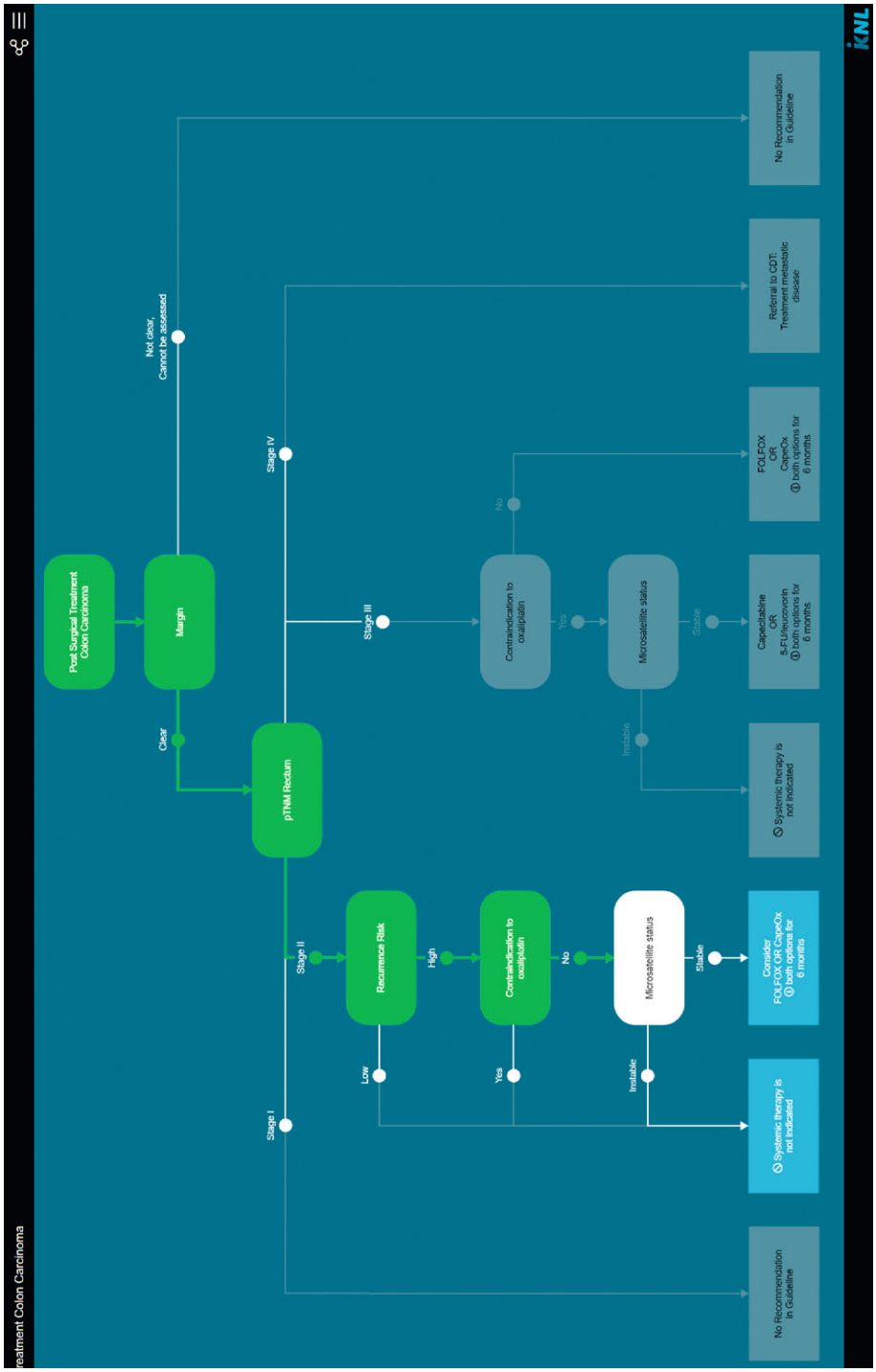


Fig. 2c Examples of clinical decision trees in Oncoguide.

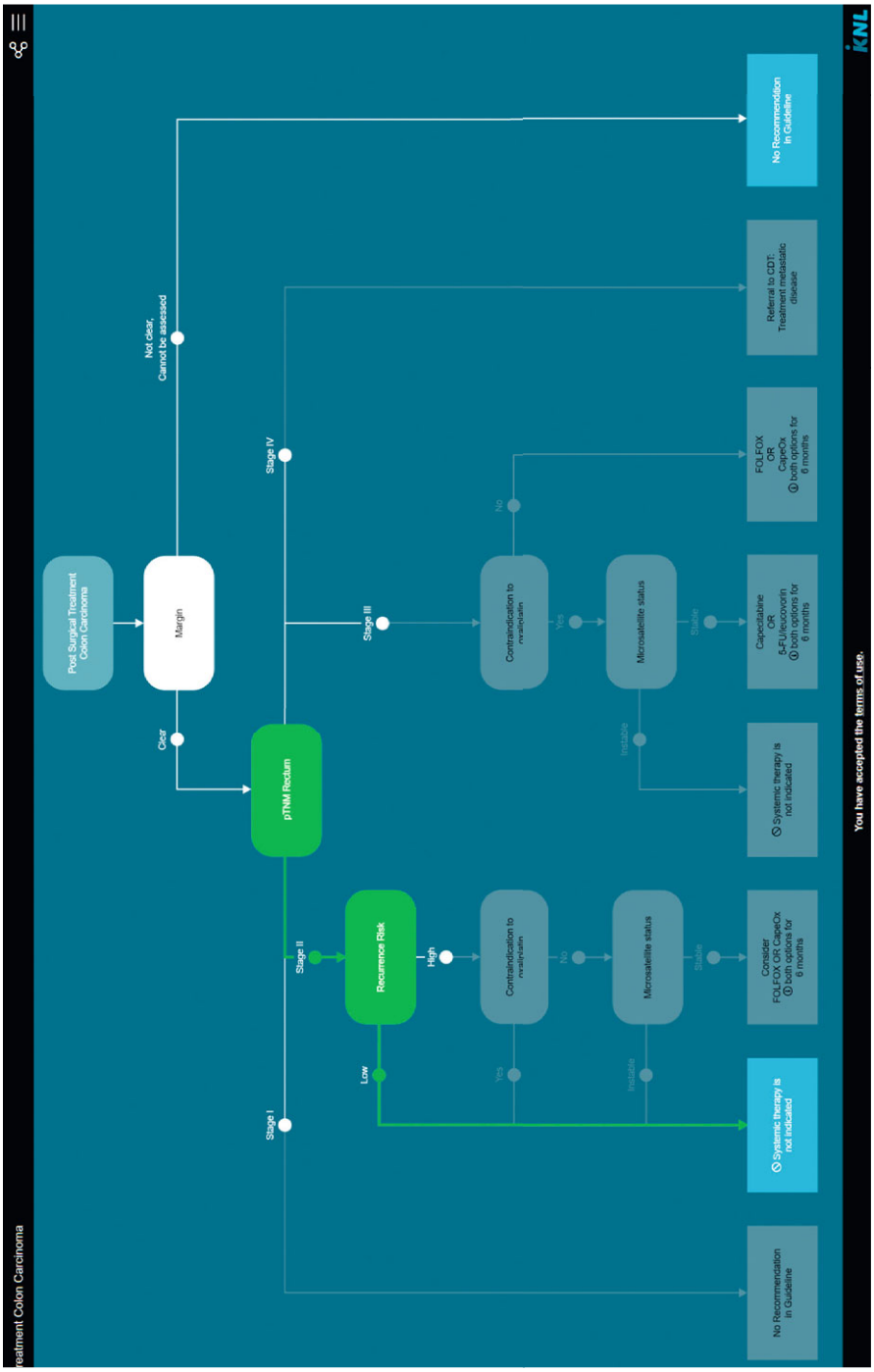


Fig. 2d Examples of clinical decision trees in Oncoguide.

Figure 2 Examples of clinical decision trees in Oncoguide.

(a) Hypothetical CDT for a specific population at a specific step in the care pathway. (b) All data-items (nodes) required by the CDT for this patient are available and filled in on each node, resulting in a single highlighted pathway, leading to a single leaf with CPG recommendation. (c) One data-item (white node) is missing, the CDT generates two possible leaves with CPG recommendations. (d) One data-item (white node) is missing. Since other data-items are known, the CDT generates two leaves with CPG recommendations. CDTs are composed of (I) a stem (defining the population and step in the care pathway the CDT applies to), (II) nodes (data-items representing patient and disease characteristics), (iii) branches (representing the possible values of the data-items) and (IV) leaves (representing recommendations from the CPG). By entering patient specific values, a single leaf with a recommendation applicable for this patient can be generated. CDT=clinical decision tree; CPG= clinical practice guideline.

Results

Inclusion

In total, 59 MDT meetings were attended in 8 different hospitals [Figure 1]. From these meetings, 355 unique cases were included: 118 cases for breast cancer (including DCIS), 111 cases for colorectal cancer and 126 cases for prostate cancer [Table 2, Figure 3].

Table 2 Patient and disease characteristics of included cases

Kolom1	Total	Breast	Colorectal	Prostate
N	355	118	111	126
Gender				
Female (%)*	162 (45.6)	117 (99.2)	45 (40.5)	na
Male (%)*	193 (54.4)	1 (0.8)	66 (59.5)	126 (100)
Age ± SD, years	66.8 ± 11.3	63.0 ± 12.5	66.3 ± 11.6	71.4 ± 7.4
TNM Stage, n (%)*				
0	23 (6.5)	23 (19.5)	na	na
I	96 (27.0)	49 (41.5)	26 (23.4)	21 (16.7)
II	88 (24.8)	38 (32.2)	19 (17.1)	31 (24.6)
III	33 (9.3)	7 (5.9)	15 (13.5)	11 (8.7)
IV	114 (32.1)	1 (0.8)	50 (45.0)	63 (50.0)
Unknown	1 (0.3)	0 (0.0)	1 (0.9)	0 (0.0)

NA not applicable; SD standard deviation. a Percentages may not equal 100% due to rounding.

Availability of data as input for CDTs

For 296 cases (83.4%), all data-items to complete a single CDT pathway were available during the MDT meeting. Per tumor type this was 102 (86.4%) for breast cancer, 90 (81.1%) for colorectal cancer and 104 (82.5%) for prostate cancer [Table 3]. In 59 cases, (16.6%) one or more data-items were not available during the MDT meetings and therefore CDTs generated multiple possible recommendations [Figure 2c-d]. Of these 59 cases, a total of 41 (11.5%) cases resulted of 2 open paths in the CDT, both leading to

a recommendation, 9 (2.5%) in 3 open paths and 9 (2.5%) in 4 or more open paths. The distribution regarding the number of highlighted pathways (2, 3, ≥4) for each disease, with stage subdivision, is shown in Table 3. An overview of the missing data-items is presented in Table 4.

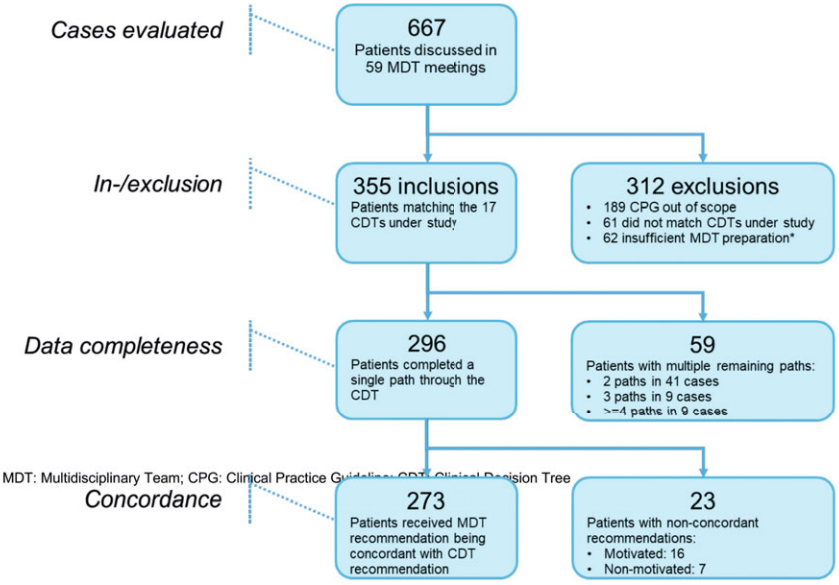


Figure 3 Flow diagram of inclusion and exclusion, data completeness and concordance.
MDT: Multidisciplinary Team; CPG: Clinical Practice Guideline; CDT: Clinical Decision Tree.
*The MDT was unable to provide a policy proposal due to lacking data.

Concordance

From the 296 generated CDT recommendations, the MDT recommendations were completely concordant, conditionally concordant and non-concordant in 249, (84.1%), 24 (8.1%)

and 23 (7.8%) cases, respectively. In 7 out of 23 (30.4%) non-concordant cases, the MDT did not provide reasons for non-concordance.

Complete and conditional concordance rates for breast cancer, colorectal cancer and prostate cancer were 85.3% and 8.8%, 88.9% and 5.6%, and 78.8% and 9.6%, respectively. For non-concordance, the results were as follows: breast cancer 5.9%, colorectal cancer 5.5% and prostate cancer 11.5% [Table 5]. Subgroup analysis on the effect of tumor stage on concordance showed that 13 (9 prostate cancer cases and 4 colorectal cancer cases) out of 16 (81.3%) motivated non-concordant cases had stage IV disease. Most common MDT motivations for guideline deviation were inclusion in a clinical trial (n = 13), age/comorbidity (n = 10) and specific tumor characteristics (n = 8). In Table 6, all motivations are listed.

CDT complexity

Complexity scores of the included CDTs are available in Tables 1 and 3. The mean concordance of the CDTs in the first quartile and fourth quartile was 89.4% and 91.1%, respectively, and did not differ statistically significantly ($P = 0.8$).

DISCUSSION

Statement of principal findings

This concordance study in breast, colorectal and prostate cancers showed concordant recommendations between CDT and MDT in a large majority (92.2%) of evaluated cases. In 16.6% of cases, concordance could not be evaluated due to insufficient available patient and disease characteristics during MDT meetings. An unconditional recommendation from a CDT depends on availability of complete data. In this study, data availability per case was higher than previously reported.[11,12,18] The systematic application of a CDT uncovers the amount of missing data required for guideline-based decision-making and thereby may stimulate a more complete reporting of necessary data.

Focusing on the most frequently found missing data-items per CDT in this study, there are some remarkable observations: (i) composite data-items like 'cN0-risk status' or 'risk on invasion (in DCIS)' are prone to be incomplete, perhaps through their complexity and unfamiliarity, (ii) a data-item like 'contraindication for oxaliplatin' is important for the final selection of chemotherapy regimen in the outpatient clinic, but it can be argued this goes beyond the scope of the MDT meeting (as assessment of contraindications may be performed by the treating physician), (iii) unavailability of 'microsatellite stability status' in colorectal cancer could indicate that this test is not incorporated as standard diagnostic entity in all hospitals and (iv) 'cT-stage' in rectal cancer is a known difficult feature, requiring assessment of a dedicated radiologist. The characterization of these data-items is very diverse in terms of data source (radiology, pathology). This emphasizes the importance of involvement of all medical disciplines for effectuating complete registration to enable MDTs making guideline-based recommendations.

In patients where concordance could be evaluated, the MDT recommendation was non-concordant with the CDT recommendation in 7.8% of cases. In nearly a third of those cases, no motivation was reported for guideline deviation. In the CDTs under study, no clear trend was found regarding CDT complexity and concordance. We therefore hypothesize that the used method of CDTs, which is following the clinical processes, is useful for MDT decision support independent of the CDT complexity.

Cases with conditional concordance were provided with a recommendation, but it can be argued that data were missing for unambiguous decision-making. This might indicate either a suboptimal preparation of the MDT or acting on newly acquired insights during the MDT session.

A relatively high number of cases (9%) were excluded from analyses since the MDT was not provided with sufficient information to properly discuss a patient. The discussion and therefore also a proposal for a policy had to be postponed. For these cases, the MDT could be considered inadequately organized. Although not investigated further, our dataset revealed differences in the percentages of exclusions between hospitals due to insufficient preparation. Despite the ubiquitous availability of data in the electronic health records, difficulties in having access to complete information is a known phenomenon in MDTs.[23]

Strengths and limitations

This prospective multicenter study included three types of solid cancer at various phases in the clinical pathway, representing a wide variety of MDT-based decisions with their associated specific challenges. Therefore, it is likely that the results of this study can be extrapolated to CDTs of other (oncological) diseases.

Table 3 Availability of data as input for CDTs.

		Total	Single pathway[α]	Two pathways[β]	Three pathways[ζ]	Four or more pathways[γ]
Breast cancer cases		118	102	16	0	0
TNM Stage	0	23	17	6	0	0
	I	49	41	8	0	0
	II	38	36	2	0	0
	III	7	7	0	0	0
	IV	1	1	0	0	0
	Unknown	0	0	0	0	0
Colorectal cancer cases		111	90	7	7	7
TNM Stage	0	NA	NA	NA	NA	NA
	I	26	22	3	0	1
	II	19	14	2	3	0
	III	15	11	1	3	0
	IV	50	43	1	0	6
	Unknown	1	0	0	1	0
Prostate cancer cases		126	104	18	2	2
TNM Stage	0	NA	NA	NA	NA	NA
	I	21	15	3	1	2
	II	31	19	11	1	0
	III	11	11	0	0	0
	IV	63	59	4	0	0
	Unknown	0	0	0	0	0
Total (%)		355	296 (83.4)	41 (11.5)	9 (2.5)	9 (2.5)

Table 4 Missing data during MDT meetings per CDT

Cancer type	CDT	Data-item (patient/disease characteristic)	Number of cases per CDT in study	CDT complexity score[ε]	Data-item missing frequency	Percentage of missing data-items per CDT under study
Breast cancer						
	Primary treatment breast cancer		67	26		
		cN0 risk status[α]			8	11,9
		Risk on invasion (DCIS)[β]			6	9,0
	Post operative adjuvant treatment breast cancer*		50	13		
		NA				
	Locoregional treatment after breast conserving therapy*		33	22		
		ER-status			1	3,0
		HER2-status			1	3,0
	Local treatment after mastectomy*		17	51		
		NA				
	Regional treatment after mastectomy*		17	25		
		NA				
	Adjuvant systemic therapy*		50	92		
		Menopausal status[ζ]			5	10,0
	Metastatic disease		1	15		
		NA				
Colorectal cancer						
	Primary treatment colon cancer		20	20		
		cT-stage			1	5,0
	Adjuvant treatment colon cancer		15	25		

Table 4 Missing data during MDT meetings per CDT (continued)

Cancer type	CDT	Data-item (patient/disease characteristic)	Number of cases per CDT in study	CDT complexity score[ε]	Data-item missing frequency	Percentage of missing data-items per CDT under study
		Contra-indication for oxaliplatin			3	20,0
		Microsatelite status			3	20,0
	Primary treatment rectal cancer		22	50		
		cT-stage			3	13,6
		Extramesorectal pathological lymph nodes			2	9,1
		Extramural invasion			2	9,1
		Tumor diameter			1	4,5
		Vascular invasion polypectomy			1	4,5
		Polypectomy performed			1	4,5
		Differentiation grade			1	4,5
		(lymph)angio-invasion			1	4,5
	Adjuvant treatment rectal cancer		5	19		
		Mesorectal fascia distance			5	100,0
		Cutting edge			1	20,0
	Metastatic disease		49	38		
		Number of resectable liver metastases			6	12,2
		Local treatability liver metastases			4	8,2
		Resectability of extrahepatic metastases			2	4,1
Prostate cancer						
	Primary local treatment		69	25		

Table 4 Missing data during MDT meetings per CDT (continued)

Cancer type	CDT	Data-item (patient/disease characteristic)	Number of cases per CDT in study	CDT complexity score[ε]	Data-item missing frequency	Percentage of missing data-items per CDT under study
		Chance of lymph node involvement[γ]			8	11,6
		Life expectancy			3	4,3
		Number of positive biopsies			3	4,3
		EAU/ESTRO risk group[δ]			1	1,4
		PSA			1	1,4
		Extensiveness disease			1	1,4
	Adjuvant treatment		2	12		
		Cutting edge			1	50,0
	Metastatic disease		55	9		
		Localization of metastases			4	7,3
	mCRPC pre-chemotherapy					
		NA				
	mCRPC post-chemotherapy					
		NA				

CDT: clinical decision tree; MDT: multidisciplinary team; DCIS: ductal carcinoma in situ; ER-status: estrogen receptor status; HER2-status: human epidermal growth factor receptor 2 Status; EAU: European Association of Urology; ESTRO: European Society for Radiotherapy and Oncology; PSA: prostate-specific antigen. N.B. In single cases, >1 data-item can be missing. NA: not applicable. a Aggregated score contains age, HER2 status, ER-status, grade, tumor diameter. b Aggregated score contains age, palpability, MRI coloring, grade, tumor diameter. c The patients' age in all five cases was ≥60 years and was therefore in our analyses considered as post-menopausal. d Aggregated score (prediction model) contains PSA, cT, Gleason variant 1, Gleason variant 2, Positives cores. e Aggregated score contains cN, cT, Gleason, iPSA. f CDT complexity scores method are displayed in Figure 3. g Multiple CDTs are applicable to each unique case. h These CDTs were filled in completely in all applicable cases and therefore had no missing data-items.

Table 5 Concordance of MDT and CDT recommendations per tumor type and stage

		Concordant cases, n (%)			Non-concordant cases, n (%)			Distribution per tumorstage in research sample in percentages	Distribution per tumorstage in the Netherlands in percentages
		Total	Concordant cases	Conditional concordant	Total	Motivated	Not motivated		
Breast cancer cases (n=102)		96 (94.1)	87 (85.3)	9 (8.8)	6 (5,9)	2 (2.0)	4 (3.9)		Incidences 2018*
TNM Stage	0		17	0		0	0	17	12
	I		36	2		0	3	40	41
	II		28	5		2	1	35	33
	III		5	2		0	0	7	9
	IV		1	0		0	0	1	5
Colorectal cancer cases (n=90)		85 (94.4)	80 (88.9)	5 (5.6)	5 (5.6)	4 (4.4)	1 (1.1)		Incidences 2017*
TNM Stage	0		NA	NA		NA	NA	NA	NA
	I		22	0		0	0	24	26
	II		13	1		0	1	17	23
	III		7	3		0	0	11	28
	IV		38	1		4	0	48	20
Prostate cancer cases (n=104)		92 (88.5)	82 (78.8)	10 (9.6)	12 (11.5)	10 (9.6)	2 (1.9)		Incidences 2016*
TNM Stage	0		NA	NA		NA	NA	NA	NA
	I		14	0		1	0	14	38
	II		18	1		0	0	18	20

Table 5 Concordance of MDT and CDT recommendations per tumor type and stage (continued)

	Concordant cases, n (%)			Non-concordant cases, n (%)			Distribution per tumorstage in research sample in percentages	Distribution per tumorstage in the Netherlands in percentages
	Total	Concordant cases	Conditional concordant	Total	Motivated	Not motivated		
III		10	1		0	0	11	17
IV		40	8		9	2	57	25
Total (n=296)	273 (92.2)	249 (84.1)	24 (8.1)	23 (7.8)	16 (5.4)	7 (2.4)		

MDT: multidisciplinary team; CPG: clinical practice guideline; CDT: clinical decision tree; NA: not applicable. a The most recent complete years per tumor type were retrieved from the Netherlands Cancer Registry.

Table 6 MDT motivations for conditional concordance and motivations for non-concordance

	Breast cancer (n)	Colorectal cancer (n)	Prostate cancer (n)
MDT motivations for conditional concondant cases*			
Uncertainty on patient/tumor characteristics (Additional testing will be performed; T-category uncertain)	26	9	21
Specific tumor characteristics (very small size, aggressive biology)	2	2	3
Comorbidity	0	2	0
Patient preference	0	1	0
Other	0	3	2
MDT motivation for non-concordant cases*			
Patient preference	0	0	1
Age	0	1	2
Comorbidity	2	3	2
Study inclusion	1	10	2
Other:			
Specific tumor characteristics (very small size, aggressive biology)	3	4	1
Current CPG outdated	0	1	2

MDT: multidisciplinary team; CPG: clinical practice guideline.
a Multiple motivations can be put forward per case.
Another strength was the attendance of an independent researcher who was able to track the course of the MDT discussion, rather than simply extracting the recommendation of the MDT found in the electronic health record, retrospectively.

The current study has a non-interventional design. MDTs were not provided with the CDT and recommendations during or after their discussion. A suggestion for future research is to confront MDTs with CDT recommendations and evaluate if this alters their decision. There are some interventional studies performed, mostly single center studies focusing on one type of malignancy.[24-26] However, obtaining strong evidence is difficult because double-blinded randomized clinical trials are difficult to perform in decision support settings, obviously. Secondly, we did not recruit a prespecified number of patients for each CDT under investigation. Patients with metastatic breast cancer (TNM stage IV) were for instance underrepresented, and patients with stage IV colorectal cancer and prostate cancer were overrepresented in our study. This might have lowered the perceived guideline adherence. Since this population has a large diversity of disease manifestation, one might expect a more individualized treatment strategy. Another potential limitation is the Hawthorne effect.[27] Being observed could influence the clinicians and this could result in recommendations that agreed to the guideline more strictly. To minimize the Hawthorne effect, the MDT sessions were not recorded. Lastly, because the data collection was performed by a single medical doctor, observer bias may have occurred.

Interpretation within the context of the wider literature

This multicenter study has investigated if innovative methods can support the decision making process in a multidisciplinary setting. Middleton *et al.* describe in their review the importance of standardized available data and development of knowledge bases for CDS, which are prominently taken into account in our study.[15] Other studies showed that a multitude of requirements must be met for successful implementation of clinical decision support.[13,14] This study has focused on several of these requirements (e.g. (i) clinicians attitude toward scientific evidence in guidelines, (ii) organizational ethos of transparency and accountability,

(iii) understanding of human interaction and workflow implications of CDS and (iv) proprietary implementations with limited interoperability and sharing) and therefore contributes in the further acceptance by clinical community of the health information technology.

Implications for policy, practice and research

The next step toward a successful data-driven healthcare system, especially in multidisciplinary settings, is the implementation and integration of CDSSs into existing clinical processes.[28,29] This requires (i) the introduction of standardized, structured high-quality reporting by MDTs, including motivation for deviations from guidelines, (ii) integration of CDTs in electronic health records in such a way that it supports clinical workflow and (iii) feedback reporting of real-world treatment recommendations in MDTs to guideline working groups. If these conditions are met, MDTs can be supported real-time for preparing and conducting their MDT meetings for individual patients. On a population level, it can be investigated if MDT decisions deviating from the guideline are attributed to situations where evidence for best practice is low, new evidence outdates the prevailing guideline or unwanted practice variation occurs.

However, the latest guidelines such as the 2020 version of the Dutch breast cancer guidelines stress in each recommendation the value of shared decision-making. Moreover, recommendations are formulated as 'to consider', rather than in an imperative way.[19] CDTs can support shared decision-making, since they identify all theoretical possible treatment options. The transparent nature of CDTs enables clinicians and patients to deliberate and judge which treatment option is most suitable.

CONCLUSION

Increasing knowledge of a myriad of tumor characteristics, internet access and appreciation of patient preferences leads to progressive individualization of choices regarding diagnostics and therapy. This evolution should be recognized, not as a threat, but rather as a continuing challenge for the MDT members and the CDT pathways to provide treatment choices instead of single options.

Acknowledgements

Agnes Jager PhD, medical oncologist, Erasmus MC, Rotterdam; Saskia van der Meer MD PhD, urologist, Jeroen Bosch Hospital, 's-Hertogenbosch; Martijn van Oijen PhD, clinical epidemiologist, Amsterdam UMC, Amsterdam; Prof. Theo M. de Reijke MD PhD, urologist, Amsterdam UMC, Amsterdam; Ton Roeleveld MD MSc, urologist, Northwest Clinics, Alkmaar; Maurice van der Sangen MD PhD, radiation therapist, Catharina Hospital, Eindhoven; Rik Somford MD PhD, urologist, Canisius Wilhelmina Hospital, Nijmegen; Prof. Cornelis Verhoef MD PhD, oncological surgeon, Erasmus MC, Rotterdam; Jurrian van der Werf PhD PDEng, clinical informatician, Netherlands Comprehensive Cancer Organization, Utrecht all in the Netherlands.

Funding

This work was not financially supported by any organization.

REFERENCES

1. Elsevier. Cancer research current trends & future directions. 2016.
2. Hendriks MP, Verbeek X, van Vegchel T, et al. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. JCO Clin Cancer Inform 2019;3:1-14.
3. Willems SM, Abeln S, Feenstra KA, et al. The potential use of big data in oncology. Oral Oncol 2019;98:8-12.
4. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. Cancer Treat Rev 2016;42:56-72.
5. Metcalfe D, Pitkeathley C, Herring J. 'Advice, not orders'? The evolving legal status of clinical guidelines. J Med Ethics 2020.
6. Rutgers EJ, Nortier JW, Tuut MK, et al. CBO-richtlijn "behandeling van het mammacarcinoom". Ned Tijdschr Geneeskd 2002;146:2144-51.
7. Patkar V, Acosta D, Davidson T, Jones A, Fox J, Keshtgar M. Using computerised decision support to improve compliance of cancer multidisciplinary meetings with evidence-based guidance. BMJ Open 2012;2.
8. Miller KE, Singh H, Arnold R, Klein G. Clinical decision-making in complex healthcare delivery systems. In: Iadanza E, ed. Clinical Engineering Handbook (Second Edition): Elsevier; 2019:858-64.
9. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)
   Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.
10. Martinez Garcia L, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. CMAJ 2014;186:1211-9.
11. Hendriks MP, Verbeek X, van Manen JG, et al. Clinical decision trees support systematic evaluation of multidisciplinary team recommendations. Breast Cancer Res Treat 2020;183:355-63.
12. Keikes L, Kos M, Verbeek X, et al. Conversion of a colorectal cancer guideline into clinical decision trees with assessment of validity. Int J Qual Health Care 2021;33.
13. Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. Implement Sci 2017;12:113.
14. Greenes RA, Bates DW, Kawamoto K, Middleton B, Osheroff J, Shahar Y. Clinical decision support models and frameworks: Seeking to address research issues underlying implementation successes and failures. J Biomed Inform 2018;78:134-43.
15. Middleton B, Sittig DF, Wright A. Clinical Decision Support: a 25 Year Retrospective and a 25 Year Vision. Yearb Med Inform 2016;Suppl 1:S103-16.
16. Medlock S, Wyatt JC, Patel VL, Shortliffe EH, Abu-Hanna A. Modeling information flows in clinical decision support: key insights for enhancing system effectiveness. J Am Med Inform Assoc 2016;23:1001-6.
17. Patkar V, Acosta D, Davidson T, Jones A, Fox J, Keshtgar M. Cancer multidisciplinary team meetings: evidence, challenges, and the role of clinical decision support technology. Int J Breast Cancer 2011;2011:831605.

18. Ebben K, Sieswerda MS, Luiten EJT, et al. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. JCO Clin Cancer Inform 2020;4:346-56.
19. Breast cancer guideline [Internet]. 2018. https//richtlijnendatabase.nl/richtlijn/borstkanker/algemeen.html (7 January 2021, date last accessed).
20. Colorectal cancer guideline [Internet]. 2014. https//richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html (7 January 2021, date last accessed).
21. Prostate cancer guideline [Internet]. 2014. https//richtlijnendatabase.nl/richtlijn/prostaatcarcinoom/prostaatcarcinoom_-_korte_beschrijving.html (7 January 2021. date last accessed).
22. Rokach L, Maimon O. Decision Trees. In: Maimon O, Rokach L, eds. Data Mining and Knowledge Discovery Handbook. Boston, MA: Springer US; 2005:165-92.
23. Rosell L, Alexandersson N, Hagberg O, Nilbert M. Benefits, barriers and opinions on multidisciplinary team meetings: a survey in Swedish cancer care. BMC Health Serv Res 2018;18:249.
24. Bouaud J, Blaszka-Jaulerry B, Zelek L, et al. Health information technology: use it well, or don't! Findings from the use of a decision support system for breast cancer management. AMIA Annu Symp Proc 2014;2014:315-24.
25. Seroussi B, Bouaud J, Gligorov J, Uzan S. Supporting multidisciplinary staff meetings for guideline-based breast cancer management: a study with OncoDoc2. AMIA Annu Symp Proc 2007;2007:656-60.
26. Seroussi B, Soulet A, Spano JP, et al. Which patients may benefit from the use of a decision support system to improve compliance of physician decisions with clinical practice guidelines: a case study with breast cancer involving data mining. Stud Health Technol Inform 2013;192:534-8.
27. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol 2014;67:267-77.
28. Cohan A, Soldaini L, Yates A, Goharian N, Frieder O. On clinical decision support. Proceedings of the 5th ACM Conference on Bioinformatics, Computational Biology, and Health Informatics. Newport Beach, California: Association for Computing Machinery; 2014:651–2.
29. Berner ES, La Lande TJ. Overview of Clinical Decision Support Systems. In: Berner ES, ed. Clinical Decision Support Systems: Theory and Practice. New York, NY: Springer New York; 2007:3-22.

PART IV

CDTs for evaluation of national real-world data

CHAPTER 6

Self-learning healthcare systems: data-driven clinical decision trees supporting evaluation of real-world breast cancer care

Mathijs P. Hendriks, Linda de Munck, Thijs van Vegchel, Agnes Jager*, Sabine Siesling*

* A.J. and S.S. contributed equally.

Abstract

Background

Clinical decision trees (CDTs) are data-driven representations of clinical practice guidelines for multidisciplinary team (MDT) decision support in cancer. Implementation of these data-driven CDTs can support evaluation of guideline implementation using real-world cancer care data. We aim to project the Netherlands Cancer Registry (NCR) breast cancer data onto data-driven CDTs as proof of principle in going towards a self-learning healthcare system.

Methods

Induced by an update of a guideline recommendation regarding the indication of neoadjuvant systemic therapy (NST) in stage 2 breast cancer this population was chosen as example. Data from patients with stage 2 breast cancer, diagnosed in the period 2016-2019, eligible for NST were selected from the nationwide NCR. Patients were stratified per hospital and the percentage NST usage was plotted in funnel plots. Based on the mean percentage NST and delta percentage NST before and after the guideline update, hospitals were categorized into 'early innovators', 'good adopters', 'slow adopters' and 'laggards', and visualized in a waterfall plot. For one good adopter and one slow innovator the NCR data were projected on the CDT showing actually delivered care patterns on national level and on individual hospital level.

Findings

NCR data revealed hospital variation in the uptake of the guideline recommendation. The change in adherence over time could identify hospitals as early innovator, good adopter, slow adopter or laggard in 33%, 25%, 25% and 16% of hospitals respectively. CDTs encoded real-world practice data and elucidated real-world treatment patterns on hospital level.

Interpretation

Comparing daily clinical practice based on real-world data with the guideline-based advices expressed in CDTs provides a good insight into changes in treatment patterns and can identify the level of change for individual hospitals. CDTs can be used as a systematical operating system of a data-driven self-learning healthcare system.

Introduction

Stimulating adherence to clinical practice guidelines (further abbreviated as guidelines) aims to support clinical decision making, improve the quality of care by reducing unwanted clinical practice variation and improve clinical outcome.[1,2] Multidisciplinary teams (MDTs) have to recommend the best treatment option(s) for each individual patient based on the guideline recommendations taking into account a growing amount of data, information and knowledge. Clinical decision-making by MDTs has an appreciable positive impact on overall survival.[3] However, guideline recommendations are mainly based on randomized clinical trials conducted in specific patient populations in which clinical features often differ from real-word patient populations.[4] Therefore, getting insights in real-world treatment patterns is important to compare actually delivered care with the expected care based on guidelines. To learn systematically from real-world data, it is essential that the actually delivered care can be evaluated at patient level which requires unambiguous registration of patient, tumor and treatment data, registration of the MDT recommendation(s) and eventually the actually delivered care after the MDT advice is discussed with the patient.

The MDT can be supported by clinical decision support systems.[5] Here we propose clinical decision trees (CDTs) as an operating data system for both data registration and clinical decision support for MDTs to guide treatment recommendations. CDTs are a data-driven representation of a guidelines and follow the clinical care path. CDTs are composed of nodes, branches and leaves representing data-items (patient and tumor characteristics), branches (data-item cut-off values) and recommendations, respectively The Dutch breast cancer guideline has been transformed into data-driven CDTs.[6]

Further, by the data-driven design of CDTs, they are also usable to evaluate treatment patterns of nationwide patient populations. The Netherlands Cancer Registry (NCR) registers the actually delivered care.[7] By projecting NCR data onto CDTs, the CDTs elucidate the expected guideline-based recommendations and to what extend these recommendations have been implemented in clinical practice. In case of deviations, the CDT shows what other treatment has been administered. As the CDTs cover the full patient journey and CDTs are data-driven, CDTs can be used for real-time monitoring of actually delivered care, and pinpoint decisions with a (trend to) higher variation. This may be valuable feedback and by learning from real-world data, the CDTs can act as a self-leaning health care system. The latter is defined as a "system in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the care process, patients and families as active participants in all elements, and new knowledge is captured as an integral by-product of the care experience".[8]

The aim of this study is to show how the data-driven CDT methodology can be used to evaluate actually delivered nationwide breast cancer care and to explore the concept of the CDTs as a self-learning healthcare system by projecting nationwide NCR data onto CDTs to analyze changes in administered care in depth for individual hospitals. We discuss the potential added value of this real-world practice data. Since the Dutch

breast cancer guideline stated in its update of January 2018 that neoadjuvant systemic therapy (NST) should be considered in stage 2 breast cancer, we use this population as a proof of principle. To visualize the concept of CDTs, we evaluate what percentage of this population actually received NST and how this altered around this guideline change at all individual hospitals.

Methods

Study design

This is a retrospective descriptive study Involving real-world data that will be projected on the CDT "primary treatment" to compare the actually delivered care with the recommended care according to the CDT (guideline). The data-driven CDTs are digitally available in Dutch via a web application www.oncoguide.nl, and the methodology has been described previously.[6] In brief, a CDT starts with a clinical question (tribe), for example "primary treatment". Based on patient characteristics (nodes), a route is followed through the CDT via data cut-off values (branches) that ends with a recommendation of intervention (leaf). The whole clinical care path of breast cancer has been captured by CDTs.

Study population & data collection

Since the guideline update of January 2018 recommended that NST should be considered in stage 2 breast cancer, all patients aged ≥ 18 years and <70 years, diagnosed with clinical stage 2 breast cancer between 1-1-2016 and 31-12-2019 in The Netherlands were included. Data were obtained from the NCR, hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). IKNL registers all malignancies based on notification by the national pathology archive (PALGA) and data was extracted directly from the patient files by trained registrars.

Statistics

In patients receiving systemic therapy (chemotherapy) for stage 2 breast cancer, we investigated the percentage of patients receiving NST. The numerator will contain all patients that received NST (plus or minus adjuvant systemic therapy) and the denominator will contain all patients that received systemic therapy, independent of neoadjuvant and/or adjuvant setting. Sub-analyses will be performed to compare individual hospitals regarding the usage and changes of NST in stage 2 breast cancer per year. Differences regarding percentages NST usage between individual hospitals will be displayed per year using Funnel plots. The mean change of the percentage of usage of NST in stage 2 breast cancer of each individual hospital will be calculated for each year, and this will be set against the mean change of all hospitals. To further investigate the change in NST usage in stage 2 breast cancer, the percentage NST-delta will be determined for each hospital comparing 2019 with 2016. To categorize hospital patterns of NST usage, a cut-off percentage NST usage in 2019 of ≥ the mean value of all hospitals in 2019 and a cut-off percentage NST-delta of ≥ the mean value of all hospitals in 2019 versus 2016 will be considered as distinctive high.

A waterfall plot is used to show percentage of patients receiving NST for stage 2 breast cancer in 2019 and 2016 per hospital. StataSE17 (StataCorp LLC, Texas, USA) was used for descriptive statistical analyses. Microsoft Excel 2016 was used to create the plots.

Results

Between 2016 up to and including 2019, 75,636 women aged ≥18 years were diagnosed with invasive breast cancer and/or in situ malignancy in the Netherlands. In this time period, 10,663 patients with clinical stage 2 breast cancer aged <70 years received systemic therapy in the neoadjuvant and/or adjuvant setting in 78 Dutch hospitals. The percentage of these patients that received NST (neoadjuvant chemotherapy with or without adjuvant chemotherapy) are shown in the funnel plots per year (Figure 1). The mean percentage of NST usage was 60.3% in 2016 and the percentages raised to 66.3%, 73.1% and 76.0% in 2017, 2018 and 2019, respectively. To illustrate the added value of data-driven CDT evaluation of cancer care to regular evaluation, two hospitals are marked as A and B. The data from these two hospitals will be described in more detail.

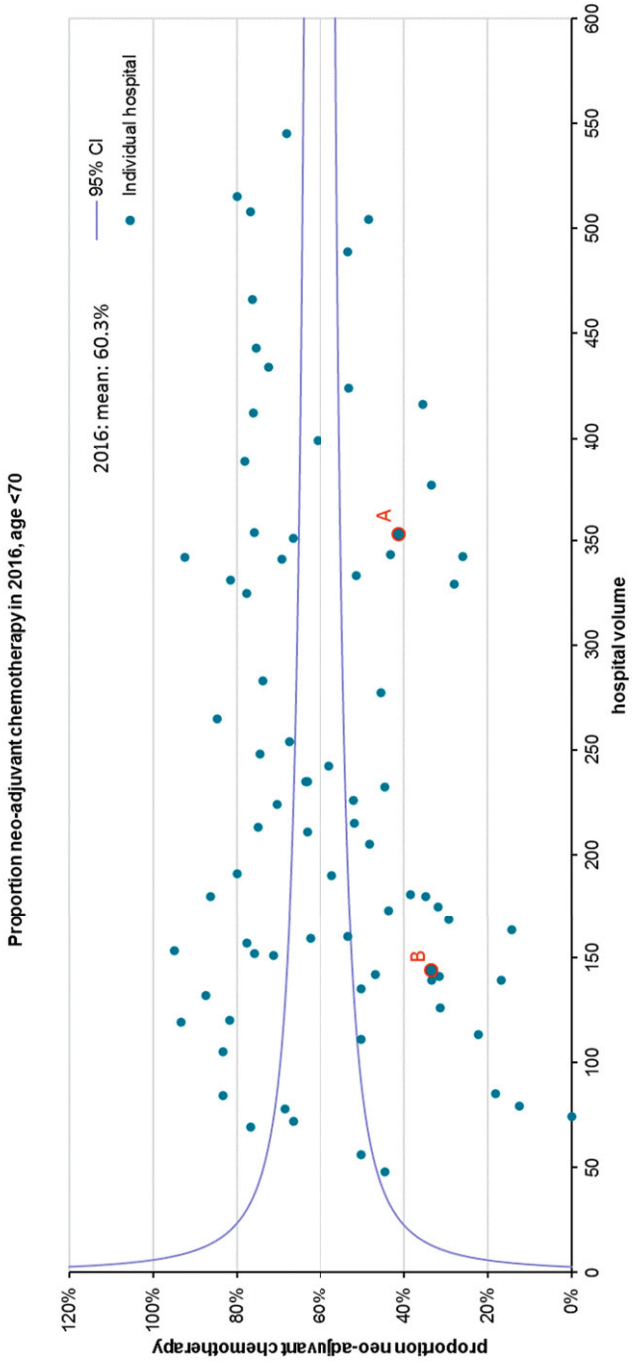

Proportion neo-adjuvant chemotherapy in 2016, age <70
2016: mean: 60.3%
95% CI
Individual hospital
A
B
proportion neo-adjuvant chemotherapy
120%
100%
80%
60%
40%
20%
0%
hospital volume
0
50
100
150
200
250
300
350
400
450
500
550
600

Figure 1A

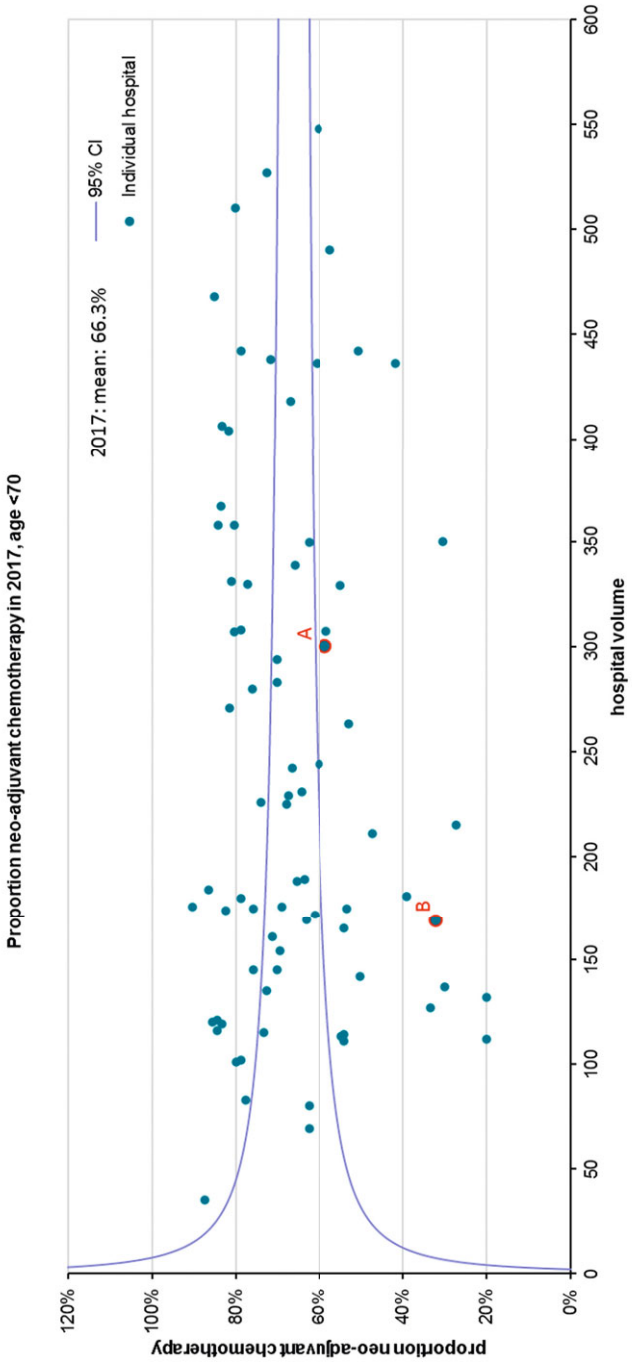

Proportion neo-adjuvant chemotherapy in 2017, age <70
2017: mean: 66.3%
95% CI
Individual hospital
A
B
proportion neo-adjuvant chemotherapy
120%
100%
80%
60%
40%
20%
0%
hospital volume
0
50
100
150
200
250
300
350
400
450
500
550
600

Figure 1B

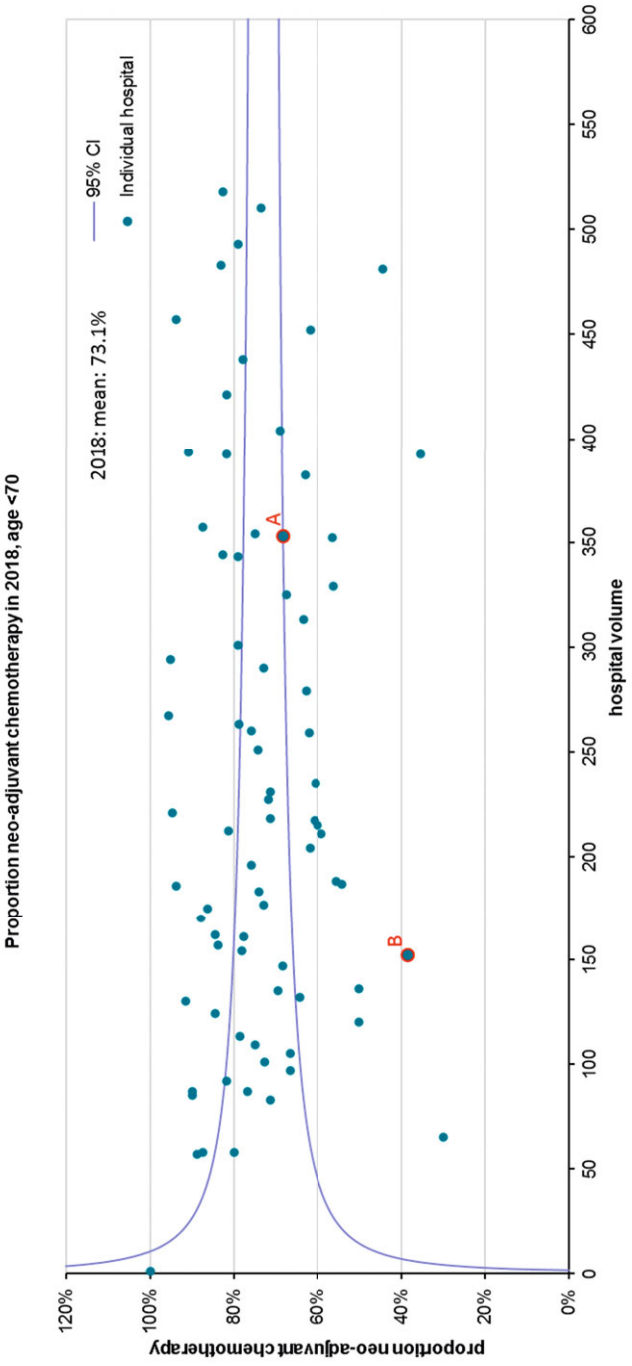

Proportion neo-adjuvant chemotherapy in 2018, age <70
2018: mean: 73.1%
95% CI
Individual hospital
A
B
proportion neo-adjuvant chemotherapy
120%
100%
80%
60%
40%
20%
0%
hospital volume
0
50
100
150
200
250
300
350
400
450
500
550
600

Figure 1C

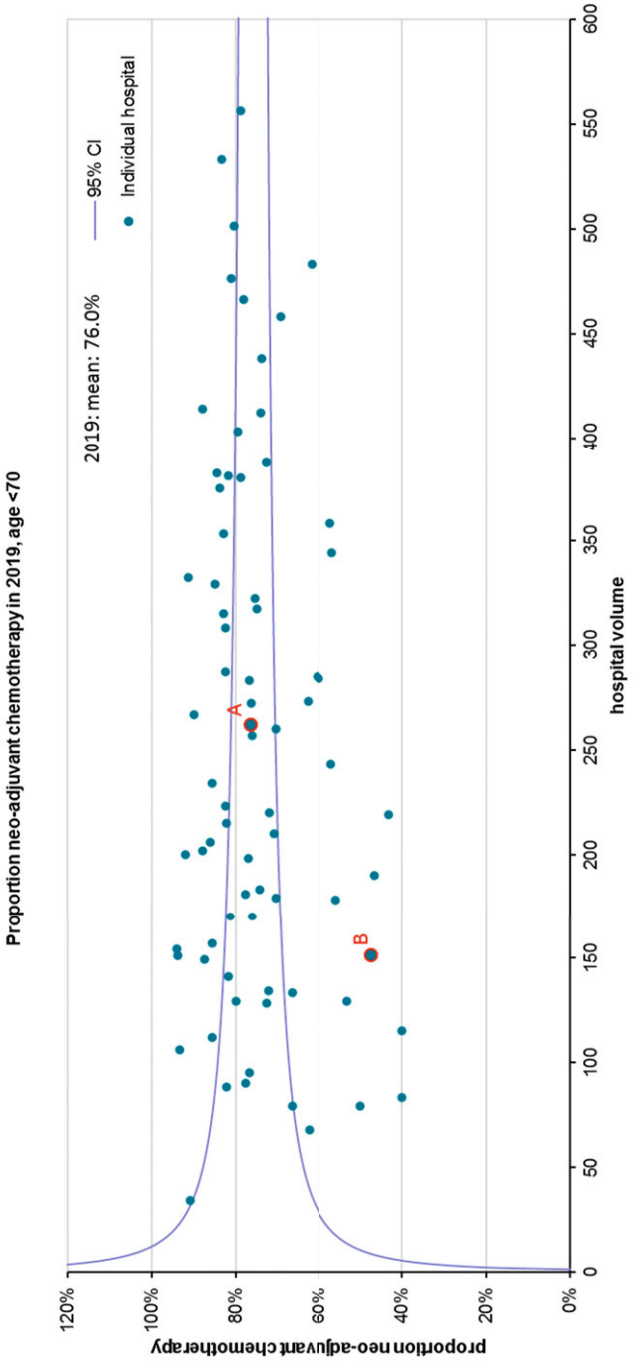

Proportion neo-adjuvant chemotherapy in 2019, age <70
2019: mean: 76.0%
95% CI
Individual hospital
A
B
hospital volume
0
50
100
150
200
250
300
350
400
450
500
550
600
proportion neo-adjuvant chemotherapy
120%
100%
80%
60%
40%
20%
0%

Figure 1D

Figure 1 Funnel plots showing patients with stage 2 breast cancer aged <70 years who received systemic therapy, with on the y-axis the percentage of patients who received NST (plus or minus adjuvant systemic therapy) of all patients who received systemic therapy. On the x-axis the mean hospital volume for 2016 – 2019 (including invasive breast cancer and in situ malignancies). The data of the marked hospitals A and B are further detailed in Figures 2 and 3.Due to the bankruptcy of three hospitals, there are still 75 hospitals left in 2019 for which data is available.

To further investigate the change in NST usage in stage 2 breast cancer, the percentage NST-delta was determined for each hospital comparing 2019 with 2018, 2017 and 2016. A percentage NST usage of ≥ 0.76 (mean value in 2019) and a percentage NST-delta of ≥ 0.187 (mean value in 2019) were considered as high. Based on the percentage NST and the percentage NST-delta before and after the guideline update, hospitals were categorized into four groups: 1) early innovators (hospitals with already high %NST usage which remained high, low delta); 2) good adopters (hospitals showing an increase of %NST usage after 2018 ending with high NST usage, high delta); 3) slow adopters (hospitals with low %NST usage that remained low , low delta); and 4) laggards (hospitals with low %NST usage with moderate increase, high delta). Figure 2a shows the individual data from an example hospital for each category. Figure 2b shows a waterfall plot with the adoption patterns of NST usage in clinical stage 2 breast cancer in all 78 hospitals.

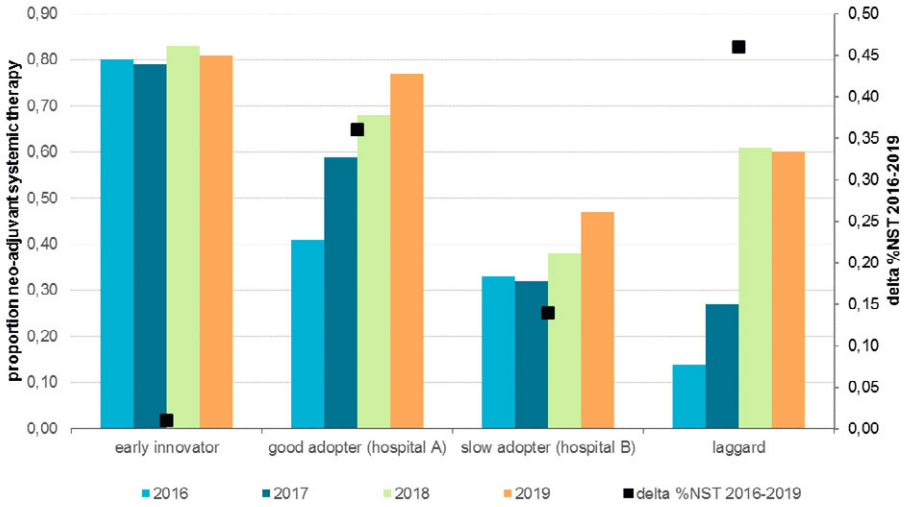


Figure 2. Adoption patters of %NST usage in stage 2 breast cancer in The Netherlands in 75 hospitals.

Figure 2a shows the data from an example hospital for each category: an early innovator (%NST usage high, low delta %NST-delta), a good adopter (%NST usage and %NST-delta usage both high; hospital A), a slow adopter (%NST usage and %NST-dela usage both low; hospital B), and a laggard (%NST usage low and %NST-delta usage high).

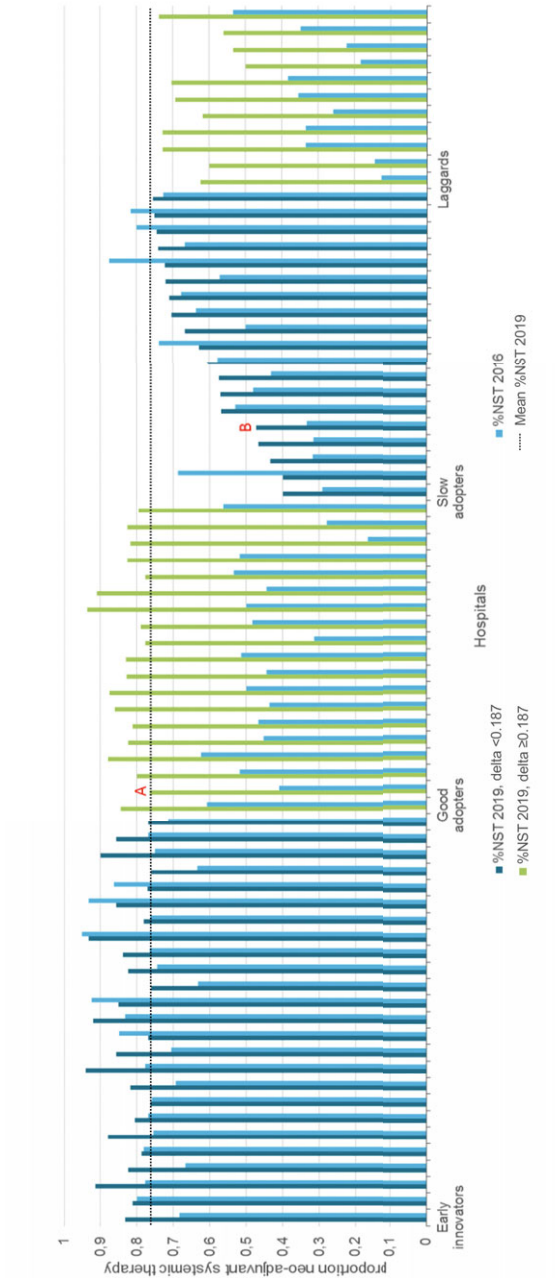


Figure 2b:

shows a waterfall plot with on the y-axis the percentage NST usage for stage 2 breast cancer in 2019 and 2016 and on the x-axis all individual hospitals sorted from high to low percentage NST usage subdivided into the four adoption patterns. Of all hospitals, 33% could be classified as early innovators, 25% as good adopters, 25% as slow adopters and 16% as laggards*. Low percentages NST-delta (<0.187) are shown in dark blue and high percentages NST-delta (≥0.187) in green.
*percentages do not equal 100 due to rounding.

NCR data projection on CDTs

The final step was to project the NCR cancer registry data of all stage 2 breast cancer patients diagnosed in 2016 - 2019 who received systemic therapy in neoadjuvant and/or adjuvant setting in the Netherlands onto the CDT "primary treatment" to show shifts in treatment patterns on national and individual hospital level (Figure 3). All data-items needed to complete the CDT were available in the NCR. Figure 3 shows the mean data of all hospitals in comparison with the data of individual hospital A (an example of a good adopter) and hospital B (an example of a slow innovator). The CDT provides insight into how the cancer care provided by an individual hospital compares to the national average (the benchmark) for all stage 2 breast cancer patients.

Discussion

NCR data revealed hospital variation in the uptake of the guideline recommendation. Based on the %NST expressed in funnel plots and the %NST-delta, the change in adherence over time could identify hospitals as early innovator, good adopter, slow adopter or laggard. CDTs encode real-world practice data and elucidated real-world treatment patterns on hospital level. We have shown that it is feasible to project NCR data on computer interpretable CDTs in Oncoguide. By the data-driven structure of CDTs, this projection can be repeated with any desired frequency, which makes monitoring of currently provided breast cancer care possible in daily practice. This means that CDTs can be used to pinpoint clinical decisions in the care path where recommendations are changing, which can generate hypotheses and help guideline committees to conduct a targeted guideline revision. When CDTs are implemented in daily care, the data captured by CDTs can directly be transferred to the NCR and used to perform the analyses described, without waiting time till data managers have captured clinical data from individual hospitals into the NCR. This can speed up the identification of slow adopters or laggards, and create an early window of opportunity to stimulate adoption of best practices and equalize the quality of care.

CDTs give insights in real-world treatment patterns for all subpopulations

This real-world data-driven feedback from actually delivered care illustrates how implementation of CDTs can support the transition towards a self-learning healthcare system. To our knowledge, the CDT methodology is the first described clinical decision support system that has potentially all properties to support a self-learning healthcare system: the uniform encoding of patient data, disease characteristics, guidelines and MDT recommendations. Further, CDTs have the functionality to guide MDTs (by generating a multidisciplinary advice), to register the actually delivered care in a uniform way, to register reasons for guideline deviations (treatment alternatives) and to analyze these real-world data. The CDT methodology is scalable across other cancer types and diseases.[6,9,10] Where most cancer care evaluation studies focus on one specific subpopulation, the data-driven CDTs can give insights in real-world treatment patterns at any decision point in the care path for all subpopulations.

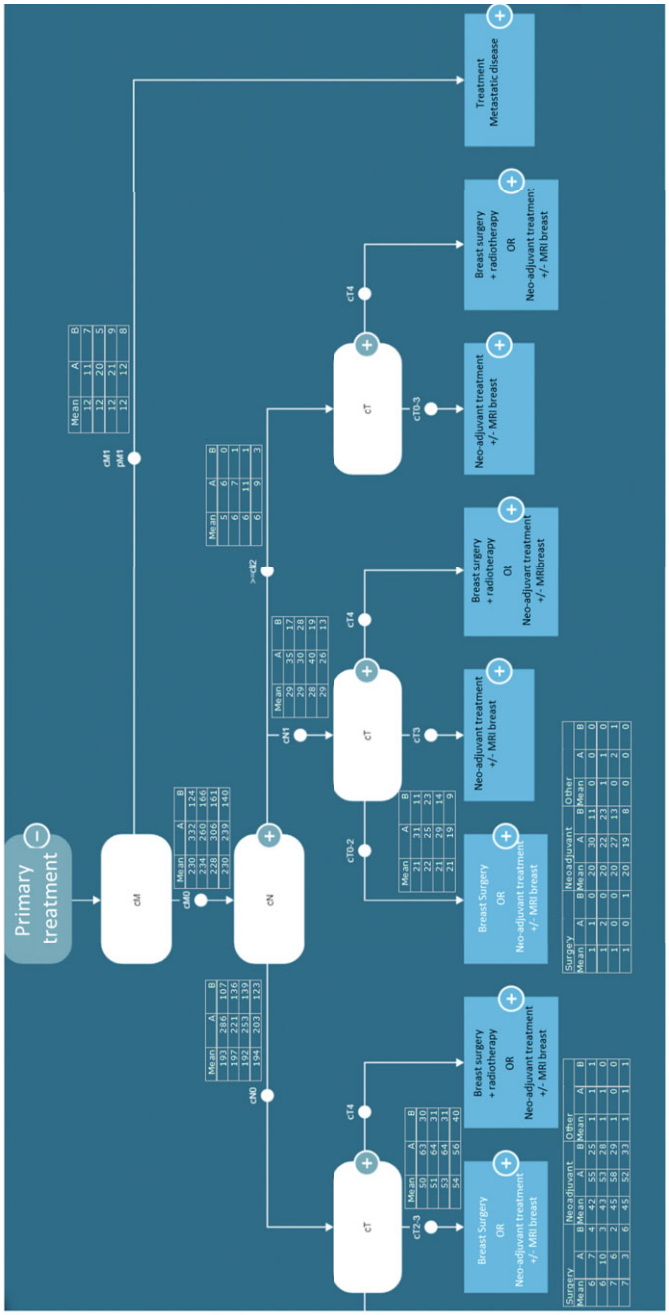


Figure 3. NCR data projection on the CDT "primary treatment" in Oncoguide.

For each data-item (node, white boxes), data cut-off value (branch) and recommendation (leaf, blue rectangles) the mean values are shown for all hospitals in year 2016-2019, and the data for individual hospital A and B. Note that Oncoguide represents the clinical practice guideline, and the projection of NCR data on the CDT shows how the clinical stage 2 breast cancer patients were treated in real-world.

Implications for daily care

CDTs encode real-world data and deliver a signaling tool to detect variations in treatment patterns, without judgement, and can provide input for discussions within multidisciplinary teams on best practices. As we have shown, CDTs can be used to benchmark real-world treatment patterns between hospitals. Variations in these patterns may reflect the availability and implementation of new scientific knowledge, or well-considered choices by clinicians and patients to opt for a more suitable treatment based on factors not (yet) included in current guidelines. The latter groups matters especially to *similar patients* (digital twins), as these patients can be better informed about outcomes of well-considered alternative treatment options, both regarding outcomes such as survival and health-related quality of life. To learn more from hospital A (early innovator) and B (slow adopter) it would be interesting to know motivations for preferring neoadjuvant versus adjuvant systemic therapy. Information on shared decision making and patients choice could be helpful in this. The comparison of outcomes for different interventions in a certain population (PICO methodology: Population, Intervention, Comparison, Outcome), is also valuable for guideline working parties.[11] It may generate hypotheses that require further investigation.

Real-world data and evidence: role for CDTs

Real-world data is receiving more attention to generate real-world evidence which can complement to and strengthen the evidence obtained from randomized clinical trials.[12,13] Real-world data itself can be used for research purposes, for example to identify clinical decisions that are more often deviated from. A call is also made to be able to evaluate clinically relevant questions at low cost in populations as treated in daily practice.[14] For example, since policy between hospitals varies on duration of treatment with anti HER2 agents in subgroups with a lower risk profile, outcomes of a shorter treatment could be evaluated .

However, there are challenges to the use of real-world data and subsequent generated real-world evidence. This includes data relevance (also in relation to confounding factors) and data reliability.[15] Further there is a need for the timely availability of these data.[16] CDTs contain only those data-items, that are relevant for making guideline-based decisions. In the CDTs, these data-items are defined in a standardized way using international classification systems to facilitate data interoperability with clinical decision support systems like Oncoguide or data sets of other patient cohorts.[6] The systematically structured design of CDTs enables capturing of all necessary data within the CDT, and data analyses using CDTs can be repeated with any desired frequency. However, the standardized reporting of relevant data for decision-making remains an international challenge.[6,16] The European Organisation for Research and Treatment of Cancer (EORTC) propose a standard to assess the quality of real-world data. These data should (1) be fit for purpose (i.e. relevant and reliable data to answer the research question); (2) have good provenance with description of the origin of the data source and all data processing steps; and (3) be transparent (i.e. accessible and understandable data processing).[17] A prerequisite is that (1) all data-items that occur in the CDT are reported unambiguously by all data sources; (2) this data can be captured real-time

during the MDT discussion; (3) the MDT advice is well reported including a motivation when the advice deviates from the CDT recommendation (guideline).

Strengths and limitations

A strength of our study is that we were able to analyze a high volume of real-world data with representation of all patients in an established nationwide population. Because NCR data could be projected on computer interpretable CDTs in Oncoguide automatically, the high continuous repeatability generates added value. Applying Oncoguide for real-world treatment patterns enables next steps in precision medicine, for example to generate hypotheses about and finally explore outcomes of patient sub-populations treated differently than expected. A limitation of our study is its retrospective design. Although the methodology was suitable regarding our aims, the concept of CDTs as a self-learning healthcare system needs to be studied further in prospective studies after the prerequisites as mentioned above are solved. Especially a prospective registration of reasons for actually delivered treatment not in concordance with guidelines will add value, for patients and guideline working parties. These data were unavailable in our retrospective analysis.

Conclusion

The data-driven structure of clinical decision trees can be used to monitor the full spectrum of real-world breast cancer care by projecting national cancer registry data onto these trees. The CDT methodology is unique because it systematically encodes patient journeys in a data-driven manner, supporting multidisciplinary teams with guideline-based recommendations and reporting. The encoded real-world data of patient and disease characteristics captured by CDTs can provide valuable feedback for individual hospitals, guideline working parties and patients. In this way CDTs transform into a self-learning healthcare system as they (1) support MDT decision-making for individual patients; (2) can register treatment patterns on hospital level; and (3) can provide aggregated real-world data of actually delivered breast cancer care generating real-world evidence which can complement to the evidence obtained by randomized clinical trials. Future challenges are implementation of standardized reporting of data, availability of these data during MDT meetings and structured MDT reporting of recommendations including reasons for guideline deviation.

Acknowledgement

We thank the data managers of the NCR for their contribution to the study by supplying the dataset, and thank Miss L. Folkert for support in the creation of the figures.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Reference list

1. Panella M, Marchisio S, Di Stanislao F. Reducing clinical variations with clinical pathways: do pathways work? *Int J Qual Health Care* 2003; 15(6): 509-21.
2. Ricci-Cabello I, Vasquez-Mejia A, Canelo-Aybar C, et al. Adherence to breast cancer guidelines is associated with better survival outcomes: a systematic review and meta-analysis of observational studies in EU countries. *BMC Health Serv Res* 2020; 20(1): 920.
3. Huang RS, Mihalache A, Nafees A, et al. The Impact of Multidisciplinary Cancer Conferences on Overall Survival: A Meta-Analysis. *J Natl Cancer Inst* 2023.
4. Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. *Cancer* 2006; 106(11): 2452-8.
5. Hendriks MP, Jager A, Ebben K, van Til JA, Siesling S. Clinical decision support systems for multidisciplinary team decision-making in patients with solid cancer: Composition of an implementation model based on a scoping review. *Crit Rev Oncol Hematol* 2024; 195: 104267.
6. Hendriks MP, Verbeek X, van Vegchel T, et al. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. *JCO Clin Cancer Inform* 2019; 3: 1-14.
7. National Cancer Registry, enabled by the Netherlands Comprehensive Cancer Organisation (IKNL), the Netherlands. https://iknl.nl/en.
8. Medicine Io. Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. Washington, DC: The National Academies Press; 2013.
9. Keikes L, Kos M, Verbeek X, et al. Conversion of a colorectal cancer guideline into clinical decision trees with assessment of validity. *Int J Qual Health Care* 2021; 33(2).
10. Ebben K, de Kroon CD, Schmeink CE, et al. A novel method for continuous measurements of clinical practice guideline adherence. *Learn Health Syst* 2023; 7(4): e10384.
11. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc* 2006; 2006: 359-63.
12. Saesen R, Van Hemelrijck M, Bogaerts J, et al. Defining the role of real-world data in cancer clinical research: The position of the European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2023; 186: 52-61.
13. Dreyer NA. Strengthening evidence-based medicine with real-world evidence. *Lancet Healthy Longev* 2022; 3(10): e641-e2.
14. Leary A, Besse B, Andre F. The need for pragmatic, affordable, and practice-changing real-life clinical trials in oncology. *Lancet* 2024; 403(10424): 406-8.
15. Castellanos EH, Wittmershaus BK, Chandwani S. Raising the Bar for Real-World Data in Oncology: Approaches to Quality Across Multiple Dimensions. *JCO Clin Cancer Inform* 2024; 8: e2300046.
16. Berger ML, Ganz PA, Zou KH, Greenfield S. When Will Real-World Data Fulfill Its Promise to Provide Timely Insights in Oncology? *JCO Clin Cancer Inform* 2024; 8: e2400039.
17. Ramsey SD, Onar-Thomas A, Wheeler SB. Real-World Database Studies in Oncology: A Call for Standards. *J Clin Oncol* 2024; 42(9): 977-80.

PART V

Summary & general discussion

CHAPTER 7

Viewpoint: self-learning evidence-based data-driven decision support for multidisciplinary clinical decision-making and reporting in breast cancer

Mathijs P. Hendriks, Agnes Jager, Sabine Siesling

Abstract

Multidisciplinary teams (MDTs) are challenged to make guideline-based recommendations for individual patients in a landscape of rapidly increasing knowledge and rise of personalized medicine. However, patients do not always resemble the study populations treated in clinical trials and may receive alternative treatments for deliberate medical reasons or patient preferences. To learn from patients treated in daily practice, there is a need for reliable, high quality, well-structured and unambiguously defined clinical data to compare real-world outcomes of care in a reliable way. Therefore, a platform is needed for registering, processing, sharing and analyzing of these data. We propose clinical decision trees (CDTs) as a novel platform for a self-learning healthcare system. CDTs are a compact digitally accessible data-driven representation of textual clinical practice guidelines that follow the clinical care path. We summarize the development of CDTs for guideline-based multidisciplinary decision support and position CDTs as a novel platform for guideline-based MDT decision-support, standardized registration of actually delivered care, real-time data interoperability between different data-sources, monitoring of actually delivered care and generation of real-world evidence aiming to better inform patients and improve the quality of care. This high quality real-world data may generate evidence that is complementary to evidence obtained in randomized controlled trials.

Introduction

Clinical practice guidelines

Clinical practice guidelines are defined as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options".[1] This is in line with the PICO system, to represent and answer clinical questions systematically in an evidence-based way. For a certain population (P) different interventions (I) can be compared (O) with regard to outcomes (O).[2] The amount of medical knowledge is increasing rapidly: in 2023 there were 30.385 publications about breast cancer in PubMed, versus 24.937, 20.194 and 13.806 in 2018, 2013 and 2008 respectively.[3] This knowledge should be applied for even more-specific patient populations as (breast) cancer treatment is more and more personalized.[4] Traditionally, clinical practice guidelines have been developed as large textual documents describing knowledge based on literature and present recommendations with level of evidence. Important drawbacks of these guidelines are being unwieldly and complex because the chapters do not follow the clinical care path and subsequent decisions, which hinders real-time usage for decision support during multidisciplinary team (MDT) meetings. Moreover, the updating process of textual guidelines is slow, increasing complex and therefore leads towards outdated guidelines unpractical in use.[4] Finally, guideline recommendations based on clinical trial populations may not be applicable to all patients in daily practice as these patients do not all resemble to these populations. For these reasons, a more suitable methodology of building guidelines is required to speed up the process of guideline updating and target relevant evidence to these populations.

Multidisciplinary decision-making

MDTs are the corner stone of clinical decision-making in solid cancer.[5] MDTs base their recommendations for diagnosis and treatment of cancer on available clinical and personal patient data at time of the meeting, clinical practice guidelines and personal experience. In general, adherence to clinical practice guidelines improves the quality of care and overall survival, and is therefore essential.[6-8] Monitoring adherence of guideline recommendations in daily practice can give insight in feasibility of implementing the recommendation, can support adjustment/improvement of the recommendation and can support benchmarking and improving quality of care.

Deliberate deviations from the guideline can be in the patient's interest. For example, MDTs can make recommendations based on new knowledge which is not yet incorporated in the guideline, or patients may opt out for the preferential guideline-based treatment and choose an alternative option due to their personal circumstances or preference. Lessons can be learned from the arguments for and outcomes of the deviations, and these real-world data may add knowledge to the classical evidence obtained by randomized clinical trials.[9,10] Decisions made for the patient at this moment in time should preferably be based on the most recent evidence to become optimal data-driven clinical decisions.

Data-driven clinical decision support

To optimize implementation of more data-driven clinical decision support for multidisciplinary decision-making there are four important challenges: the availability of 1) compact digitally accessible data-driven guideline-based MDT decision support, 2) standardized registration of actually delivered care which means availability of reliable, high quality, well-structured and unambiguously defined clinical data 3) real-time data interoperability between different data-sources, and 4) monitoring for comparing real-world outcomes of care in a reliable way to learn from actually delivered care aiming to better inform patients and improve the quality of care.

In this viewpoint we describe where we currently stand in implementing data-driven multidisciplinary clinical decision support for breast cancer. We summarize the development of clinical decision trees (CDTs) for guideline-based multidisciplinary decision support. CDTs are a compact digitally accessible data-driven representation of textual clinical practice guidelines that follow the clinical care path. We propose CDTs as a novel platform for guideline-based MDT decision-support, standardized registration of actually delivered care, real-time data interoperability between different data-sources, monitoring of actually delivered care and generation of real-world evidence aiming to better inform patients and improve the quality of care. In this way, CDTs enable a self-learning healthcare system.

Translation of textual guidelines into compact data-driven ones

In 1994, Shiffman described a method to improve clinical practice guidelines with logic and decision-table techniques.[11] Starting from 2007, a French group published several articles about local guideline-based decision rules formulated by "if-then"

rules aiming to support decision-making during MDT meetings.[12,13] Guidelines such as those of the National Comprehensive Cancer Network (NCCN) are displayed as compact guideline-based "if-then" algorithms or flowcharts to provide guidance for clinical decision-making. However, all these initiatives were not using a fully data modulated methodology, meaning that not all (possible) combinations of patient/disease characteristics and subsequent guideline recommendations were covered.[4] Further, these algorithms lacked the capability of interoperability with data sources on patient level such as the electronic health record or a national cancer registry for capturing these data directly into these algorithms. Therefore, the methodology of data-driven clinical decision trees (CDTs) has been developed (**Chapter 3**): a scalable method to transform textual guidelines into systematically designed, modular, data-driven CDTs. CDTs are constructed by nodes, branches and leaves covering systematically all possible combinations of patient/disease characteristics within the CDTs (figure 1).[4]

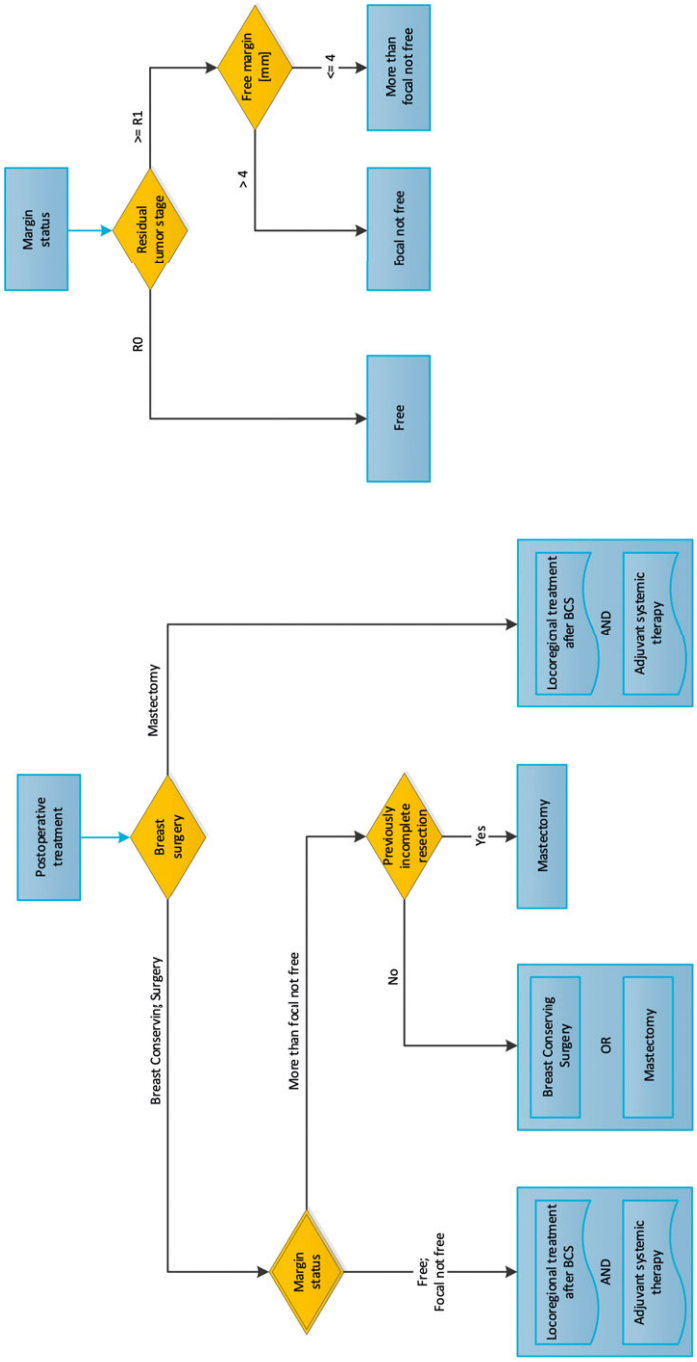


Figure 1 (adopted from Hendriks et al. JCO CCI 2019[4]): Example of a clinical decision tree.

A path through a CDT follows "nodes" via "branches" that represent patient- and/or disease characteristics (i.e. data-items) and data-item values respectively, resulting in a "leaf" representing a guideline recommendation. In each CDT, there are one or more possible routes to reach one of the leaves, each of them representing a specific patient subpopulation. All data-items and data-item values are described unambiguously, using international classification systems when possible.
(A) The top rectangle reflects the trunk of the CDT postoperative treatment. The rhombuses reflect the nodes and represent the data items. The branches define the cutoff values, which lead to additional nodes (rhombuses) or guideline recommendations (bottom rectangles; a delineated recommendation [rectangle with a curly bottom] means referral to another CDT, such as locoregional treatment after breast-conserving surgery[BCS]). (B) Note the node 'margin status', which can be unfolded to define the value of margin status.

The next step was to evaluate whether a clinical guideline could be transformed into data-driven CDTs. The Dutch guideline "breast cancer", developed by the National Breast Cancer Consultation Netherlands (NABON), was successfully converted into CDTs. Interestingly, only 114 data-items were needed to describe the guideline in CDTs that covered 376 unique subpopulations (i.e. unique routes through the CDTs).[4,14] Of all data-items, 101 (89%) could be classified by existing classification and coding systems such as TNM, BIRADS and SNOMED CT.[15-17]. Ten of the remaining 13 data-items were too ambiguous to be classified. All CDTs were integrated in an interactive decision support app (Oncoguide, www.oncoguide.nl/#!/projects/7/guideline) aiming to enable interoperability with data sources from the electronic health record for real-time data-driven decision support.[4,18]

For optimal use of Oncoguide during MDT meetings, availability of required data to complete the CDT is a prerequisite. Furthermore, this data must be standardized and should be reported in such way, that these data can be reused for clinical decision support system (CDSS) implementation, auditing parties and monitoring of actually delivered care. Finally, due to the modular design of CDTs, modular guideline revision is easily possible to specifically implement new available knowledge into the guideline.

Verification, analytical validation and clinical validation of CDTs

A CDSS is defined as a system intended to improve healthcare delivery by enhancing medical decisions with targeted clinical knowledge, patient information, and other health information.[19] To determine the fitness for purpose of the digital accessible CDTs (Oncoguide) as CDSS, the three steps as proposed by Goldsack *et al.* were followed.[20] The CDTs in Oncoguide were verified by all members of the Dutch breast cancer guideline committee. Oncoguide was classified as a medical device and received a CE mark. The second step involves analytic validation. For this Oncoguide was evaluated retrospectively in a single-center study (**Chapter 4**), and investigation of four pivotal CDTs (chosen for their clinical relevance) showed that some data-items and treatment alternatives were underreported, stressing the importance of standardized reporting of needed data.[21] This requires (inter)national agreement from guideline working parties regarding the definitions and coding of all data-items and data-item values that are used for guideline recommendations, which together form the information standard. Introduction of standardized MDT reporting forms making use of this standard resulted

indeed in improvement of quality of MDT documentation, without increasing clinical workload.[22] For implementing guideline-based clinical decision support during MDT meetings, it is essential that relevant data for decision-making are available during these meetings.

The third step is clinical validation. A prospective, multi-center, observational, cross-sectional study with Oncoguide (**Chapter 5**) investigated seventeen CDTs (for breast-, colorectal- and prostate cancer). For 294 of 355 included unique cases (83.4%) all patient data were available for providing a CDT recommendation. Of these 294 cases, the MDT recommendations were concordant in 249 (84.1%) cases, conditionally concordant in 24 (8.1%) cases and non-concordant in 23 (7.8%) of cases. In nearly one third of these non-concordant cases the MDT did not motivate the reason for guideline deviation. Further, there was no trend between CDT complexity and concordance. These data indicate a potential role for implementation of CDTs to support MDTs.[23] After the completion of the three mentioned steps, further studies regarding the implementation of CDT usage in daily practice are needed.

Data-driven clinical decision support for breast cancer MDTs

A scoping review (**Chapter 2**) focusing on the currently reported CDSSs for MDT decision-making in solid cancer, and facilitators and barriers for CDSS implementation, included 44 papers describing 20 different CDSSs. The most frequently reported CDSSs were Watson for Oncology, OncoDoc 2, GL-DSS and Oncoguide.[24] WFO used a cognitive computing system which used artificial intelligence algorithms to generate treatment recommendations as knowledgebase, the other three CDSSs used decision trees as knowledgebase. Importantly, Watson for Oncology was not trained with real patient data and recommendations were based on expertise of a single center. The other three CDSSs were trained with real patient data and recommendations were based on local or national guidelines. The latter methodology is more in line with evidence-based medicine. The main objective of most studies included in the scoping review was to evaluate the concordance rate between CDSS and MDT generated recommendations, and only four studies compared concordance rates in both the situations where the CDSS was or was not used (control arm).[24]

The scoping review identified 188 reported barriers and facilitators for CDSS implementation, and the most frequently reported categories of barriers and facilitators included: CDSS maintenance (e.g. incorporating guideline updates), CDSS validity of recommendations, loco-regional feasibility of recommendations (e.g. availability and reimbursement of recommended drugs), CDSS usability, CDSS interoperability (with the electronic health record for instance) and the information standard used (i.e., usage of consequent and equivocal definitions). Based on the most important categories, an implementation model was composed describing clinical utility, analytic validity and clinical validity to guide CDSS integration at the point of care more successfully, aiming to better support MDTs (figure 2).[24]

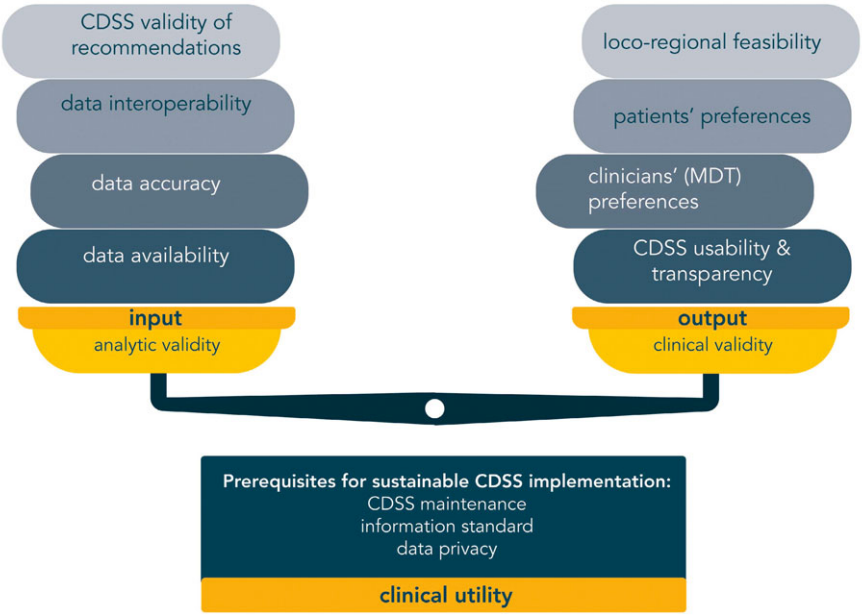


Figure 2 (adopted from Hendriks et al. CROH 2024[24]): A CDSS implementation model. The left side of the scale reflects the analytic validity of the input of the CDSS: necessary data for the CDSS need to be available, accurate and interoperable between data sources (e.g. electronic health records) and the CDSS. The generated recommendations by the CDSS need to be valid (e.g. they should adequately adhere to the reference database of the CDSS such as a guideline). The right part of the scale represents the clinical validity of the CDSS: is the CDSS usable and transparent? Can preferences of the MDT and the patient be integrated? Are the generated recommendations of CDSS locally feasible in the clinic? The bottom of the scale shows the prerequisites for sustainable CDSS implementation: the maintenance (i.e. governance, regular updating the CDSS), an information standard (to preserve that the right data are processed at the input level of the CDSS) and data privacy (to comply with international standards like the General Data Protection Regulation). And "clinical utility" at the very bottom reflects the validity of the CDSS as a whole.

Learning from systematically data-driven registration of real-world breast care

It is important to be aware of actually delivered care in daily practice and how this relates to the expected care that should have been provided according to current clinical practice guidelines. Disadvantages of classic (retrospective) guideline adherence studies includes the long lead time between the moment of actually delivered care and the research outcomes of guideline adherence. Consequently, it is not possible to analyze real-time the reasons for certain types guideline deviations and to assess whether a targeted adjustment to improve the guideline is appropriate. To overcome the shortcomings, the data-driven design of the CDT methodology can be used for mapping Netherlands cancer registry data onto de CDTs (**Chapter 6**).[25]

It has proven possible to analyze trends in detail regarding guideline adherence for specific decisions using the data-driven design of the CDT methodology. With continuous monitoring of actually delivered care using CDTs, trends in deviations for certain recommendations can be picked up early, analyzed (using the PICO methodology and following the principles of the PDCA cycle of Deming to manage change), discussed e.g. on hospital or network level and improve quality of care.[2,26] Early adopters of new knowledge may for instance deliberately deviate from the guideline when they believe that the guideline recommendation is outdated. This feedback can also help guideline committees to perform modular guideline revisions which can promote timely implementation of new knowledge. In case of slow adoption or unwanted practice variation, hospitals can receive transparent feedback, which for example can be discussed during regional tumor working groups meetings or by national organizations such as NABON or NBCA (NABON Breast Cancer Audit).[18,27]

Thus, CDTs can generate an advice for individual patients. Further, CDTs can support the systematically registration of clinical data (for example in Oncoguide) and on a aggregated level CDTs can disclose which treatments have been provided to a group of patients. Especially when MDTs (and treating clinicians) will register why they deviate from a guideline-based recommendation, then there will be prospectively systematically recorded data available from daily clinical practice. Therefore, the CDT methodology offers a method to convert clinical information into systematically reported reusable high quality data. By learning from these real-world care data CDTs transform into a learning healthcare system following the principles of the PICO methodology (figure 3).[2] For the latter, solid outcomes as overall survival and soft outcomes such as health-related quality of life can apply. This may contribute to effective care according to the principles of value-based healthcare.[28]

Evidence-based decision support for MDTs: from current practice towards a novel conceptual data-driven model

In current practice of guidelines in relation to care, MDT decision-making is guided by evidence obtained from randomized clinical trials and consensus based evidence captured in clinical guidelines (figure 3a). Based on accumulated individual patient data (patient and disease characteristics) MDTs formulate diagnostic and treatment recommendation. The MDT advice is discussed with the patient, and by applying shared decision-making this results in actually delivered care. Important to note that actually delivered care data does not influence guideline development in current practice.

Here we propose a novel data-driven model with CDTs as platform for a self-learning healthcare system following the principles of the PICO system (figure 3b). The rule based evidence that is captured in clinical practice guidelines is transformed into data-driven CDTs by encoding all data-items and data-values in an unambiguous way.[4] For each individual patient decision, the CDTs lead to a guideline-based recommendation(s) with intervention(s). However, MDTs and patients may deliberately deviate from this recommendation and reasons for this can be registered, for instance using categories like explicit patient wish, comorbidity etc. In this way, encoded data are generated both about the expected care based on the guideline and the actually delivered care.

This feedback from real-world based care may provide evidence for guideline working parties to generate hypotheses or guideline revisions.

Facilitators for implementation of data-driven multidisciplinary care

To bring data-driven care a step further, implementation of CDTs could be a solution. The methodology of CDTs is suitable for setting clinical practice guidelines in a transparent and unambiguously manner. When guideline committees agree on which data-items are essential for taking a certain decision, then the corresponding CDT will have to contain these data-items and support in this way the structured gathering of uniform data. To learn from actually delivered care in practice, CDTs can provide inside as they can show -for every decision- which population received which care by projecting national cancer registry data onto the CDTs or obtain structured data directly from the electronic health records. This projection can be repeated infinite times, resulting in continuous data-driven monitoring of actually delivered care. Analyzing these patterns of variation can provide valuable feedback to improve the quality of care by encouraging hospitals with a slow adoption of new guideline recommendations and to adjust clinical practice guidelines when early innovating hospitals implement new knowledge more timely. Subsequent assessment should take place into the causes of changing treatment patterns and the level of evidence to justify modular adjustment of the guideline. And if the level of evidence is low, it could be assessed by the Netherlands cancer registry in collaboration with the scientific associations whether a clinical study is necessary to address the knowledge gap. In the future, CDTs could also be used for data registration purposes, including MDT reporting of reasons for recommendations not adhering to current guidelines, and treating clinician reporting of reasons to deviate from MDT recommendations. Further insight into patient groups that have received treatment B (digital twins) instead of treatment A according to the guideline is valuable because the outcomes of those groups, both in terms of survival and quality of life, are important for better informing new patients about the pros and cons of treatment alternatives. Ultimately, a large cohort of patients will emerge with reliable, high-quality data that are suitable for scientific analyzes (including artificial intelligence techniques such as machine learning) to gather real-world evidence in a timely manner. This continuous process of learning from real-world data underlines the value of CDTs as a platform for a self-learning healthcare system.

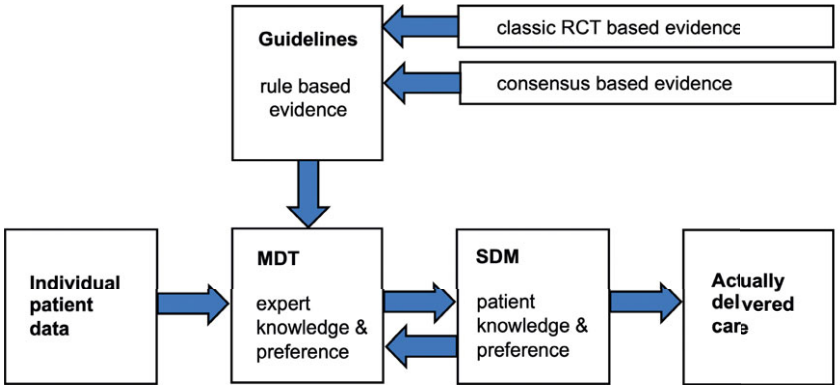


Figure 3A

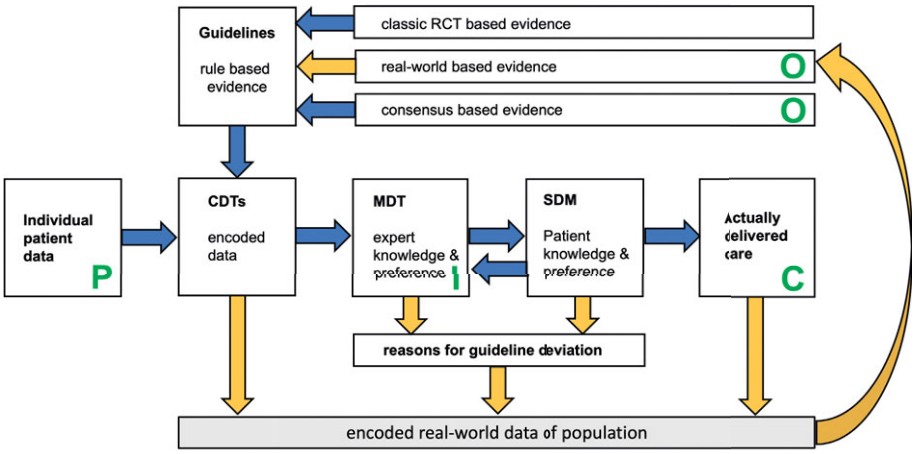


Figure 3B

Figure 3. A conceptual PICO-based model of evidence-based decision support for MDTs using CDTs as platform for a self-learning healthcare system.

Figure 3a shows the current practice of evidence-based decision making by MDTs. Figure 3b illustrates how implementation of CDTs and incorporation of PICO (in green) can transform breast cancer care into a self-learning healthcare system. PICO is the most commonly used model for building structured clinical questions to facilitate literature review for obtaining high-quality evidence. Further, CDTs can follow the PDCA-cycle. Plan stands for the data-driven clinical practice guideline-based recommendations. Do reflects the real-world actually delivered care, as registered by national cancer registries. Check involves projection of real-world data on the CDTs of the clinical practice guideline. And Act involves targeted modular guideline revision by adjusting CDTs of the guideline.
Abbreviations: RCT = randomized clinical trials; MDT = multidisciplinary team; SDM = shared decision-making; CDT = clinical decision tree; P, I, C and O refer to PICO = population, intervention, comparison, outcome.

CHAPTER 7

Conclusion

CDTs are a compact digitally accessible data-driven representation of textual clinical practice guidelines that follow the clinical care path. CDTs can support clinical decision-making in a landscape where scientific knowledge and personalized medicine is increasing rapidly. Prerequisites are the availability of standardized high-quality data, that are reusable and interoperable between different data sources. CDTs provide a methodology for data-driven care, both to support multidisciplinary team decision-making for individual patients as well as for registration and monitoring of actually delivered care. CDTs can elucidate and analyze real-world care based on standardized data in a timely manner, hereby generating real-world evidence which is complementary to evidence obtained from randomized clinical trials. We propose CDTs as a central platform for a self-learning health care system for multidisciplinary clinical decision support, for data registration and for generating feedback to guideline committees based on real-world treatment patterns, aiming to improve the quality and the effectiveness of care.

References

1. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.
2. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc* 2006; 2006: 359-63.
3. PubMed. 2024/02/12. https://pubmed.ncbi.nlm.nih.gov/?term=breast+cancer&sort=date.
4. Hendriks MP, Verbeek X, van Vegchel T, et al. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. *JCO Clin Cancer Inform* 2019; 3: 1-14.
5. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. *Cancer Treat Rev* 2016; 42: 56-72.
6. Panella M, Marchisio S, Di Stanislao F. Reducing clinical variations with clinical pathways: do pathways work? *Int J Qual Health Care* 2003; 15(6): 509-21.
7. Brown GTF, Bekker HL, Young AL. Quality and efficacy of Multidisciplinary Team (MDT) quality assessment tools and discussion checklists: a systematic review. *BMC Cancer* 2022; 22(1): 286.
8. Ricci-Cabello I, Vasquez-Mejia A, Canelo-Aybar C, et al. Adherence to breast cancer guidelines is associated with better survival outcomes: a systematic review and meta-analysis of observational studies in EU countries. *BMC Health Serv Res* 2020; 20(1): 920.
9. Dreyer NA. Strengthening evidence-based medicine with real-world evidence. *Lancet Healthy Longev* 2022; 3(10): e641-e2.
10. Saesen R, Van Hemelrijck M, Bogaerts J, et al. Defining the role of real-world data in cancer clinical research: The position of the European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2023; 186: 52-61.
11. Shiffman RN, Greenes RA. Improving clinical guidelines with logic and decision-table techniques: application to hepatitis immunization recommendations. *Med Decis Making* 1994; 14(3): 245-54.
12. Séroussi B, Bouaud J, Gligorov J, Uzan S. Supporting multidisciplinary staff meetings for guideline-based breast cancer management: a study with OncoDoc2. *AMIA Annu Symp Proc* 2007; 2007: 656-60.
13. Bouaud J, Séroussi B. Revisiting the EBM decision model to formalize non-compliance with computerized CPGs: results in the management of breast cancer with OncoDoc2. *AMIA Annu Symp Proc* 2011; 2011: 125-34.
14. NABON (national breast cancer consultation in the Netherlands).
15. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67(4): 290-303.
16. D'Orsi CJ SE, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology. 2013.
17. SNOMED CT.
18. NABON (national breast cancer consultationin the Netherlands).
19. Osheroff JA, Teich JM, Levick D, et al. Improving outcomes with clinical decision support: an implementer's guide: Himss Publishing; 2012.

20. Goldsack JC, Coravos A, Bakker JP, et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). *NPJ Digit Med* 2020; 3: 55.
21. Hendriks MP, Verbeek X, van Manen JG, et al. Clinical decision trees support systematic evaluation of multidisciplinary team recommendations. *Breast Cancer Res Treat* 2020; 183(2): 355-63.
22. Ebben K, Sieswerda MS, Luiten EJT, et al. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. *JCO Clin Cancer Inform* 2020; 4: 346-56.
23. Ebben K, Hendriks MP, Markus L, et al. Using guideline-based clinical decision support in oncological multidisciplinary team meetings: A prospective, multicenter concordance study. *Int J Qual Health Care* 2022; 34(1).
24. Hendriks MP, Jager A, Ebben K, van Til JA, Siesling S. Clinical decision support systems for multidisciplinary team decision-making in patients with solid cancer: composition of an implementation model based on a scoping review. *Crit Rev Oncol Hematol* 2024; 195: 104267.
25. Ebben K, de Kroon CD, Schmeink CE, et al. A novel method for continuous measurements of clinical practice guideline adherence. *Learn Health Syst* 2023; 7(4): e10384.
26. Deming cycle (PDCA)DEMING CYCLEPlan-do-check act (PDCA)(PDCA). In: Swamidass PM, ed. Encyclopedia of Production and Manufacturing Management. Boston, MA: Springer US; 2000: 155-.
27. NBCA (NABON Breast Cancer Audit). https://dica.nl/registratie/borstkanker-nbca/.
28. Porter ME, Teisberg EO. Redefining health care: creating value-based competition on results: Harvard business press; 2006.

CHAPTER 8

English summary

English summary

One in seven women in The Netherlands will develop breast cancer during her lifetime and the incidence is still increasing. Importantly, breast cancer is a heterogeneous disease. Scientific knowledge is growing fast, and personalized treatment is rising. This is challenge for timely updating of clinical practice guidelines. It is known that guideline-based recommendations by multidisciplinary teams (MDTs) improve the quality of care and overall survival.

However, the current textual clinical practice guidelines are not practical to use in daily practice for the reasons of being extensive and not structured into logical subsequent decisions following the care path. Furthermore, the process of keeping current guidelines up to date is very slow. Therefore, a new methodology is needed to compactly represent the clinical guideline in decision support systems and to support multidisciplinary teams during clinical decision-making. It is also necessary to take steps to improve care by learning from the care provided in daily practice. This so-called real-world data must then be presented in a standardized manner with the aim of supporting practice monitoring and generating data to achieve a self-learning healthcare system.

The first part of this thesis summarizes what is currently known about multidisciplinary clinical decision support systems for clinical decision-making in oncology multidisciplinary team meetings. In the second part, the new methodology of clinical decision trees to support multidisciplinary teams is described and analyzed. In the third part, the clinical decision trees are examined for evaluation of care actually provided nationally, by projecting data from the Netherlands Cancer Registry onto clinical decision trees. The last part contains a general discussion of all the knowledge generated in this thesis. Based on this, a new model for implementation of multidisciplinary evidence-based clinical decision-making is proposed.

Part I: clinical decision support systems for multidisciplinary teams

multidisciplinary teams are the basis where all available data about the patient and the disease, all knowledge and medical disciplines come together and individual treatment plans are drawn up. The treatment is based on many (biomarker) data and is therefore increasingly unique per patient. The guidelines must therefore be drawn up for increasingly smaller and more specific patient populations, making them more complex. Clinical decision support systems (CDSS) can support multidisciplinary teams in their clinical decision-making process.

Chapter 2 is a scoping review describing the currently available CDSS for multidisciplinary decision-making in solid cancer, the experiences with the implementation of CDSS and a proposal for an implementation model. Twenty different CDSS were identified, and only three of these have been further investigated. From the 44 studies included in this review, 102 barriers and 86 facilitators of CDSS implementation were identified. Based on these factors, a CDSS implementation model was developed with the aim of

contributing to a more successful CDSS implementation. The model consists of three important pillars. The first pillar concerns the analytical validity of the input of a CDSS: data availability, data accuracy, data interoperability between data sources and CDSS validity of the recommendations. The second pillar concerns the clinical validity of the CDSS output: usability and transparency of CDSS, physician preferences, patient preferences and locoregional feasibility of recommendations. The third pillar includes clinical usefulness: this sets conditions for CDSS maintenance, information standards and data privacy.

Part II: clinical decision support using clinical decision trees

Guidelines can support the clinical decision-making process. However, the textual format of most guidelines makes them cumbersome and not easy and accessible to use. In addition, guideline texts are often drawn up in ambiguous terms.

Chapter 3 describes the development of a scalable method for presenting textual guideline recommendations. Systematically designed, modular, data-driven clinical decision trees that follow the care pathway were used (Figure 1). The 'trunk' of the clinical decision tree represents the step in the care pathway to which the recommendation applies, for example the advice of the correct primary treatment. The 'nodes' represent patient or tumor characteristics, for example the stage of the tumor (stage T1, T2, T3 or T4). The 'branches' represent further specification of the 'nodes' using cut-off values, for example stage ≤ T2. The 'branches' can lead to other nodes and ultimately end in a 'leaf' that displays patient-specific recommendations based on collected patient data following the route taken by the clinical decision tree. The feasibility of the new clinical decision tree methodology was demonstrated by applying this method to a complex guideline, namely the Dutch breast cancer guideline. Data items comprising the clinical decision tree are unambiguously defined based on international classification and coding systems. This means that the definition of a data item is clearly defined, resulting in a number of fixed values that this data item can assume (for example, tumor stage (cT) 1 includes all tumors with a diameter of up to 20 mm). In this way, interoperability with electronic health records and the implementation of clinical decision trees in CDSSs can be facilitated. A patient with a breast tumor of, for example, 16 mm falls within the decision tree under cT1 and therefore under the branch cT0-2.

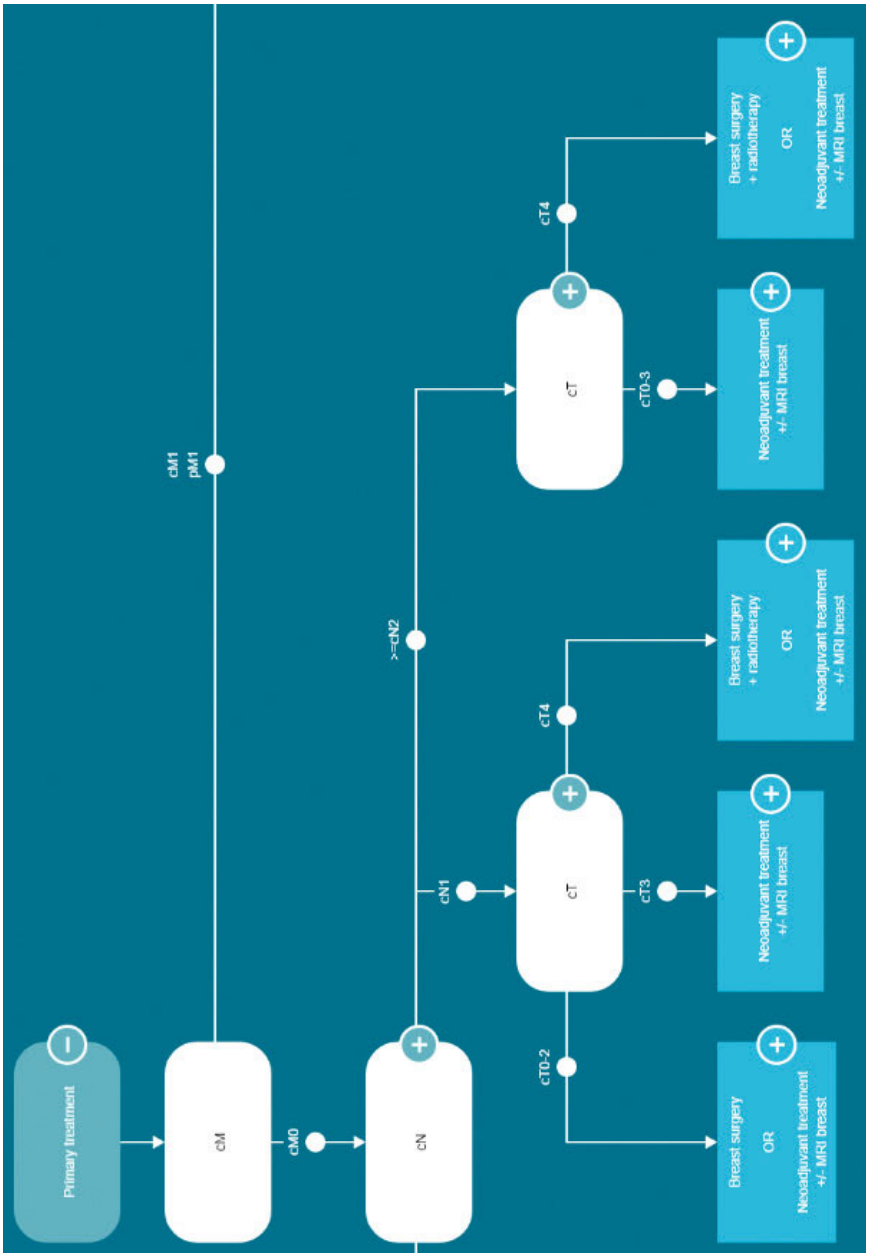


Figure 1: Clinical decision tree 'primary treatment'.

The top left block in the figure shows the trunk ('primary treatment'). The white blocks are the nodes representing the data items cM (distant metastases), cN (lymph node stage) and cT (tumor stage), respectively. The branches describe the values of the node. For example, the tumor stage (cT) can be stages 0 to 2, T3 or T4. Depending on the route through the decision tree (i.e. the combination of clinical data), a recommendation follows at the bottom of the decision tree (in the leaves of the decision tree, shown in the blue rectangles).

The complete Dutch breast cancer guideline could be represented in 60 clinical decision trees describing a total of 376 unique patient populations. Only 114 unique data items, which could be classified into 89% of all data items by existing classification and coding systems, were found to be necessary to describe all clinical decision trees. All clinical decision trees were successfully integrated into the interactive clinical decision support app Oncoguide. Clinical data can be entered via this app. Then, the app generates a corresponding route through the decision tree and provides a guideline-based recommendation based on the entered data.

A prerequisite for making a guideline-based decision is that sufficient data items for a specific clinical decision tree are available during multidisciplinary team meetings. **Chapter 4** describes a retrospective study of the availability of required data items during multidisciplinary team meetings, as verifiable in the electronic medical records, for four clinical decision trees: indication for magnetic resonance imaging (MRI) at diagnosis, indication for systemic treatment before and/or after breast surgery and finally the indication for immediate breast reconstruction. Patients were randomly selected from the Netherlands Cancer Registry in the period 2012 – 2015. Of the 394 included patients, the necessary minimum data items required per clinical decision tree were available for 70%, 13%, 97% and 13%, respectively. The two most underreported data items were "clinical M stage (cM)" (87%) and "evaluability of mammography" (28%). Since guidelines often indicate more than one treatment option, it was also investigated whether these treatment alternatives have been considered by multidisciplinary teams. Treatment alternatives were reported by multidisciplinary teams in 32% for primary treatment and in 28% for breast reconstruction. Both the availability of data in patient records that are essential for formulating guideline-based recommendations and the reporting of possible treatment alternatives from the clinical decision trees examined were low. We recommended that information that is implicitly known should be made explicit by multidisciplinary teams. Furthermore, we recommended that multidisciplinary teams should adhere to clear definitions of data items in their reporting.

Chapter 5 describes a prospective multicenter study analyzing the agreement between the recommendations arising from the clinical decision trees in breast cancer, colorectal cancer and prostate cancer and the recommendation given by the multidisciplinary teams. Seventeen clinical decision trees were selected, based on the current Dutch guidelines for breast (n=7), colon (n=5) and prostate cancer (n=5). 59 multidisciplinary team meetings were observed in eight hospitals in the Netherlands, where a total of 355 patients were discussed. In 83.4% of these patients (n = 296), all patient data were available for making an unconditional CDT recommendation. Unconditional means that all data items to complete the clinical decision tree were available during the multidisciplinary team meeting. Of these 296 patients, the multidisciplinary team recommendations were concordant in 249 (84.1%) cases, conditionally concordant in 24 (8.1%) of the cases (this means that the multidisciplinary team gives advice under the condition that a missing data item has a certain value, for example: advice on breast-conserving surgery if an MRI scan confirms that the breast tumor is not larger than 20 mm) and non-concordant in 23 (7.8%) of the cases, of which in 7 of these 23 cases the reason for deviation from the guideline advice generated by the clinical

decision tree was not motivated. It was concluded that the perceived concordance of recommendations between multidisciplinary teams and clinical decision trees and the completeness of data during multidisciplinary team meetings indicate a potential role for the implementation of clinical decision trees to support multidisciplinary team decision-making with greater attention to treatment alternatives when formulating recommendations.

Part III: clinical decision trees for the evaluation of national real-world data

By projecting the data from the Netherlands Cancer Registry onto the clinical decision trees, the clinical decision trees can analyze per treatment decision what care has been provided in practice in relation to the expected care that should be administered according to the guideline. Insights into real-world data can provide valuable feedback and accelerate guidance updates. Learning from this data can improve the quality of care.

Chapter 6 examines the feasibility of projecting data from the Netherlands Cancer Registry onto clinical decision trees, with the aim of mapping care in daily practice, and the applicability of clinical decision trees as a self-learning healthcare system. This concept is explained using a clinical example. Because the guideline regarding the indication of neoadjuvant (prior to surgery) systemic therapy for stage 2 breast cancer has been amended in the recent period, this patient population has been chosen as an example. Based on patient and tumor characteristics, these patients are classified per hospital and the percentage of neoadjuvant systemic therapy use is plotted in so-called 'funnel plots'. Based on the percentage of neoadjuvant systemic therapy and the delta percentage (% 2019 versus % 2016) of neoadjuvant systemic therapy before and after the guideline revision, hospitals were divided into early innovators, good adopters, slow adopters and laggards, and visualized in a 'waterfall plot' . Finally, the data from the Netherlands Cancer Registry were projected onto the clinical decision tree. Data from the Netherlands Cancer Registry showed that there were differences between hospitals in the extent to which guideline advice was adopted. Through repeated measurements (monitoring), the change in guideline adherence over time could identify hospitals as early innovators, good adopters, slow adopters, or laggards. The successful projection of data from the Netherlands Cancer Registry onto the clinical decision tree provided a deeper insight into the treatments that were actually performed. Clinical decision trees are the operating system of a self-learning healthcare system that can add evidence obtained from clinical practice data to evidence obtained from randomized controlled trials and consensus-based evidence.

Part IV: Self-learning evidence-based data-driven decision support for multidisciplinary clinical decision-making and reporting in breast cancer

In **Chapter 7**, the main findings of the research conducted for this thesis are discussed, and a viewpoint on how clinical decision trees can be implemented in daily care is presented. A new conceptual model is being launched for evidence-based

multidisciplinary decision support in (breast) cancer with clinical decision trees as a platform for a self-learning healthcare system. Data-driven clinical decision trees can support clinical decision-making in a landscape where scientific knowledge and personalized medicine are rapidly increasing. Clinical decision trees provide a methodology for data-driven care, both to support multidisciplinary decision-making for individual patients and for reporting and monitoring of actually delivered care. Clinical decision trees can present and analyze the actual care provided in real-time based on standardized data. This analysis can take place at hospital level where hospitals can be benchmarked. It can be specifically investigated at which points in the care path deviations from the then applicable guideline occur more often than expected. This may, for example, indicate the implementation of new knowledge by innovative hospitals. This generates real-world evidence that can be complementary to evidence obtained from randomized clinical trials. Based on all the insights provided by the research for this thesis, a new conceptual model has been composed with clinical decision trees as a central platform for a self-learning healthcare system for multidisciplinary clinical decision support, for data registration, for benchmarking hospitals and for generating feedback to guideline committees based on treatment patterns from daily practice, aiming to improve the quality and effectiveness of care. Challenges for implementation include the availability of standardized data, which is reusable and interoperable between different data sources.

Appendices

Nederlandse samenvatting
Dankwoord
Curriculum vitae
List of publications

NEDERLANDSE SAMENVATTING

Eén op de zeven vrouwen in Nederland krijgt tijdens haar leven borstkanker en de incidentie neemt nog steeds toe. Belangrijk is dat borstkanker een heterogene ziekte is. De wetenschappelijke kennis groeit snel en de gepersonaliseerde behandeling neemt toe. Dit is een uitdaging voor het tijdig updaten van klinische richtlijnen. Het is bekend dat op richtlijnen gebaseerde aanbevelingen door multidisciplinaire teams de kwaliteit van de zorg en de algehele overleving verbeteren.

De huidige klinische richtlijnen zijn in tekst weergegeven en hierdoor niet eenvoudig in de dagelijkse praktijk te gebruiken, omdat ze omvangrijk zijn en niet gestructureerd naar logische opeenvolgende beslissingen volgens het zorgpad dat een patiënt doorloopt. Bovendien verloopt het proces om de huidige richtlijnen actueel te houden erg traag. Daarom is er een nieuwe methodologie nodig om de klinische richtlijn compact weer te geven in beslisondersteunende systemen en om multidisciplinaire teams te ondersteunen tijdens de klinische besluitvorming. Ook is het noodzakelijk stappen te zetten in het verbeteren van de zorg door te leren van de geleverde zorg in de dagelijkse praktijk. Deze zogenaamde real-world data dienen dan te worden gepresenteerd op een gestandaardiseerde manier met als doel de praktijkmonitoring te ondersteunen en informatie te genereren om te komen tot een zelflerend zorgsysteem.

Het eerste deel van dit proefschrift vat samen wat er momenteel bekend is over multidisciplinaire klinische beslisondersteunende systemen voor de klinische besluitvorming bij oncologische multidisciplinaire team-bijeenkomsten. In het tweede deel wordt de nieuwe methodologie van klinische beslisbomen ter ondersteuning van multidisciplinaire teams beschreven en geanalyseerd. In het derde deel worden de klinische beslisbomen onderzocht voor evaluatie van landelijk daadwerkelijk geleverde zorg, door gegevens uit de Nederlandse Kanker Registratie op klinische beslisbomen te projecteren. In het laatste deel volgt een algemene discussie van alle in dit proefschrift gegenereerde kennis. Op basis hiervan wordt een nieuw model voorgesteld voor implementatie van multidisciplinaire, op bewijs gebaseerde klinische besluitvorming.

Deel I: klinische beslisondersteunende systemen voor multidisciplinaire teams

Multidisciplinaire teams zijn de basis waar alle beschikbare gegevens over de patiënt en de ziekte, alle kennis en medische disciplines samenkomen en individuele behandelplannen worden opgesteld. De behandeling wordt gebaseerd op vele (biomarker)gegevens en daardoor steeds unieker per patiënt. De richtlijnen moeten daarom opgesteld worden voor steeds kleinere en specifiekere patiëntenpopulaties, waardoor deze complexer worden. Klinische beslisondersteunende systemen (CDSS) kunnen multidisciplinaire teams ondersteunen bij hun klinisch besluitvormingsproces.

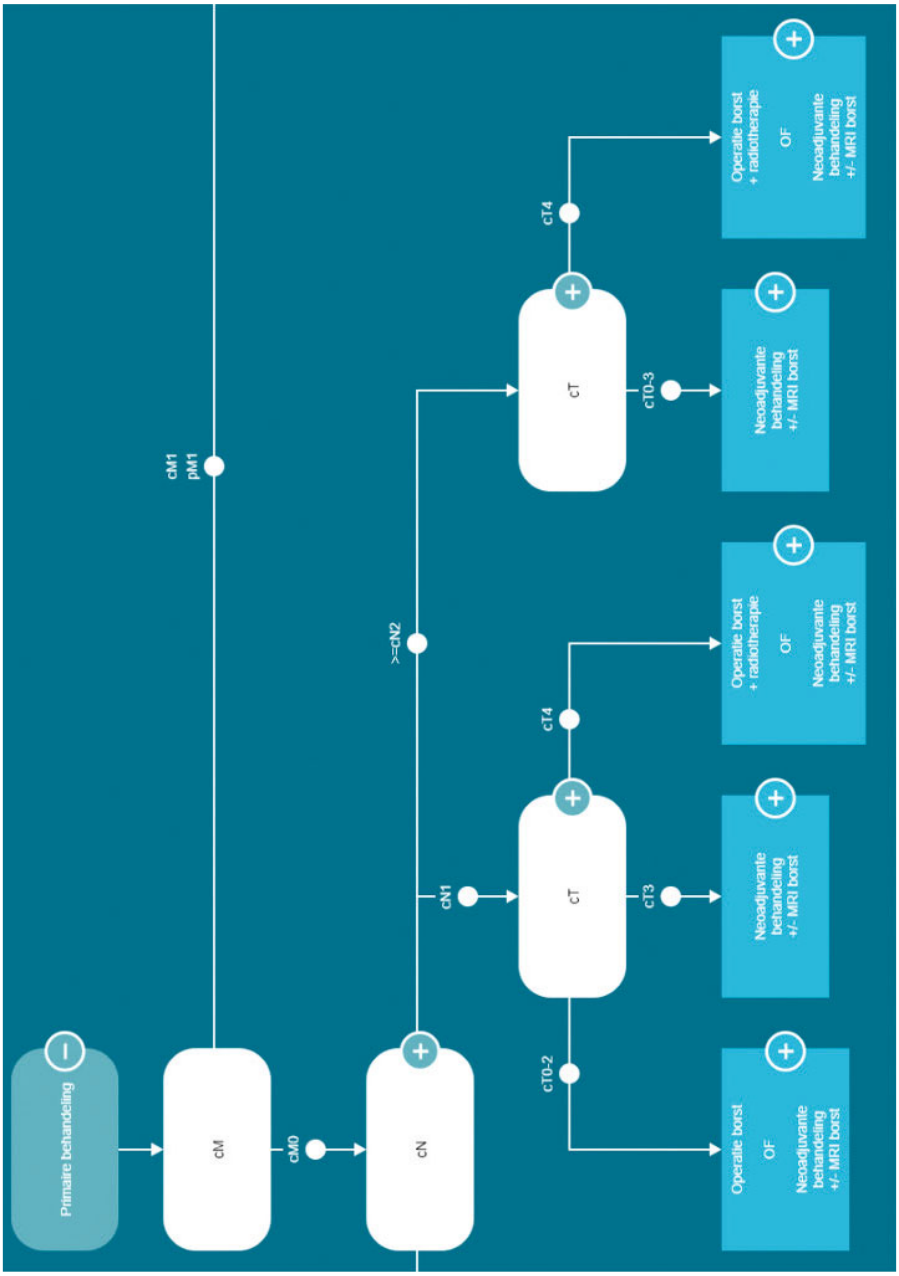
Hoofdstuk 2 betreft een scoping review waarin de momenteel beschikbare CDSS voor multidisciplinaire besluitvorming bij solide kanker, de ervaringen met de implementatie van CDSS en een voorstel voor een implementatiemodel wordt beschreven. Er werden twintig verschillende CDSS geïdentificeerd, en slechts drie daarvan zijn verder

onderzocht. Uit de 44 studies die in dit review zijn opgenomen, zijn 102 belemmerende en 86 bevorderende factoren van de CDSS-implementatie geïdentificeerd. Op basis van deze factoren werd een CDSS-implementatiemodel ontwikkeld met als doel om bij te dragen aan een succesvollere CDSS-implementatie. Het model bestaat uit drie belangrijke pijlers. De eerste pijler heeft betrekking op de analytische validiteit van de input van een CDSS: beschikbaarheid van data, datanauwkeurigheid, data-interoperabiliteit tussen databronnen en CDSS-validiteit van de aanbevelingen. De tweede pijler betreft de klinische validiteit van de CDSS-output: bruikbaarheid en transparantie van CDSS, voorkeuren van artsen, voorkeuren van patiënten en locoregionale haalbaarheid van aanbevelingen. De derde pijler omvat het klinische nut: dit stelt voorwaarden aan CDSS-onderhoud, informatiestandaard en data privacy.

Deel II: klinische beslisondersteuning met behulp van klinische beslisbomen

Richtlijnen kunnen het proces van klinische besluitvorming ondersteunen. Het tekstuele formaat van de meeste richtlijnen maakt ze echter omslachtig en niet gemakkelijk en toegankelijk in het gebruik. Daarnaast zijn richtlijnteksten vaak in dubbelzinnige bewoordingen opgesteld.

In **hoofdstuk 3** wordt de ontwikkeling van een opschaalbare methode voor het weergeven van tekstuele richtlijnaanbevelingen beschreven. Hierbij is gebruik gemaakt van systematisch ontworpen, modulaire, data-gestuurde klinische beslisbomen die het zorgpad volgen (figuur 1). De 'stam' van de klinische beslisboom vertegenwoordigt de stap in het zorgpad waarop de aanbeveling van toepassing is, bijvoorbeeld het advies van de juiste primaire behandeling. De 'knooppunten' vertegenwoordigen patiënt- of tumorkenmerken, bijvoorbeeld het stadium van de tumor (stadium T1, T2, T3 of T4). De 'takken' vertegenwoordigen verdere specificatie van de 'knooppunten' middels afkapwaarden, bijvoorbeeld stadium ≤ T2. De 'takken' kunnen naar andere knooppunten leiden en eindigen uiteindelijk in een 'blad' dat patiënt-specifieke aanbevelingen weergeeft op basis van verzamelde patiëntgegevens volgens de route die door de klinische beslisboom gevolgd is.



Figuur 1: beslisboom primaire behandeling.

Linksboven in de figuur geeft de stam weer ('primaire behandeling'). De witte blokken zijn de knooppunten die respectievelijk de data-items cM (uitzaaiingen op afstand), cN (lymfklierstadium) en cT (tumorstadium) weergeven. De takken beschrijven de waarden van het knooppunt. Het tumorstadium (cT) kan bijvoorbeeld stadium 0 tot en met 2 zijn, T3 of T4. Afhankelijk van de route door de beslisboom (dat wil zeggen de combinatie van klinische gegevens), volgt onder in de beslisboom een aanbeveling (in de bladeren van de beslisboom, weergegeven in de blauwe rechthoeken).

De haalbaarheid van de nieuwe klinische beslisboom-methodologie werd aangetoond door deze methode toe te passen op een complexe richtlijn, te weten de Nederlandse borstkankerrichtlijn. Data-items waaruit de klinische beslisboom bestaat, zijn ondubbelzinnig gedefinieerd op basis van internationale classificatie- en coderingssystemen. Dit betekent dat de definitie van een data-item eenduidig is vastgelegd, wat resulteert in een aantal vaste waarden die dit data-item kan aannemen (bijvoorbeeld tumorstadium (cT) 1 omvat alle tumoren met een diameter van maximaal 20mm). Op deze manier kan de interoperabiliteit met elektronische medische dossiers en de implementatie van klinische beslisbomen in CDSS's worden vergemakkelijkt. Een patiënt met een borsttumor van bijvoorbeeld 16mm valt binnen de beslisboom onder cT1 en dus onder de tak cT0-2.

De volledige Nederlandse borstkankerrichtlijn bleek in 60 klinische beslisbomen weergegeven te kunnen worden die in totaal 376 unieke patiëntenpopulaties beschrijven. Er bleken slechts 114 unieke data-items nodig, die in 89% van alle data-items konden worden geclassificeerd door bestaande classificatie- en coderingssystemen, om alle klinische beslisbomen te kunnen beschrijven. Alle klinische beslisbomen werden met succes geïntegreerd in de interactieve klinische beslisondersteunende app Oncoguide. Via deze app kunnen klinische gegevens worden ingevoerd en genereert de app een daarbij horende route door de beslisboom en geeft een op de richtlijn gebaseerde aanbeveling op basis van de ingevoerde gegevens.

Een voorwaarde voor het nemen van een op richtlijnen gebaseerde beslissing is dat er voldoende data-items in een bepaalde klinische beslisboom beschikbaar zijn tijdens multidisciplinaire team-bijeenkomsten. **Hoofdstuk 4** beschrijft een retrospectieve studie naar de beschikbaarheid van de vereiste data-items tijdens multidisciplinaire team-bijeenkomsten, zoals verifieerbaar in de elektronische medische dossiers, voor vier klinische beslisbomen: indicatie voor het verrichten van een magnetische resonantie beeldvorming (MRI) bij de diagnose , indicatie voor systemische behandeling voorafgaand en/of na de borstoperatie en ten slotte de indicatie voor directe borstreconstructie. Patiënten werden willekeurig geselecteerd uit de Nederlandse Kanker Registratie in de periode 2012 – 2015. Van de 394 geïncludeerde patiënten waren de noodzakelijke minimale data-items die nodig was per klinische beslisboom beschikbaar voor respectievelijk 70%, 13%, 97% en 13%. De twee meest onder gerapporteerde data-items waren "klinisch M-stadium (cM)" (87%) en "beoordeelbaarheid van de mammografie" (28%). Aangezien richtlijnen vaak meer dan één behandeloptie aangeven, is ook onderzocht of deze behandelalternatieven zijn overwogen door multidisciplinaire teams. Behandelingsalternatieven werden door multidisciplinaire teams gemeld bij 32% wat betreft de primaire behandeling en bij 28% wat betreft borstreconstructie. Zowel de beschikbaarheid van gegevens in patiëntendossiers die essentieel zijn voor formulering van op richtlijnen gebaseerde aanbevelingen als de rapportage van mogelijke behandelalternatieven van de onderzochte klinische beslisbomen waren laag. We hebben aanbevolen dat informatie die impliciet wel bekend is, door multidisciplinaire teams moet worden geëxpliciteerd. Verder hebben we aanbevolen dat multidisciplinaire teams zich in hun rapportage aan duidelijke definities van gegevensitems zouden moeten houden.

Hoofdstuk 5 beschrijft een prospectieve multicentrische studie waarin de overeenstemming wordt geanalyseerd tussen de aanbevelingen voortkomend uit de klinische beslisbomen bij borstkanker, colorectale kanker en prostaatkanker en de aanbeveling gegeven vanuit de multidisciplinaire teams. Er werden zeventien klinische beslisbomen geselecteerd, gebaseerd op de geldende Nederlandse richtlijnen voor borst- (n=7), darm- (n=5) en prostaatkanker (n=5). In acht ziekenhuizen in Nederland werden 59 multidisciplinaire team-bijeenkomsten geobserveerd, waarin in totaal 355 patiënten besproken zijn. Bij 83,4% van deze patiënten (n = 296) waren alle patiëntgegevens beschikbaar voor het geven van een onvoorwaardelijke CDT-aanbeveling. Onvoorwaardelijk wil zeggen dat alle gegevensitems om de klinische beslisboom te voltooien beschikbaar waren tijdens de multidisciplinaire team-bijeenkomst. Van deze 296 patiënten waren de multidisciplinaire team-aanbevelingen concordant in 249 (84,1%) gevallen, voorwaardelijk concordant in 24 (8,1%) van de gevallen (daarmee wordt bedoeld dat het multidisciplinaire team een advies geeft onder de voorwaarde dat een nog missend data-item een bepaalde waarde heeft, bijvoorbeeld: advies borstsparende operatie indien een MRI scan bevestigd dat de borsttumor niet groter is dan 20mm) en niet-concordant in 23 (7,8%) van de gevallen, waarvan in 7 van deze 23 gevallen de reden voor afwijking van het door de klinische beslisboom gegenereerde richtlijnadvies niet werd gemotiveerd. Er werd geconcludeerd dat de waargenomen overeenstemming van de aanbevelingen tussen multidisciplinaire teams en klinische beslisbomen en de volledigheid van de gegevens tijdens multidisciplinaire team-bijeenkomsten wijzen op een potentiële rol voor de implementatie van klinische beslisbomen ter ondersteuning van de multidisciplinaire team-besluitvorming met meer aandacht voor behandelalternatieven bij de formulering van aanbevelingen.

Deel III: klinische beslisbomen voor de evaluatie van landelijke real-world data

Door de gegevens van de Nederlandse Kanker Registratie op de klinische beslisbomen te projecteren, kunnen de klinische beslisbomen per behandelbeslissing analyseren welke zorg er in de praktijk is geleverd in relatie tot de te verwachten zorg die volgens de richtlijn had moeten plaatsvinden. Inzichten in gegevens uit de praktijk kunnen waardevolle feedback opleveren en updates van richtlijnen versnellen. Leren van deze gegevens kan de kwaliteit van de zorg verbeteren.

Hoofdstuk 6 onderzoekt de haalbaarheid van het projecteren van gegevens uit de Nederlandse Kanker Register op de klinische beslisbomen, met als doel de zorg in de dagelijkse praktijk in beeld te brengen en de toepasbaarheid van klinische beslisbomen als een zelflerend gezondheidszorgsysteem. Dit concept wordt uitgelegd aan de hand van een klinisch voorbeeld. Omdat de richtlijn met betrekking tot de indicatie neoadjuvante (voorafgaand aan de operatie) systemische therapie bij stadium 2 borstkanker in de afgelopen periode is aangepast, is deze patiënten populatie als voorbeeld gekozen. Op basis van de patiënt- en tumorkenmerken zijn deze patiënten per ziekenhuis ingedeeld en is het percentage neoadjuvante systemische therapie-gebruik uitgezet in zogenaamde ‘funnel plots’. Op basis van het percentage neoadjuvante systemische therapie en het deltapercentage (% 2019 versus %

2016) neoadjuvante systemische therapie voor en na de richtlijn herziening werden ziekenhuizen onderverdeeld in vroege vernieuwers, goede volgers, langzame volgers en achterblijvers, en gevisualiseerd in een 'waterfall plot'. Ten slotte werden de gegevens van de Nederlandse Kanker Registratie op de klinische beslisboom geprojecteerd. Uit gegevens van de Nederlandse Kanker Registratie bleek dat er tussen ziekenhuizen verschillen bestonden in de mate waarin een richtlijnadvies werd overgenomen. Door herhaalde metingen (monitoring) kon de verandering in richtlijn opvolging in de loop van de tijd ziekenhuizen identificeren als vroege vernieuwer, goede volger, langzame volger of achterblijver. De succesvolle projectie van gegevens van de Nederlandse Kanker Registratie op de klinische beslisboom zorgde voor een dieper inzicht in de behandelingen die daadwerkelijk werden uitgevoerd. Klinische beslisbomen zijn het besturingssysteem van een zelflerend gezondheidszorgsysteem dat bewijs wat verkregen is uit klinische praktijkgegevens kan toevoegen aan bewijs wat verkregen is uit gerandomiseerd gecontroleerd onderzoek en op consensus gebaseerd bewijs.

Deel IV: Zelflerende, op bewijs gebaseerde, data-gestuurde beslisondersteuning voor multidisciplinaire klinische besluitvorming en verslaglegging bij borstkanker

In **Hoofdstuk 7** worden de belangrijkste bevindingen van het onderzoek dat voor dit proefschrift is uitgevoerd besproken, en wordt een standpunt over hoe klinische beslisbomen in de dagelijkse zorg kunnen worden geïmplementeerd benoemd. Er wordt een nieuw conceptueel model gelanceerd voor evidence-based multidisciplinaire beslisondersteuning bij (borst)kanker met klinische beslisbomen als platform voor een zelflerend gezondheidszorgsysteem. Data-gestuurde klinische beslisbomen kunnen de klinische besluitvorming ondersteunen in een landschap waarin wetenschappelijke kennis en gepersonaliseerde geneeskunde snel toenemen. Klinische beslisbomen bieden een methodologie voor data-gestuurde zorg, zowel ter ondersteuning van multidisciplinaire besluitvorming voor individuele patiënten als voor verslaglegging en monitoring van daadwerkelijk geleverde zorg. Klinische beslisbomen kunnen real-time de daadwerkelijk geleverde zorg presenteren en analyseren op basis van gestandaardiseerde gegevens. Deze analyse kan plaatsvinden op ziekenhuisniveau waarbij ziekenhuizen onderling kunnen worden vergeleken, het zogenaamde benchmarken. Hierbij kan gericht worden onderzocht op welke momenten in het behandelproces er vaker wordt afgeweken van de dan geldende richtlijn dan verwacht. Dit kan bijvoorbeeld wijzen op implementatie van nieuwe kennis door vernieuwende ziekenhuizen. Hierdoor wordt real-world bewijsmateriaal gegenereerd dat complementair kan zijn aan bewijsmateriaal verkregen uit gerandomiseerde klinische onderzoeken. Op basis van alle inzichten die het onderzoek voor dit proefschrift heeft opgeleverd is een nieuw conceptueel model opgesteld met klinische beslisbomen als een centraal platform voor een zelflerend gezondheidszorgsysteem voor multidisciplinaire klinische beslisondersteuning, voor dataregistratie, voor het benchmarken van ziekenhuizen en voor het genereren van feedback aan richtlijncommissies op basis van behandelpatronen uit de praktijk, met als doel de kwaliteit en effectiviteit van de zorg te verbeteren. Uitdagingen voor implementatie zijn de beschikbaarheid van gestandaardiseerde gegevens, die herbruikbaar zijn en interoperabel zijn tussen verschillende gegevensbronnen.

DANKWOORD

Een proefschrift kan onmogelijk tot stand komen zonder samenwerking met anderen. Het vormen van een goed team is essentieel, en ingrediënten als deskundigheid, optimisme, flexibiliteit en humor dragen absoluut bij aan een positief onderzoekklimaat. Als eerste wil ik mijn promotor, Sabine Siesling en mijn co-promotor, Agnes Jager bedanken. Sabine, toen wij elkaar ontmoetten viel mij direct jouw tomeloze energie, enthousiasme en schaterlach op. Je hebt me altijd vrijgelaten om zelf een koers uit te zetten. Ik waardeer je eerlijkheid en dat je altijd denkt in kansen. Dat maakt dat ik (bijna) altijd positieve energie kreeg na een overleg. Je bent een duizendpoot en pakt alles aan. Dat leidt tot drukke agenda's maar voor belangrijke dingen was je er altijd. Agnes, jij kwam iets later in het team omdat ik toch het perspectief van een collega oncoloog miste. Je denkt nog sneller dan je praat en met jouw *dose-dense* input van gedachtes werden onze discussies enorm verrijkt. Je kritische houding, ook naar je eigen bijdrage, waardeer ik enorm. Dat is een belangrijke eigenschap voor een goede onderzoeker. Ik prijs me gelukkig dat ik met jou en Sabine kan blijven samenwerken gezien de klinische studies die we samen (gaan) doen.

Ook wil ik Xander Verbeek bedanken. Xander, jij was bij de start van het onderzoek betrokken. Vanuit jouw technisch perspectief had je een wereld aan ideeën als het ging om digitale innovatie ter verbetering van zorgprocessen en besluitvorming. Je aanstekelijke enthousiasme en *out-of-the-box* denken hebben mij enorm geïnspireerd. Dank daarvoor. Het is dan ook enorm spijtig dat je wegens persoonlijke omstandigheden niet meer als co-promotor betrokken kon zijn.

Tevens wil ik graag de leescommissie, bestaande uit prof. dr. T.J.M. Ruers, prof. dr. M.C. Mikkers, prof. dr. M. Koopman, prof. dr. I.H.J.T. de Hingh, prof. dr. M.A.W. Merkx en dr. H.J.G.D. van den Bongard, bedanken voor het beoordelen van mijn proefschrift.

Verder wil ik alle co-auteurs bedanken voor hun bijdrage. Jullie inzichten en suggesties hebben mij geholpen om de manuscripten te verbeteren. En natuurlijk ook dank aan alle collega's bij IKNL. Thijs, wat hebben we veel aan de tekentafel gezeten om de beslisbomen te ontwerpen en wat waren we vaak verbaasd over de vele inconsistenties die we tegenkwamen in de richtlijn. We hadden toen nog geen idee waar deze methodiek uiteindelijk concreet toe zou kunnen leiden. Ghita en Linda, ik wil jullie enorm bedanken voor jullie ondersteuning bij het gebruik maken van data uit de Nederlandse kankerregistratie. Jullie zijn echt experts. Ook dank aan de collega promovendi bij IKNL. De *brain-boost* lunches en de jaarlijkse schrijfweek op de hei waren inspirerend en gezellig, al zijn we in 2022 in Woold wel bijna bevroren. De riante woonboerderij beschikte niet over centrale verwarming en iedereen zat onder dekens te schrijven in afwachting van de komst van een gaskachel.

Het promotieonderzoek vond plaats naast mijn *full-time job* als internist-oncoloog. Dat was een uitdagende combinatie, maar als je bij de leukste maatschap van Nederland werkt maakt dat het wel draaglijker. Lieve collega's, heel veel dank voor de ruimte die jullie mij hebben gegeven, jullie begrip en jullie belangstelling. We mogen ons gelukkig

prijzen met de goede sfeer die we met elkaar neerzetten, het elkaar laagdrempelig kunnen benaderen en de manier waarop we de internistenopleiding samen vormgeven. We zijn echt één team, samen met een nieuwe generatie dokters. Kortom een inspirerend klimaat om te werken met ook heel veel leuke sociale gebeurtenissen. Hierbij denk ik aan onze regelmatige borrels, de opleidingsbarbecue, het kerstdiner met ongecensureerde sketches en de jaarlijkse weekendtrip om te skiën of cultuur op te snuiven. Ook veel dank aan alle collega's van Noordwest die mij op verschillende manieren hebben geholpen, in het bijzonder mijn poliassistentes, collega's van het trialbureau en wetenschapsbureau.

Het is enorm inspirerend als je met onderzoek kan bijdragen aan de verbetering van zorg. Maar het is nog leuker als je ook een rol kan hebben bij het opzetten van nieuw onderzoek. Bijvoorbeeld het project *FAPI-for-CUP*. Dank Sophie, Esther, Eric, Walter, Caroline en Warnyta voor de fijne samenwerking. En fantastisch dat de studie goed loopt. En natuurlijk de SYMPHA en eChemoCoach studie. Wat geweldig dat we voor beide projecten subsidie hebben gekregen. Dank aan alle betrokkenen die dit mogelijk maken. In het bijzonder dank aan Agnes, Sabine, Corina, Lois, Rubin, Nienke, Ingrid, Jeroen, Manon, Chris, Stans, Elise en Ilse. Het is een voorrecht om te mogen werken met zo'n goed op elkaar ingespeeld team. Jullie zijn toppers!

Lieve familie en vrienden, dank voor alle interesse tijdens het schrijven van mijn proefschrift.

Dan wil de mensen extra bedanken die mij het meest dierbaar zijn. Ralph, jij bent een echte ondernemer en hebt van je passies je werk gemaakt. Ik bewonder je analytisch vermogen en de vertaalslag die je hiermee maakt om problemen echt op te lossen. We delen onze liefde voor Italië. Net als onze geliefde Paul, die ons helaas veel te vroeg heeft moeten verlaten. Als jouw proefschrift ook is afgerond wordt het weer tijd voor een bezoek aan *Centro Storico*. Wellicht is Galloni er dan ook weer.

Dave, we ontmoetten elkaar toen we beide in Nijmegen studeerden. Hoewel we in vele opzichten van elkaar verschillen, delen we een aantal passies. En dit heeft er zelfs toe geleid dat we, samen met Paul, drie maal de Grand Prix Saint Hubert hebben gewonnen. Al waren we toen broekies, we versloegen alle professionele teams. De eerste overwinning hadden we in het geheel niet verwacht, anders waren we wel tot de prijsuitreiking gebleven. Ik betreur het dat Paul de dag van mijn promotie niet meer kan meemaken.

Dokter uit Gilze, Jack, Hans, Kees, Pascal, wat hebben we al een hoop mooie avonturen meegemaakt. Jullie hebben allemaal het hart op de juiste plek. Het is altijd fijn om jullie te zien.

Mannen van KURK, en Veritable, de meeste van ons kennen elkaar nu zo'n 20 jaar. Onze gedeelde passie bracht ons samen en heeft vriendschappen voor het leven gesmeed. Ik geniet enorm van de ongedwongen sfeer waarin iedereen zichzelf is. We vieren het

leven en naast serieuze momenten maken we vooral heel veel plezier samen. Ik voel me bevoorrecht met jullie. Onze connecties zijn ook grenzeloos geworden.

Daarin speelt John een grote rol. John is in meerdere opzichten groot, maar vooral zijn hart. Dank kameraad voor je aanwezigheid in mijn leven. Ik koester vele bijzondere momenten, en de residentie in Pommard voelt als thuis. *Un merci spécial à Mélissa. Votre hospitalité, votre personnalité et votre talent pour emmerder les bonnes personnes nous apportent tellement de joie de vivre. Quel privilège que nos chemins se soient croisés. Tu es une belle personne*.

En dank aan mijn paranimfen. Peter, het was een voorrecht om voor jou en Elise op te treden als buitengewoon ambtenaar van de burgerlijke stand en jullie huwelijk te voltrekken. We kennen elkaar al lang en elkaar zien voelt altijd als thuiskomen. Ik waardeer je doortastendheid, scherpe blik en neus om snel in de gaten te hebben waar je moet zijn voor lekker eten en een mooi glas. Als geen ander weet jij wat delen is. Freek, jij bent misschien wel de grootste Italië fan van allemaal. En dat al heel lang. Onze vriendschap bestaat ook al heel lang en sinds we in dezelfde stad wonen is deze alleen maar hechter geworden. Ik bewonder je ornithologische kennis en de gedrevenheid waarmee jij je in nieuwe dingen verdiept. *Maestro, grazie mille per essere mio amico*.

Liever Sander, broeder. Onze levens zijn in vele opzichten heel anders maar we vinden elkaar altijd. Ik bewonder je vakmanschap en doorzettingsvermogen. Je hebt ondanks enige tegenwind een fantastisch bedrijf neergezet. En daarnaast haal je met jouw karakter ook het beste uit je gezin naar boven. Ik ben trots op jou. Lieve Elisabeth, jij bent het beste wat mijn broer is overkomen, en we zijn allemaal blij met je. Lieve Isabel, Fenna en Sofie, het boekje van oom Thijs is nu eindelijk af. Jullie maakten je zorgen of jullie de feestelijke dag wel mee zouden kunnen maken, maar jullie horen er natuurlijk helemaal bij!

Lieve ouders, dank voor al jullie inspanningen om mij te vormen tot wie ik nu ben. De waarden die jullie mij hebben meegeven zijn zeer behulpzaam geweest bij mijn ontwikkeling als dokter en onderzoeker. Papa, nieuwsgierigheid en oplossingsgericht werken heb ik zeker van jou. Jij bent echt een homo universalis. Er is weinig wat jij niet weet of niet kan. De houten zeilboot die je naast het huis gebouwd hebt staat nog op mijn netvlies. Mama, creativiteit en zorgzaamheid passen echt bij jou. Je hebt talent voor schilderen en het bereiden van lekker eten. Als ik alle hapjes die je altijd aanbiedt zou hebben opgegeten was ik nu uit mijn vel gegroeid.

Ik wil jullie bedanken voor de veilige basis die jullie mij hebben gegeven. En voor jullie altijd aanwezige belangstelling en steun. Hard werken is ons altijd met de paplepel ingegoten. Als je iets wil bereiken moet je er iets voor doen. En er ook iets voor laten. Maar alles draait om balans. En het is heel fijn om af en toe in de weekenden thuis te komen en iedereen te zien. De band die we als gezin hebben is en blijft bijzonder. Daar genieten we allemaal van. Dank daarvoor.

CURRICULUM VITAE

Mathijs Pieter Hendriks was born on April 1st, 1977 in Tiel, The Netherlands. In 1995 he completed secondary school at Griftland College Soest. After one year studying business economics at HEAO Utrecht, he started medical school in 1996 at Radboud University Nijmegen. Because of his interest in healthcare in developing countries, a part of his internships were accomplished at Sengerema Hospital, Mwanza region, Tanzania. In 2003, he started his traineeship in internal medicine (AIOS) and registered as a medical specialist in internal medicine in 2009. One year later he completed his traineeship in medical oncology which led to registration as medical oncologist.

Mathijs has been working as medical specialist in internal medicine and medical oncologist at Northwest Clinics (Alkmaar, The Netherlands) since December 2010. Besides involvement in direct patient care, he has completed various management courses and was appointed medical manager to redesign breast cancer care in the context of the value-based health care project "the Breast Clinic" in Northwest region. During his medical career, Mathijs has always been interested in conducting research. At Northwest Clinics, he is local primary investigator of multiple (inter)national studies and is managing medical director of the oncology trial office.

In 2016, a PhD trajectory was initiated, leading to this thesis. Mathijs was appointed as an external PhD candidate at the University of Twente, in close cooperation with the Netherlands Comprehensive Cancer Organisation (IKNL). His PhD-research focused on self-learning evidence-based data-driven decision support for multidisciplinary decision-making and reporting in breast cancer. His scientific interest focus on clinical trials, organization of care, medical informatics and data-driven innovation from a clinical perspective aiming to improve patient care. His work and collaboration with other researchers have recently resulted in the award of three major research grants from KWF Dutch Cancer Society. Mathijs will conduct these studies next to his clinical work at Northwest Clinics.

LIST OF PUBLICATIONS

Included in this thesis

Hendriks MP, Jager A, Ebben KCWJ, van Til JA, Siesling S. Clinical decision support systems for multidisciplinary team decision-making in patients with solid cancer: composition of an implementation model based on a scoping review. *Crit Rev Oncol Hematol*. 2024 Feb 2:104267.

Hendriks MP, Verbeek XAAM, van Vegchel T, van der Sangen MJC, Strobbe LJA, Merkus JWS, Zonderland HM, Smorenburg CH, Jager A[#], Siesling S[#]. Transformation of the National Breast Cancer Guideline Into Data-Driven Clinical Decision Trees. *JCO Clin Cancer Inform*. 2019;3:1–14.

Hendriks MP, Verbeek XAAM, van Manen JG, van der Heijden SE, Go SHL, Gooiker GA, van Vegchel T, Siesling S[#], Jager A[#]. Clinical decision trees support systematic evaluation of multidisciplinary team recommendations. *Breast Cancer Res Treat*. 2020 Sep;183(2):355-363.

Ebben KCWJ[*], **Hendriks MP[*]**, Markus L, Kos M, de Hingh IHJT, Oddens JR, Rothbarth J, de Wilt JHW, Strobbe LJA, Bessems M, Mellema CT, Siesling S, Verbeek XAAM. Using Guideline-Based Clinical Decision Support in Oncological Multidisciplinary Team Meetings: A Prospective, Multicenter Concordance Study. *Int J Qual Health Care*. 2022 Mar 19;34(1):mzac007.

Hendriks MP, van Vegchel T, de Munck L, Jager A[#], Siesling S[#]. Self-learning health care systems: data-driven clinical decision trees supporting evaluation of real-world breast cancer care. *Submitted*

Hendriks MP, Jager A, Siesling S. Self-learning evidence-based data-driven decision support for multidisciplinary clinical decision-making and reporting in breast cancer. *Submitted*

[*]Co-first authors; [#]Co-senior authors

Other publications

Vrancken Peeters NJMC, Koppert LB, Jager A, **Hendriks MP**, Siesling S, van den Hurk CJG. Symptom Monitoring and Health-Related Quality of Life in Non-metastatic Breast Cancer Patients: A Systematic Review. *Curr Breast Cancer Rep*. 2024.

Ham L, Fransen HP, de Graeff A, **Hendriks MP**, de Jong WK, Kloover J, Kuip E, Mandigers C, Sommeijer D, van de Poll L, Raijmakers N, van Zuylen L. Relatives' Unmet Needs in the Last Year of Life of Patients With Advanced Cancer: Results of a Dutch Prospective, Longitudinal Study (eQuiPe). *J Palliat Care*. 2024 Mar 22:8258597241239614.

Haaksman M, Ham L, Brom L, Baars A, van Basten JP, van den Borne BEEM, **Hendriks MP**, de Jong WK, van Laarhoven HWM, van Lindert ASR, Mandigers CMPW, van der Padt-Pruijsten A, Smilde TJ, van Zuylen LC, van Vliet LM, Raijmakers NJH. Open communication between patients and relatives about illness & death in advanced cancer-results of the eQuiPe Study. *Support Care Cancer.* 2024 Mar 6;32(4):214.

Klaver KM, Duijts SFA, Geusgens CAV, Kieffer JM, Agelink van Rentergem J, **Hendriks MP**, Nuver J, Marsman HA, Poppema BJ, Oostergo T, Doeksen A, Aarts MJB, Ponds RWHM, van der Beek AJ, Schagen SB. Internet-based cognitive rehabilitation for working cancer survivors: results of a multicenter randomized controlled trial. *JNCI Cancer Spectr.* 2024 Jan 4;8(1):pkad110.

Smit KC, Derksen JWG, Stellato RK, van Lanen AS, Wesselink E, Belt EJT, Cloos-van Balen M, Coene PPLO, Dekker JWT, de Groot JW, Haringhuizen AW, van Halteren HK, van Heek TT, Helgason HH, **Hendriks MP**, de Hingh IHJT, Hoekstra R, Houtsma D, Janssen JJB, Kok N, Konsten JLM, Los M, Meijerink MR, Mekenkamp LJM, Peeters KCMJ, Polée MB, Rietbroek RC, Schiphorst AHW, Schrauwen RWM, Schreinemakers J, Sie MPS, Simkens L, Sonneveld EJA, Terheggen F, Valkenburg-van Iersel L, Vles WJ, Wasowicz-Kemps DK, de Wilt JHW, Kok DE, Winkels RM, Kampman E, van Duijnhoven FJB, Koopman M, May AM. Determinants of Physical Activity among Patients with Colorectal Cancer: From Diagnosis to Five Years after Diagnosis. *Med Sci Sports Exerc*. 2023 Dec 11.

Schaeffers AWMA, Devriese LA, van Gils CH, Dankbaar JW, Voortman J, de Boer JP, Slingerland M, **Hendriks MP**, Smid EJ, Frederix GWJ, de Bree R. Low dose cisplatin weekly versus high dose cisplatin every three weeks in primary chemoradiotherapy in head and neck cancer patients with low skeletal muscle mass: The CISLOW-study protocol. *PLoS One*. 2023 Nov 27;18(11):e0294147.

Ham L, Fransen HP, Raijmakers NJH, van den Beuken-van Everdingen MHJ, van den Borne B, Creemers GJ, de Graeff A, **Hendriks MP**, de Jong WK, van Laarhoven H, van Leeuwen L, van der Padt-Pruijsten A, Smilde TJ, Stellingwerf M, van Zuylen L, van de Poll-Franse LV. Trajectories of emotional functioning and experienced care of relatives in the last year of life of patients with advanced cancer: A longitudinal analysis of the eQuiPe study. *Psychooncology*. 2023 Oct 26.

Bakkerus L, Buffart LM, Buffart TE, Meyer YM, Zonderhuis BM, Haasbeek CJA, Versteeg KS, Loosveld OJL, de Groot JWB, **Hendriks MP,** Verhoef C, Verheul HMW, Gootjes EC. Health-Related Quality of Life in Patients With Metastatic Colorectal Cancer Undergoing Systemic Therapy With or Without Maximal Tumor Debulking. *J Natl Compr Canc Netw*. 2023 Oct;21(10):1059-1066.e5.

Versluis MAJ, Raijmakers NJH, Baars A, van den Beuken-van Everdingen MHJ, de Graeff A, **Hendriks MP**, de Jong WK, Kloover JS, Kuip EJM, Mandigers CMPW, Sommeijer DW, van der Linden YM, van de Poll-Franse LV. Trajectories of health-related quality of life and symptom burden in patients with advanced cancer towards the end of life: Longitudinal results from the eQuiPe study. *Cancer*. 2023 Oct 13.

van Elst T, van Basten JP, van den Berg P, van den Bergh R, Bloem S, van Dodewaard-de Jong J, **Hendriks M**, Klaver S, Lalmahomed Z, Luijendijk D, van de Luijtgaarden A, Roelofs L, Vis A, Vreugdenhil G, Vrijhof E, Wijsman B, Bloemendal H, Mulders P, Mehra N. TripleAiM1: a nationwide registry of de novo metastatic hormone-sensitive prostate cancer with prospective quality-of-life assessment. BMJ Open. 2023 Aug 29;13(8):e072572.

Bond MJG, Bolhuis K, Loosveld OJL, de Groot JWB, Droogendijk H, Helgason HH, **Hendriks MP**, Klaase JM, Kazemier G, Liem MSL, Rijken AM, Verhoef C, de Wilt JHW, de Jong KP, Gerhards MF, van Amerongen MJ, Engelbrecht MRW, van Lienden KP, Molenaar IQ, de Valk B, Haberkorn BCM, Kerver ED, Erdkamp F, van Alphen RJ, Mathijssen-van Stein D, Komurcu A, Lopez-Yurda M, Swijnenburg RJ, Punt CJA; Dutch Colorectal Cancer Study Group. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. *Lancet Oncol*. 2023 Jun 14:S1470-2045(23)00219-X.

Hueting TA, van Maaren MC, **Hendriks MP**, Koffijberg H, Siesling S. External validation of 87 clinical prediction models supporting clinical decisions for breast cancer patients. *Breast*. 2023 Apr 17;69:382-391.

Dijkstra EA, Zwart WH, Nilsson PJ, Putter H, Roodvoets AGH, Meershoek-Klein Kranenbarg E, Frödin JE, Nygren P, Østergaard L, Kersten C, Verbiené I, Cervantes A, **Hendriks MP**, Capdevila J, Edhemovic I, van de Velde CJH, Marijnen CAM, van Etten B, Hospers GAP, Glimelius B; collaborative investigators. The value of post-operative chemotherapy after chemoradiotherapy in patients with high-risk locally advanced rectal cancer-results from the RAPIDO trial. *ESMO Open*. 2023 Mar 3;8(2):101158.

Geurts BS, Battaglia TW, van Berge Henegouwen JM, Zeverijn LJ, de Wit GF, Hoes LR, van der Wijngaart H, van der Noort V, Roepman P, de Leng WWJ, Jansen AML, Opdam FL, de Jonge MJA, Cirkel GA, Labots M, Hoeben A, Kerver ED, Bins AD, Erdkamp FGL, van Rooijen JM, Houtsma D, **Hendriks MP**, de Groot JB, Verheul HMW, Gelderblom H, Voest EE. Efficacy, safety and biomarker analysis of durvalumab in patients with mismatch-repair deficient or microsatellite instability-high solid tumours. *BMC Cancer*. 2023 Mar 4;23(1):205.

Bos-van den Hoek DW, van Laarhoven HWM, Ali R, Bakker SD, Goosens A, **Hendriks MP**, Pepels MJAE, Tange D, de Vos FYFL, van de Wouw AJ, Smets EMA, Henselmans I. Blended online learning for oncologists to improve skills in shared decision making about palliative chemotherapy: a pre-posttest evaluation. *Support Care Cancer*. 2023 Feb 23;31(3):184.

van Veenendaal H, Peters LJ, van Weele E, **Hendriks MP**, Schuurman M, Visserman E, Hilders CGJM, Ubbink DT. Effects and Working Mechanisms of a Multilevel Implementation Program for Applying Shared Decision-Making while Discussing Systemic Treatment in Breast Cancer. *Curr Oncol*. 2022 Dec 23;30(1):236-249.

Dijkstra EA, Nilsson PJ, Hospers GAP, Bahadoer RR, Meershoek-Klein Kranenbarg E, Roodvoets AGH, Putter H, Berglund Å, Cervantes A, Crolla RMPH, **Hendriks MP**, Capdevila J, Edhemovic I, Marijnen CAM, van de Velde CJH, Glimelius B, van Etten B; and collaborative investigators. Locoregional Failure During and After Short-course Radiotherapy followed by Chemotherapy and Surgery Compared to Long-course Chemoradiotherapy and Surgery - A Five-year Follow-up of the RAPIDO Trial. *Ann Surg*. 2023 Jan 20.

Hueting TA, van Maaren MC, **Hendriks MP**, Koffijberg H, Siesling S. The majority of 922 prediction models supporting breast cancer decision-making are at high risk of bias. *J Clin Epidemiol*. 2022 Oct 27;152:238-247.

Eijkelboom AH, de Munck L, de Vries M, Francken AB, **Hendriks MP**, Strobbe L, Witteveen A, van Maaren MC, Siesling S. Routine and interval detection of locoregional breast cancer recurrences and risk of subsequent distant metastasis. *Breast Cancer Res Treat*. 2022 Oct 31.

Franken MD, Vink G, van Grevenstein WMU, Verkooijen HM, Punt CJA, Koopman M, May AM; On behalf of the PLCRC Study Group (including **Hendriks MP**). Work Ability in Patients With Stage I to IV Colon Cancer: Results of the Dutch Prospective Colorectal Cancer Cohort. *Dis Colon Rectum*. 2023 Jan 1;66(1):50-58.

Qaderi SM, van der Heijden JAG, Verhoeven RHA, de Wilt JHW, Custers JAE; PLCRC study group (including **Hendriks MP**). Trajectories of health-related quality of life and psychological distress in patients with colorectal cancer: A population-based study. *Eur J Cancer*. 2021 Oct 16;158:144-155.

Ham L, Fransen HP, van Roij J, van den Borne B, Creemers GJ, **Hendriks MP**, Kuip E, van Laarhoven HW, van Leeuwen L, van der Padt-Pruijsten A, Smilde T, Stellingwerf M, van Zuylen L, van de Poll-Franse L, Raijmakers NJ. Emotional functioning during bereavement after the death of patients with advanced cancer and associated factors. *Psychooncology*. 2022 Sep 12.

Hamers PAH, Vink GR, Elferink MAG, Stellato RK, Dijksterhuis WPM, Punt CJA, Koopman M, May AM; QUALITAS study group (including **Hendriks MP**). Quality of Life and Survival of Metastatic Colorectal Cancer Patients Treated With Trifluridine-Tipiracil (QUALITAS). *Clin Colorectal Cancer*. 2022 Jun;21(2):154-166.

Punt CJA, Kwakman JJM, Mol L; PLCRC working group (including **Hendriks MP**). Long-Term Safety Data on S-1 Administered After Previous Intolerance to Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer. *Clin Colorectal Cancer*. 2022 Sep;21(3):229-235.

Dijkstra EA, Hospers GAP, Kranenbarg EM, Fleer J, Roodvoets AGH, Bahadoer RR, Guren MG, Tjalma JJJ, Putter H, Crolla RMPH, **Hendriks MP**, Capdevila J, Radu C, van de Velde CJH, Nilsson PJ, Glimelius B, van Etten B, Marijnen CAM. Quality of life and late toxicity after short-course radiotherapy followed by chemotherapy or chemoradiotherapy for locally advanced rectal cancer - The RAPIDO trial. *Radiother Oncol*. 2022 Jun;171:69-76.

Vliek SB, Noordhoek I, Meershoek-Klein Kranenbarg E, van Rossum AGJ, Dezentje VO, Jager A, Hokken JWE, Putter H, van der Velden AWG, **Hendriks MP**, Bakker SD, van Riet YEA, Tjan-Heijnen VCG, Portielje JEA, Kroep JR, Nortier JWR, van de Velde CJH, Linn SC. Daily Oral Ibandronate With Adjuvant Endocrine Therapy in Postmenopausal Women With Estrogen Receptor-Positive Breast Cancer (BOOG 2006-04): Randomized Phase III TEAM-IIB Trial. *J Clin Oncol*. 2022 Sep 1;40(25):2934-2945.

Göker E, **Hendriks MP**, van Tilburg M, Barcaru A, Mittempergher L, van Egmond A, Kleijn M, Generali D; of the NBREaST II Investigators Group. Treatment response and 5-year distant metastasis-free survival outcome in breast cancer patients after the use of MammaPrint and BluePrint to guide preoperative systemic treatment decisions. *Eur J Cancer*. 2022 May;167:92-102.

Holleman MS, Huygens SA, Al MJ, Kuppen MCP, Westgeest HM, van den Bergh ACM, Bergman AM, van den Eertwegh AJM, **Hendriks MP**, Lampe MI, Mehra N, van Moorselaar RJA, van Oort IM, Somford DM, de Wit R, van de Wouw AJ, Gerritsen WR, Groot CAU. Being Transparent About Brilliant Failures: An Attempt to Use Real-World Data in a Disease Model for Patients with Castration-Resistant Prostate Cancer. *Drugs Real World Outcomes*. 2022 Jun;9(2):275-285.

Smit KC, Derksen JWG, Beets GLO, Belt EJT, Berbée M, Coene PPLO, van Cruijsen H, Davidis MA, Dekker JWT, van Dodewaard-de Jong JM, Haringhuizen AW, Helgason HH, **Hendriks MP**, Hoekstra R, de Hingh IHJT, IJzermans JNM, Janssen JJB, Konsten JLM, Los M, Mekenkamp LJM, Nieboer P, Peeters KCMJ, Peters NAJB, Pruijt HJFM, Quarles van Ufford-Mannesse P, Rietbroek RC, Schiphorst AHW, Schouten van der Velden A, Schrauwen RWM, Sie MPS, Sommeijer DW, Sonneveld DJA, Stockmann HBAC, Tent M, Terheggen F, Tjin-A-Ton MLR, Valkenburg-van Iersel L, van der Velden AMT, Vles WJ, van Voorthuizen T, Wegdam JA, de Wilt JHW, Koopman M, May AM, On Behalf Of The Plcrc Study Group. Physical Activity Is Associated with Improved Overall Survival among Patients with Metastatic Colorectal Cancer. *Cancers* (Basel). 2022 Feb 16;14(4):1001.

Hoes LR, van Berge Henegouwen JM, van der Wijngaart H, Zeverijn LJ, van der Velden DL, van de Haar J, Roepman P, de Leng WJ, Jansen AML, van Werkhoven E, van der Noort V, Huitema ADR, Gort EH, de Groot JWB, Kerver ED, de Groot DJ, Erdkamp F, Beerepoot LV, **Hendriks MP**, Smit EF, van der Graaf WTA, van Herpen CML, Labots M, Hoeben A, Morreau H, Lolkema MP, Cuppen E, Gelderblom HJ, Verheul HMW, Voest EE. Patients With Rare Cancers in the Drug Rediscovery Protocol (DRUP) benefit from Genomics - Guided Treatment. *Clin Cancer Res*. 2022 Jan 19:clincanres.3752.2021.

Smilde BJ, Louwerenburg AF, van Santen MM, **Hendriks MP**. Leptomeningeal Metastases From Colorectal Signet-Ring Cell Cancer: A Case Report and Literature Review. *Clin Colorectal Cancer*. 2021 Nov 28:S1533-0028(21)00126-2.

van der Kruijssen DEW, Elias SG, Vink GR, van Rooijen KL, 't Lam-Boer J, Mol L, Punt CJA, de Wilt JHW, Koopman M; CAIRO4 Working Group (including **Hendriks MP**). Sixty-Day Mortality of Patients With Metastatic Colorectal Cancer Randomized to Systemic Treatment vs Primary Tumor Resection Followed by Systemic Treatment: The CAIRO4 Phase 3 Randomized Clinical Trial. *JAMA Surg*. 2021 Oct 6.

van Nassau SC, Bond MJ, Scheerman I, van Breeschoten J, Kessels R, Valkenburg-van Iersel LB, Verheul HM, Buffart TE, Mekenkamp LJ, Lemmens VE, Koopman M, Bol GM; EXCITE (From Clinical Trial to Bedside: Triplet Chemotherapy in Metastatic Colorectal Cancer) Study Group (including **Hendriks MP**). Trends in Use and Perceptions About Triplet Chemotherapy Plus Bevacizumab for Metastatic Colorectal Cancer. *JAMA Netw Open*. 2021 Sep 1;4(9):e2124766.

Westgeest HM, Kuppen MCP, van den Eertwegh FAJM, van Oort IM, Coenen JLLM, van Moorselaar JRJA, Aben KKH, Bergman AM, Huinink DTB, van den Bosch J, **Hendriks MP**, Lampe MI, Lavalaye J, Mehra N, Smilde TJ, Somford RDM, Tick L, Weijl NI, van de Wouw YAJ, Gerritsen WR, Groot CAU. High-Intensity Care in the End-of-Life Phase of Castration-Resistant Prostate Cancer Patients: Results from the Dutch CAPRI-Registry. *J Palliat Med*. 2021 Aug 19.

Ham L, Fransen HP, van den Borne B, **Hendriks MP**, van Laarhoven HW, van der Padt-Pruijsten A, Raijmakers N, van Roij J, Sommeijer DW, Vriens BE, van Zuylen L, van de Poll-Franse L. Bereaved relatives' quality of life before and during the COVID-19 pandemic: Results of the prospective, multicenter, observational eQuiPe study. *Palliat Med*. 2021 Jul 20:2692163211034120.

Mendelaar PAJ, Smid M, van Riet J, Angus L, Labots M, Steeghs N, **Hendriks MP**, Cirkel GA, van Rooijen JM, Ten Tije AJ, Lolkema MP, Cuppen E, Sleijfer S, Martens JWM, Wilting SM. Author Correction: Whole genome sequencing of metastatic colorectal cancer reveals prior treatment effects and specific metastasis features. *Nat Commun*. 2021 Jan 25;12(1):574.

Leeneman B, Blommestein HM, Coupé VMH, **Hendriks MP**, Kruit WHJ, Plaisier PW, van Ruth S, Ten Tije AJ, Wouters MWJM, Franken MG, Uyl-de Groot CA. Real-world healthcare costs of localized and regionally advanced cutaneous melanoma in the Netherlands. *Melanoma Res*. 2021 Apr 12.

van der Heijden JAG, Qaderi SM, Verhoeven R, Custers JAE, Klarenbeek BR, Maaskant-Braat AJG, de Wilt JHW; on behalf of the PLCRC group (including **Hendriks MP**). Transanal total mesorectal excision and low anterior resection syndrome. *Br J Surg*. 2021 Aug 19;108(8):991-997.

Kroon LL, van Roij J, Korfage IJ, Reyners AKL, van den Beuken-van Everdingen MHJ, den Boer MO, Creemers GJ, de Graeff A, **Hendriks MP**, Hunting JCB, de Jong WK, Kuip EJM, van Laarhoven HWM, van Leeuwen L, van Lindert ASR, Mandigers CMPW, Nieboer P, van der Padt-Pruijsten A, Smilde TJ, Sommeijer DW, Thijs MF, Tiemessen MA, Vos AH, Vreugdenhil A, Werner PT, van Zuylen L, van de Poll-Franse LV, Raijmakers NJH; eQuiPe study group. Perceptions of involvement in advance care planning and emotional functioning in patients with advanced cancer. *J Cancer Surviv*. 2021 Apr 10.

Moncada-Torres A, van Maaren MC, **Hendriks MP**, Siesling S, Geleijnse G. Explainable machine learning can outperform Cox regression predictions and provide insights in breast cancer survival. *Sci Rep*. 2021 Mar 26;11(1):6968.

Derksen JWG, Vink GR, Elferink MAG, Roodhart JML, Verkooijen HM, van Grevenstein WMU, Siersema PD, May AM, Koopman M; PLCRC Study Group (including **Hendriks MP**). The Prospective Dutch Colorectal Cancer (PLCRC) cohort: real-world data facilitating research and clinical care. *Sci Rep*. 2021 Feb 16;11(1):3923.

Mendelaar, P.A.J., Smid, M., van Riet, J., Angus L, Labots M, Steeghs N, **Hendriks MP**, Cirkel GA, van Rooijen JM, Ten Tije AJ, Lolkema MP, Cuppen E, Sleijfer S, Martens JWM, Wilting S. M. Whole genome sequencing of metastatic colorectal cancer reveals prior treatment effects and specific metastasis features. *Nat Commun*. 2021 Jan 25;12(1):574.

Mohammadi P, Heitbrink MA, Wagenaar JFP, **Hendriks MP**. Brain lesions in a patient with rectal cancer: mind your step. *Neth J Med*. 2020 Dec;78(6):381-384.

Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Meershoek-Klein Kranenbarg E, Roodvoets AGH, Nagtegaal ID, Beets-Tan RGH, Blomqvist LK, Fokstuen T, T en Tije AJ, Capdevila J, **Hendriks MP**, Edhemovic I, Cervantes A, Nilsson PJ, Glimelius B, van de Velde CJH, Hospers GAP. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021 Jan;22(1):29-42.

Brinkman-Stoppelenburg A, Vergouwe Y, Booms M, **Hendriks MP**, Peters LA, van Ufford-Mannesse PQ, Terheggen F, Verhage S, van der Vorst MJDL, Willemsen I, Polinder S, van der Heide A. The Impact of Palliative Care Team Consultation on Quality of Life of Patients with Advanced Cancer in Dutch Hospitals: An Observational Study. *Oncol Res Treat*. 2020;1-7.

Jansen T, Geleijnse G, Van Maaren M, **Hendriks MP**, Ten Teije A, Moncada-Torres A. Machine Learning Explainability in Breast Cancer Survival. *Stud Health Technol Inform*. 2020;270:307-311.

van der Valk MJM, Marijnen CAM, van Etten B, Dijkstra EA, Hilling DE, Meershoek-Klein Kranenbarg E, Putter H, Roodvoets AGH, Bahadoer RR, Fokstuen T, Jan Ten Tije A, Capdevila J, **Hendriks MP**, Edhemovic I, Cervantes AMR, de Groot DJA, Nilsson PJ, Glimelius B, van de Velde CJH, Hospers GAP; Collaborative investigators. Erratum to "Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. *Radiother Oncol*. 2020 Jun;147:e1.

Gootjes EC, van der Stok EP, Buffart TE, Bakkerus L, Labots M, Zonderhuis BM, Tuynman JB, Meijerink MR, van de Ven PM, Haasbeek CJA, Ten Tije AJ, de Groot JW, **Hendriks MP**, van Meerten E, Nuyttens JJME, Grunhagen DJ, Verhoef C, Verheul HMW. Safety and Feasibility of Additional Tumor Debulking to First-Line Palliative Combination Chemotherapy for Patients with Multiorgan Metastatic Colorectal Cancer. *Oncologist*. 2020 Aug;25(8):e1195-e1201.

Kuppen MC, Westgeest HM, van der Doelen MJ, van den Eertwegh AJM, Coenen JL, Aben KK, van den Bergh AC, Bergman AM, van den Bosch JV, Celik F, **Hendriks MP**, Lavalaye J, van der Meer SV, Polee MB, Somford DM, van Oort IM, Uyl-de Groot CA, Gerritsen WR. Real-world outcomes of radium-223 dichloride for metastatic castration resistant prostate cancer. *Future Oncol*. 2020 Jul;16(19):1371-1384.

Ebben KCWJ, Sieswerda MS, Luiten EJT, Heijns JB, van der Pol CC, Bessems M, Honkoop AH, **Hendriks MP**, Verloop J, Verbeek XAAM. Impact on Quality of Documentation and Workload of the Introduction of a National Information Standard for Tumor Board Reporting. *JCO Clin Cancer Inform*. 2020;4:346–356.

van der Valk MJM, Marijnen CAM, van Etten B, Dijkstra EA, Hilling DE, Meershoek-Klein Kranenbarg E, Putter H, Roodvoets AGH, Bahadoer RR, Fokstuen T, Ten Tije AJ, Capdevila J, **Hendriks MP**, Edhemovic I, Cervantès AMR, de Groot DJ, Nilsson PJ, Glimelius B, van de Velde CJH, Gospers GAP. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. *Radiother Oncol*. 2020;147:75–83.

Kuppen MCP, Westgeest HM, van den Eertwegh AJM, Coenen JLLM, van Moorselaar RJA, van den Berg P, Geenen MM, Mehra N, **Hendriks MP**, Lampe MI, van de Luijtgaarden ACM, Peters FPJ, Roeleveld TA, Smilde TJ, de Wit R, van Oort IM, Gerritsen WR, Uyl-de Groot CA. Health-related quality of life and pain in a real-world castration resistant prostate cancer population: results from the PRO-CAPRI-study in the Netherlands. *Clin Genitourin Cancer*. 2020 Jun;18(3):e233-e253.

Brinkman-Stoppelenburg A, Polinder S, Olij BF, van den Berg B, Gunnink N, **Hendriks MP**, van der Linden YM, Nieboer D, van der Padt-Pruijsten A, Peters LA, Roggeveen B, Terheggen F, Verhage S, van der Vorst MJ, Willemen I, Vergouwe Y, van der Heide A. The association between palliative care team consultation and hospital costs for patients with advanced cancer: An observational study in 12 Dutch hospitals. *Eur J Cancer Care* (Engl). 2020;29(3):e13198.

Kuppen MCP, Westgeest HM, van den Eertwegh AJM, van Moorselaar RJA, van Oort IM, Coenen JLLM, van den Bergh ACMF, Mehra N, Somford DM, Bergman AM, ten Bokkel Huinink D, Fossion L, Geenen MM, **Hendriks MP**, van de Luijtgaarden ACM, Polee MB, Weijl NI, van de Wouw AJ, de Wit R, Uyl-de Groot CA, Gerritsen WR. Real-world Outcomes of Sequential Androgen-receptor Targeting Therapies with or Without Interposed Life-prolonging Drugs in Metastatic Castration-resistant Prostate Cancer: Results from the Dutch Castration-resistant Prostate Cancer Registry. *Eur Urol Oncol*. 2019 Oct 7:S2588-9311(19)30146-4.

Overgaauw AJC, Speijers-van der Plas LM, **Hendriks MP**, Smorenburg CH. Outcome and feasibility of palliative chemotherapy in very elderly patients with metastatic breast cancer. *Breast J*. 2020;26(3):433–439.

Hoveling LA, van Maaren MC, Hueting T, Strobbe LJA, **Hendriks MP**, Sonke GS, Siesling S. Validation of the online prediction model CancerMath in the Dutch breast cancer population. *Breast Cancer Res Treat*. 2019;178(3):665–681.

Westgeest HM, Kuppen MCP, van den Eertwegh AJM, de Wit R, Coenen van den Berg HPP, Mehra N, van Oort IM, Fossion LMCL, Hendriks MP, Bloemendal HJ, van de Luijtgaarden ACM, ten Bokkel Huinink D, van den Bergh ACMF, van den Bosch J, Polee MB, Weijl N, Bergman AM, Uyl-de Groot CA, Gerritsen WR. Second-Line Cabazitaxel Treatment in Castration-Resistant Prostate Cancer Clinical Trials Compared to Standard of Care in CAPRI: Observational Study in the Netherlands. *Clin Genitourin Cancer*. 2019;17(5):e946–e956.

Ham JC, Driessen CM, **Hendriks MP**, Fiets E, Kreike B, Hoeben A, Slingerland M, van Opstal CC, Kullberg BJ, Jonker MA, Adang EM, Kaanders JH, van der Graaf WT, van Herpen CM. Prophylactic antibiotics reduce hospitalisations and cost in locally advanced head and neck cancer patients treated with chemoradiotherapy: A randomised phase 2 study. *Eur J Cancer*. 2019;113:32–40.

Kwakman JJM, van Werkhoven E, Simkens LHJ, van Rooijen JM, van de Wouw YAJ, Ten Tije AJT, Creemers GM, **Hendriks MP**, Los M, van Alphen RJ, Polée MB, Muller EW, van der Velden AMT, van Voorthuizen T, Koopman M, Mol L, Punt CJA. Updated Survival Analysis of the Randomized Phase III Trial of S-1 Versus Capecitabine in the First-Line Treatment of Metastatic Colorectal Cancer by the Dutch Colorectal Cancer Group. *Clin Colorectal Cancer*. 2019 Jan 29.

Leeneman B, Franken MG, Coupé VMH, **Hendriks MP**, Kruit W, Plaisier PW, van Ruth S, Verstijnen JAMC, Wouters MWJM, Blommestein HM, Uyl-de Groot CA. Stage-specific disease recurrence and survival in localized and regionally advanced cutaneous melanoma. *Eur J Surg Oncol*. 2019 Feb 5.

Kraaijenbrink BV, Schindhelm RK, **Hendriks MP**. Uw diagnose? *Nederlands Tijdschrift voor Hematologie*. 2018; 15: 132-3.

PLCRC onderzoeksteam (including **Hendriks MP**). Prospectief Landelijk CRC-cohort: een infrastructuur voor klinische studies naar darmkanker. *Nederlands Tijdschrift voor Oncologie*. 2018; 15: 60-3.

van Kalleveen van MW, Walraven M, **Hendriks MP**. Pazopanib-related tumor lysis syndrome in metastatic clear cell renal cell carcinoma: a case report. *Invest New Drugs*. 2018 Feb 20.

Latenstein AEJ, **Hendriks MP**, van Halsema EE, van Hooft EJ, van Berkel AM. Long-Term Colon Stent Patency for Obstructing Colorectal Cancer Combined with Bevacizumab. *Case Rep Gastroenterol*. 2017;11:703-709.

Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, de Wit R, van den Bergh ACM, Coenen JLLM, Beerlage HP, **Hendriks MP**, Bos MMEM, van den Berg P, Agnes van de Wouw, Spermon R, Boerma MO, Geenen MM, Tick LW, Polee MB, Bloemendal HJ, Cordia I, Peters FPJ, de Vos AI, van den Bosch J, van den Eertwegh AJM, Gerritsen WR. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry. *Eur Urol Focus*. 2016 Oct 13.

Kwakman JJ, Simkens LH, van Rooijen JM, van de Wouw AJ, Ten Tije AJ, Creemers GJ, **Hendriks MP**, Los M, van Alphen RJ, Polée MB, Muller EW, van der Velden AM, van Voorthuizen T, Koopman M, Mol L, van Werkhoven E, Punt CJ. Randomised phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group. *Ann Oncol*. 2017 Apr 5.

Beekmans N, Eggink EA, Opdam FL, **Hendriks MP**. "Chemotherapie geïnduceerde leverschade." *Nederlands Tijdschrift voor Oncologie*. 2016; 13: 156-62.

Bakker SF, Moolenaar W, Santen van MM, **Hendriks MP**. "Diarrhoea caused by diffuse metastatic lobular breast cancer." *Case Rep in Oncol Med*. 2016;2016:1785409.

Rootjes PA, Gelderblom H, **Hendriks MP**. A 29-year-old woman with multiple pulmonary masses. Synovial sarcoma. *Neth J Med*. 2015 Jul;73(6):299-301

Leeneman B, Franken MG, Blommestein HM, van Gils CW, van der Meijde E, Wouters MW, Plaisier PW, Kruit WH, van Ruth S, Ten Tije AJ, **Hendriks MP**, Coupe VM, Uyl-de Groot CA. The Importance of Long-Term Surveillance of Stage IB Melanomas: Unexpectedly Low Survival Subsequent to Recurrence. *Value Health*. 2014 Nov;17(7):A618-9.

Hendriks MP, Laarhoven HW, Sande van de MJ, van Weel-Baumgarten E, Verhagen CA, Visser KC. Palliative care for an islamic patient: changing frameworks. *J Palliat Med*. 2012 Oct; 15(10):1053-5

Hendriks MP, Driessen CM, van Laarhoven HW, Janssens GO, Verbist BM, van der Graaf WT, Slootweg PJ, Merkx MA, Herpen CM. Aggressive fibromatosis in the head and neck region: a benign tumor with often mutilating effects. *Head Neck*. 2012 aug 21.

Oomen JW, Smits BW, Swinkels DW, Schreurs BW, Bloem BR, **Hendriks MP**. A toxic shot from the hip. *J Neurol Neurosurg Psychiatry*. 2011 Mar; 82(3): 353-4.

Hendriks MP, Wanten GJ, Drenth JP. Management of hemobilia and pancreatitis after liver biopsy: a key role for endoscopic retrograde cholangiopancreaticography. *Liver Transpl*. 2009 Nov; 15(11):1653-4.

Hendriks MP, van Deuren M. A woman with a painful and swollen hand. *Neth J Med*. 2009 Mar;67(3):27-28.

Hendriks MP, Janssens GO, Sprong T, Bleeker-Rovers CP, van Laarhoven HW, van Herpen CM, Merkx MA. Agressieve fibromatose in het hoofdhalsgebied: een benigne tumor met vaak mutilerende effecten. *Nederlands Tijdschrift voor Oncologie*. 2008;5:311-6.

Hendriks MP, de Sévaux RGL, Hilbrands LB. Response to letter to the editor. *Neth J Med*. 2008 Oct;66(9):397.

Hendriks MP, de Sévaux RGL, Hilbrands LB. Encapsulating peritoneal sclerosis in patients on peritoneal dialysis for end-stage renal failure: a case series and review of the literature. *Neth J Med*. 2008 Jul-Aug;66(7):269-74.

Preijers FWMB, **Hendriks MP**, Schaap NPM, Schattenberg A. T cell and B cell depletion in an allogeneic stem cell transplantation setting by employing CD3+/CD19+ cell depletion and enrichment of CD34+ cells. *CliniMACS newsletter* 2008.

Hendriks MP, van Krieken JHJM, de Witte TJM, Schaap NPM. Twee volwassen patiënten met auto-immuun lymfoproliferatief syndroom. *Nederlands Tijdschrift voor Hematologie*. 2007; 6: 232-6.

Hendriks MP, Blijlevens NMA, Schattenberg AVMB, Burger DM, Donnelly JP. Cyclosporine short infusion and C2 monitoring in haematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2006 Oct; 38(7): 521-5.

Akol H, **Hendriks MP**, Koolen MI, Jansen JLJ, Hollander AAMJ. Acute renal failure associated with salmonella enteritidis infection. *Neth J Med*. 2001; 58: A69.

Other contribution to research

Investigator in the Keynote-045 trial. Bellmunt J *et al*. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med*. 2017 Mar 16;376(11):1015-1026.

Investigator in the Keynote-412 trial. Machiels JP *et al*. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2024 May;25(5):572-587.

Investigator in the CAIRO4 study. Van der Kruijssen DEW *et al*. Upfront resection versus no resection of the primary tumor in patients with synchronous metastatic colorectal cancer: the randomized phase 3 CAIRO4 study conducted by the Dutch Colorectal Cancer Group and the Danish Colorectal Cancer Group. *Ann Oncol*. 2024 Jun 7:S0923-7534(24)00722-1.