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BY
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DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

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CV

Lasse Lefevre Samson received his BSc in Biomedical Engineering from Aalborg University in 2010. In 2012, he received his MSc in Biomedical Engineering with specialization in medical informatics from Aalborg University. From October 2012, he was employed for six months as a research assistant at the Medical Informatics Group, Department of Health Science and Technology, Aalborg University. In March 2013, he started his PhD study as a part of the MuxBCT project at the Medical Informatics Group, Department of Health Science and Technology, Aalborg University.

The thesis is based on the following five papers:

Paper A:

L.L. Samson, L.B. Pape-Haugaard, M. Søgaard, H.C. Schønheyder, O.K. Hejlesen, Exploring end users' system requirements for a handheld computer supporting both sepsis test workflow and current IT solutions., Stud. Health Technol. Inform. 192 (2013) 524–8.

Conference paper presented at MEDINFO 2013, Copenhagen.

Paper B:

L.L. Samson, L.B. Pape-Haugaard, M. Søgaard, H.C. Schønheyder, O.K. Hejlesen, Participatory heuristic evaluation of a tablet computer system for clinical microbiology., Stud. Health Technol. Inform. 205 (2014) 910–4.

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Paper C:

L.L. Samson, L. Pape-Haugaard, M.C. Meltzer, M. Fuchs, H.C. Schønheyder, O. Hejlesen, Design of a Tablet Computer App for Facilitation of a Molecular Blood Culture Test in Clinical Microbiology and Preliminary Usability Evaluation., JMIR mHealth uHealth. 4 (2016) e20.

Paper D:

L.L. Samson, L. Pape-Haugaard, H.C. Schønheyder, O. Hejlesen, Tablet App Facilitating Workflow of a Rapid Molecular Diagnostic Test for Clinical Microbiology.

Submitted to International Journal of Medical Informatics.

Paper E:

L.L. Samson, L. Pape-Haugaard, M.C. Meltzer, M. Fuchs, H.C. Schønheyder, O. Hejlesen, Rapid Molecular Identification of Blood Culture Isolates Supported by a Tablet Computer.

Submitted to Journal of Microbiological Methods.

ENGLISH SUMMARY

Tablets and smartphones are increasingly often being used to support workflows of healthcare professionals in clinical settings. Studies have shown that mobile devices can facilitate workflows by providing access to clinical information systems while supporting the mobility requirements of the users. The use of tablets is promising as they provide a reasonable screen size while remaining easily portable. Studies have primarily reported on the effects on workflow by using tablets in patient wards. There is an interest in the use of tablets in clinical microbiology, where they can potentially be used to facilitate workflows of advanced diagnostic tests to provide accurate and timely results.

In recent years, many advanced molecular diagnostic tests have become available for use in clinical microbiology. The tests can provide earlier identification of pathogens infecting the bloodstreams that often leads to sepsis. Sepsis is associated with high mortality, but early identification of the causative microorganisms allows for a targeted antimicrobial treatment of sepsis patients that can improve the outcome. A disadvantage of the advanced molecular diagnostic tests is that they often have workflows that are more complex than the routine diagnostic methods.

This PhD thesis is part of a research project that aims to develop a rapid molecular diagnostic test called MuxBCT, which is used for the identification of microorganisms from positive blood cultures (BCs). The objective of this PhD thesis was to investigate how to design and evaluate a MuxBCT tablet app that aims to facilitate the MuxBCT diagnostic test.

Four studies were conducted as a part of this PhD thesis. The first study was an observational study of the workflow of medical laboratory scientists (MLSs) during BC analysis, which provided a set of requirements that the MuxBCT app needed to support. Based on the findings from the first study, a prototype of MuxBCT was designed. In study two, four usability experts and four MLSs evaluated the prototype in a participatory heuristic evaluation, which revealed domain-related usability issues. The results of study two guided the further design of the MuxBCT app and led to an optimization of the user interface and changed the app functionality.

In study three, the MuxBCT app design and system architecture was evaluated through a clinical simulation. Four MLSs used the MuxBCT app in a clinical microbiology laboratory to guide the use of a simulated MuxBCT test for identification of eight microorganisms from mocked BCs. The study findings indicated that the system design was feasible for supporting the MuxBCT test as all eight microorganisms were correctly identified. Study four was a non-interventional study, where the MuxBCT app was used together with a prototype of the MuxBCT test. Four MLSs analyzed positive BCs in a clinical microbiology laboratory in

parallel with routine diagnostics. For 124 BCs, the MuxBCT results had an accuracy of 92.7% and were available near the time of preliminary routine test results. Additionally, the users reported that the app had successfully facilitated the use of the MuxBCT test.

In conclusion, this PhD thesis demonstrates that specialized tablet apps can be used to support the workflows of advanced diagnostic tests in clinical laboratories.

DANSK RESUME

Tablets og smartphones bliver i stigende grad anvendt til at understøtte arbejdsgange af sundhedsprofessionelle i kliniske miljøer. Studier har vist, at de mobile enheder kan facilitere arbejdsgange ved at give adgang til kliniske informationssystemer imens brugerens behov for mobilitet understøttes. Brugen af tablets er lovende, da de tilbyder en rimelig skærm størrelse imens de er nemt flytbare. Studier har primært rapporteret effekten af tablets på arbejdsgange i patientafsnit. Der er en interesse i brugen af tablets i klinisk mikrobiologi, hvor de kan bruges til at facilitere arbejdsgange relateret til avancerede diagnostiske tests for at opnå præcise og rettidige resultater.

Igennem de seneste år er mange avancerede molekylære diagnostiske tests blevet tilgængelige til brug i klinisk mikrobiologi. Testene kan på kortere tid identificere mikroorganismer, der inficerer blodbanerne og som ofte leder til sepsis. Sepsis er forbundet med en høj dødelighed, men en tidlig identifikation af de forårsagende mikroorganismer tillader en målrettet antibakteriel behandling, der kan forbedre udfaldet af behandling. En ulempe ved de avancerede molekylære diagnostiske tests er, at de generelt medfører arbejdsgange som er mere komplekse end de rutinemæssige diagnostiske metoder.

Denne ph.d.-afhandling er en del af et forskningsprojekt, hvor fokus har været udviklingen af en hurtig molekylær diagnostisk test kaldet MuxBCT, der bruges til identifikation af mikroorganismer fra positive bloddyrkninger. Målet for denne ph.d.-afhandling var at designe og evaluere en MuxBCT tablet app, der har som mål at facilitere brugen af den diagnostiske MuxBCT test.

Fire studier blev udført som en del af denne ph.d.-afhandling. Det første studie var et observationsstudie af bioanalytikeres arbejdsgang ved analyse af bloddyrkninger, hvilket udmundende i nogle basale krav, der skulle understøttes af MuxBCT appen. Baseret på fundene fra studiet blev en prototype af MuxBCT designet. I studie to blev prototypen analyseret af fire usability eksperter og fire bioanalytikere igennem en participatorisk heuristisk evaluering, der viste domæne-relaterede usabilityproblemer. Resultaterne af studie to guidede det videre design af MuxBCT appen og førte til en optimeret brugergrænseflade og ændringer i appens funktionalitet.

I studie tre blev design og systemarkitektur af MuxBCT appen evalueret igennem et klinisk simulationsstudie. Fire bioanalytikere anvendte MuxBCT appen i et klinisk mikrobiologisk laboratorium til at guide brugen af en simuleret MuxBCT test til at identificere otte mikroorganismer fra kunstige bloddyrkninger. Studiets resultater indikerede, at det med systemdesignet var muligt at understøttede MuxBCT testen, da alle otte mikroorganismer blev identificeret korrekt. Studie fire var et ikke-interventionsstudie, hvor MuxBCT appen blev brugt sammen med en prototype af

MuxBCT testen. Fire bioanalytikere analyserede i alt 124 positive bloddyrkninger i et klinisk mikrobiologisk laboratorium, hvilket foregik i parallel med den rutinemæssige diagnostik. MuxBCT resultaterne havde en nøjagtighed på 92,7% og var tilgængeligt nær tidspunktet for det rutinemæssige præliminære testresultat. Ydermere rapporterede brugerne at MuxBCT appen med succes havde faciliteret brugen af MuxBCT testen.

Som konklusion har denne ph.d.-afhandling vist at specialiserede tablet apps kan anvendes til at understøtte arbejdsgange af avancerede diagnostiske tests i kliniske laboratorier.

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PREFACE

This PhD thesis has been submitted for assessment in partial fulfillment of the PhD degree at the Department of Health Science and Technology, Aalborg University, Denmark. This thesis presents the work I conducted during my PhD study in the period March 2013 to March 2016. The work of this PhD study was done under the supervision of Ole Hejlesen and Louise Pape-Haugaard, Aalborg University.

The PhD study was carried out as a part of the Multiplex Blood Culture Test (MuxBCT) project. The project was supported by a grant from the Danish National Advanced Technology Foundation (now Innovation Fund Denmark). The other partners in the project were:

- AdvanDx, Inc.
- Department of Clinical Microbiology, Aalborg University Hospital
- DTU Nanotech
- DTU Systems Biology

This thesis is based on four studies that were conducted during the PhD study. Five papers were prepared from the results of the four studies, which are presented in Chapter 7. Two papers were accepted and presented at conferences, one paper has been published in a journal, and two papers have been submitted to journals. Some of the material in this thesis is a part of these papers.

The descriptions of MuxBCT diagnostic test in this thesis are based on a prototype of the test, which was used in the final study that is a part of this thesis. The MuxBCT test is likely to undergo further changes in its development, and future versions of the test may deviate from the descriptions in this thesis.

Throughout this thesis, the term tablet will refer to a tablet computer. The term app will refer to an application, i.e., a software application designed for use on tablets and/or smartphones.

ABBREVIATIONS

AST	Antimicrobial stewardship team
BC	Blood culture
BSI	Bloodstream infection
CIS	Clinical information system
EHR	Electronic health record
FISH	Fluorescence in situ hybridization
LIS	Laboratory information system
MLS	Medical laboratory scientist
PDA	Personal digital assistant
PNA	Peptide nucleic acid
SOA	Service-oriented architecture
SUS	System usability scale
TAT	Turnaround time

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

Handheld mobile computers such as tablets and smartphones have in recent years become ubiquitous in daily life, and the devices are being introduced in clinical settings [1–5]. Mobility is an important aspect of many workflows in clinical settings, and the use of these modern mobile devices has the potential for supporting access to patient information while providing the mobility required by the users [2,6]. However, there is a need for more research to optimize the use of smartphones and tablets as a part of the clinical workflow [2,7].

Informatics have an important role in clinical microbiology as the laboratory information systems (LIS) is continuously used throughout many diagnostic workflows [8]. The integration of informatics in clinical microbiology is considered important to provide timely and accurate results of microbiological testing [8]. Some diagnostic test instruments have the ability to communicate data directly with the LIS, which facilitates the operator's workflow by reducing hands-on time, and by reducing errors related to manual entry of results [8,9].

In the past decade advances in molecular diagnostic tests for use in clinical microbiology has provided an opportunity for earlier identification of the microorganism causative of bloodstream infection (BSI). BSIs often lead to sepsis, which is associated with a high risk of mortality. While commercial molecular diagnostic tests are available, they have not replaced the common diagnostic tools [10–12]. Studies have shown that the molecular tests reduce time to administration of an effective antimicrobial therapy, which can improve patient outcome [12]. However, the use of molecular diagnostic tests often requires a more complex workflow in comparison to the use of routine diagnostic methods [11,13,14].

This thesis is based on studies conducted as part of a research project called the MuxBCT project. The focus of the MuxBCT project is the research, development, and evaluation of a new molecular diagnostic test called MuxBCT. The MuxBCT test is a fluorescence in situ hybridization (FISH) molecular diagnostic test. The test aims to provide direct identification of 18 microorganisms at a species or group level from positive blood cultures (BCs) within an hour.

Tablets and smartphones present an opportunity to support the complex diagnostic workflows that take place in clinical laboratories through the development of specialized apps. Tablets provide a reasonable compromise between screen size user mobility. A tablet app may be able to facilitate the workflow of advanced diagnostic test such as MuxBCT by providing context-based test guidance and by offering the means of integration with the LIS to promote efficient communication of test results.

CHAPTER 2. BACKGROUND

This chapter introduces the background for the thesis. It aims to provide a description of sepsis, the importance of a timely initiated effective treatment, and how advanced molecular diagnostic tests are available for providing an early identification of the causative pathogens. The background also describes the growing use of tablets in clinical workflows, the benefits that may be gained by use of tablets in clinical settings, the importance of usability of such systems, and how the usability can be evaluated during the design and development of the systems.

2.1. SEPSIS

Sepsis is a severe inflammatory response to an infection in which the body causes damage to its tissue and organs [11,15]. The underlying pathogens that are causative of sepsis can be bacteria, yeasts, viruses or parasites [16]. Most available data on the epidemiology of sepsis is from developed countries [17]. However, sepsis is considered a global burden and a major challenge in medicine as the estimated incidence of severe sepsis is 18-20 million cases each year [11,16,18]. It is estimated, that sepsis is the cause of death for up to 5.3 million people annually [18]. The treatment of sepsis patients is associated with large expenses [19]. Infants, the elderly, and those with weakened immune systems or chronic diseases are at an increased risk of being affected [19,20].

Sepsis is categorized by degree of severity as sepsis, severe sepsis or septic shock. The mortality of sepsis increases with the severity with a mortality of around 13-17% for sepsis, 20-30% for severe sepsis, and up to 50% for septic shock [16,18,19,21–24]. The severity can progress rapidly if proper treatment is not administered [23]. Each hour of delay in the initiation of an effective antimicrobial therapy leads to an increase in mortality [25].

In the US, 2% of all hospitalized patients are estimated to have sepsis of which half require intensive care treatment [26]. However, half of all sepsis patients in the need of intensive care are never transferred to an intensive care unit [23]. Those who initially survive sepsis have a high mortality in the years following hospital discharge [27]. Additionally, the quality of life is often reduced due to physical and cognitive decline [27,28].

2.1.1. TREATMENT

The treatment of sepsis relies on an early recognition and the initiation of treatment bundles. International guidelines recommend that once a patient is diagnosed with sepsis, an antimicrobial therapy must be initiated quickly [25]. The initial therapy

typically covers a broad spectrum to be effective against all likely pathogens. The choice of antibiotics is a complex decision, which can depend on individual patient factors such as underlying disease, known infections, and general antibiotic susceptibility of pathogens that are prevalent in the community of the patient and the hospital [25].

For 9-27% of sepsis patients the initially administered antimicrobial therapy is not appropriate [29–32]. If the initial antimicrobial therapy is inadequate, i.e. a therapy not effective against the causative pathogen, it is associated with an increased patient mortality [29–31]. For patients with septic shock every hour of delay before an effective treatment is started after the onset of hypotension, the mortality of the septic shock patient rises by nearly 8% [22]. Septic shock patients who initially receive an inadequate therapy has a fivefold increase in mortality [29].

Identification of the underlying causative pathogen and its susceptibility is necessary to guide the treatment of a sepsis patient. When results become available from microbiological testing, the initial antimicrobial therapy can be changed if the treatment is found ineffective or it can be deescalated to an antibiotic with a narrow-spectrum [25].

BCs are considered the gold standard for the identification of microorganisms causative of bacteremia [33]. Once a patient is diagnosed with sepsis, sets of two or three BCs are collected before initiation of antimicrobial therapy to avoid sterilization of the samples. The BCs contain media that is optimized for the growth of either aerobic or anaerobic microorganisms. The BCs are drawn from different locations, which may include vascular devices such as catheters [25]. Once the BCs have been collected, they are transported to a clinical microbiology laboratory, where the BCs are incubated.

BCs typically require a microorganism growth time of 6 to 48 hours before they are signaled as positive by the automated incubator system [34,35]. Although BCs are considered the gold standard, their use is not optimal due the delay in pathogen identification caused by microorganism growth time. An additional issue is that 30-40% of BCs are negative for patients with sepsis [16,21].

Once BCs are signaled as positive, they are routinely examined by Gram stain and wet mount microscopy [36]. This provides a preliminary result about the pathogen's Gram stain reaction, morphology, and motility. The Gram stain is a quick test to conduct, and studies have shown that Gram stains have a very high accuracy [36,37]. The timely availability of Gram stain results is critical, as the Gram stain reaction can guide optimizations of the patient's treatment. The communication of the Gram stain results has shown to have a greater impact on antimicrobial therapy changes than the communication of antibiotic susceptibility results [38]. Delays in the availability of Gram stain results have shown to lead to an increased patient mortality [39]. After

the availability of Gram stain results 30-45% of patients have their initial antimicrobial therapy adjusted [36]. The preliminary results are followed by a subculture of microorganisms on plate media, which requires grows overnight before the causative pathogen can be identified [10]. Antibiotic susceptibility testing requires additional time before availability.

2.1.2. MOLECULAR DIAGNOSTIC TESTS

Treatment of sepsis requires diagnostic tests that can rapidly provide specific identification of pathogens and potentially provide information on antibiotic susceptibility [40,41]. The sepsis diagnostic tests should ideally be simple to use, and they should support quick communication of results to the attending staff of the sepsis patient. To support result communication, the test should ideally be integrated into existing clinical information systems (CISs) such as the LIS [40]. The development of rapid diagnostic tests and their integration into the clinical microbiology laboratory use is expected to lead to an improved outcome for sepsis patients and a reduction in the associated treatment costs [40]. This section will introduce molecular diagnostic tests for sepsis, and then provide further information on peptide nucleic acid (PNA) FISH molecular diagnostic tests.

During the last decade, many rapid molecular diagnostic tests based on different technologies have become commercially available for use in rapid pathogen identification for sepsis patients, and their potential benefits over routine methods have generated a substantial interest [10,12,33,40,42–45]. The rapid tests have the ability to reduce identification time of pathogens from positive BCs to hours instead of days. This allows for selection of an antimicrobial therapy based on the hospital's empiric antibiogram for the identified pathogens before susceptibility testing results are available [46].

There are general disadvantages to the molecular diagnostic tests as they have grown more complex to operate [13,14,40]. Additionally, their results may be difficult to interpret and requires the assistance of an expert (e.g. a clinical microbiologist or an infectious disease physician) [40]. Furthermore, many of the molecular tests are labor intensive and require manual processing steps for analysis preparation, which can introduce workload issues and increases the risks of errors during processing (e.g. sample contamination) [41].

QuickFISH and PNA-FISH (AdvanDx, Inc., Woburn, MA, USA) are two commercially available FISH-based rapid diagnostic tests that are are used for identification of microorganisms from positive BCs. The tests function by containing PNA probes with fluorescent markers that bind to specific rRNA sequences of a target microorganism. The targeted microorganisms can then be identified by fluorescence microscopy. There are several variants of QuickFISH and PNA-FISH, which each target two or three different microorganisms at a species or group level

(e.g. *Staphylococcus aureus* or *coagulase-negative staphylococci*). The QuickFISH tests can provide results within 1 hour while the PNA-FISH tests require 2-3 hours. Studies of QuickFISH tests have shown an accuracy of 98-99% when compared with routine diagnostic methods [47–49]. A limitation of these tests is that they do not provide information on antimicrobial resistance thus further testing is still required. The tests are not integrated into automated instruments and, therefore, require manual processing and interpretation. Results obtained from the tests are initially noted on paper forms and then digitized at a workstation. When used together with an antimicrobial stewardship team (AST) the tests can provide an earlier optimized treatment, which has been shown that their use can lead to a reduced length of stay, reduced mortality, and lower treatment costs [50,51].

The use of rapid molecular diagnostic tests has the potential to improve patient treatment by providing the information necessary to begin an effective antimicrobial therapy. However, if the rapid diagnostic tests are not effectively implemented into the diagnostic workflow, their benefits may be lost [52]. The results obtained from the tests require quick communication from the clinical microbiology laboratory to the patient's attending staff to ensure an effect of the antimicrobial therapy [44,52]. The use of an AST can assist in ensuring an efficient communication of results and provide the expertise needed to optimize patient treatment based on the rapid diagnostic test results. This may lead to improved patient survival, decreased length of stay in the hospital, and decreased treatment costs [35,46,53]. This is supported by a recent review by Buehler et al., which suggests that the implementation of rapid molecular diagnostic tests combined with direct communication of results may provide an earlier optimization of the antimicrobial therapy and thus improve patient outcome [42].

2.1.3. TEST TURNAROUND TIME

A quick turnaround time (TAT) for sepsis diagnostic tests is essential to provide a timely effective antimicrobial therapy for sepsis patients. Together with the accuracy of test results the TAT is considered the important aspects of test results by physicians [54]. If test results are delivered too late, they may not be able to have an impact on the antimicrobial therapy of a patient.

There are many different challenges in optimizing the TAT of diagnostic tests that aim to detect the causative pathogens of a BSI based on positive BCs. Once a BC has been drawn, four main phases affect microbiological testing TAT for the BC as shown in Figure 1.

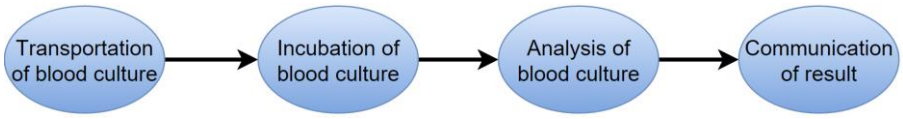

Figure 1. Four main phases of the diagnostic processing of BC analysis once a sample has been drawn, which combined make up the TAT for microbiological testing of a BC.

The introduction of rapid molecular tests into routines procedures will likely reduce the time for a final identification of a microorganism (i.e. the time for analysis of the positive BC). However, it will not affect the other phases of the BC diagnostic process, e.g., sample transportation time and result communication time. To make an efficient diagnostic workflow and improve the TAT, it is not enough to introduce rapid diagnostic tests, but the entire diagnostic process should be considered [55].

Transportation time from drawing of BCs until incubation plays a role in the TAT, but may also influence BC positivity. Samples collected at hospitals without local clinical microbiology departments may require transportation to a centralized laboratory. Additionally, samples that are collected during night shifts may take longer to be brought to the laboratory. Akan et al. demonstrated that delays for more than 24 hours until initiation of BC incubation leads to an increase in BC negativity, which may require more samples to be collected [56].

The incubation time of BCs until they are signaled for positive growth varies, but for many microorganisms a typical growth time is 6-48 hours [34]. Clinical microbiology laboratories are often not staffed for 24 hours daily. If a BC is signaled positive for growth outside working hours of the laboratory, it will be analyzed the next morning. If BCs are drawn outside the operating hours of the laboratory, they risk being stored for a period before incubation is started. Such delays in BC incubation may negatively influence the time to detection of growth. A study by Kerremans et al. showed that the use of an intermediate BC incubator accessible outside laboratory's working hours can lead to a median reduction of 10 hours in the time to detection of microorganism growth [57]. Some molecular diagnostic tests can operate directly on whole blood, which can eliminate the incubation time [45,58].

Positive BC analysis results are considered critical values, which means there is a high priority on communicating them from the clinical microbiology laboratory to the patient's attending staff [59]. The communication of results relies primarily on phone calls. A commonly reported challenge in the communication of critical values is to communicate them directly to the patient's attending physician [60]. Automatic notification systems have shown potential to reduce communication time and decrease the risk of communication errors [61,62]. While automated communication is promising it can be difficult to implement as many clinical microbiologists prefer to communicate preliminary BC results over the telephone to ensure that the results are interpreted correctly [54].

Batching of diagnostic tests to optimize workflow and reduce costs is a common occurrence in clinical microbiology laboratories when processing BCs with routine methods or molecular tests [35,63]. The unloading of positive BCs may be done at specified times throughout the day instead of immediately when the BCs are signaled as positive. If the laboratory does not operate during the night, then there may also be a large amount of positive BCs for processing in the morning.

To summarize, many factors influence the TAT of diagnostic processing of a BC. Some of these factors can be improved by the introduction of rapid diagnostic tests. However, a focus on optimizing the entire workflow will likely bring improvements to patient outcome [64]. Informatics play a large role in the diagnostic workflow in clinical microbiology, and efficient use of informatics tools has shown to improve the workflow leading to improved testing both accuracy and timeliness [8]. The integration of diagnostic test instruments can reduce the hands-on time for operators and reduce a need for double documentation [8,9]. Furthermore, integration of rapid diagnostic tests with the LIS may provide the foundations for a more efficient communication of results [40].

2.2. TABLETS IN CLINICAL SETTINGS

Clinical workflows in healthcare are generally complex and often requires that staff move around to different locations, e.g., patient wards, diagnostic departments, and laboratories [6,65,66]. Access to CISs plays a major role in many of aspects of the workflows, e.g., to access patient information and document work. Mobile computing devices in the form of personal digital assistants (PDAs), smartphones, and tablets are tools that can potentially help meet the needs for access to patient-related information of healthcare workers while allowing them to remain mobile. The potential benefits of mobile access to CISs as part of a workflow in hospitals have been of interest to researchers for over a decade [66]. The ability to access clinical information and lookup guidelines at the point of care has the potential to improve workflows, which may lead to better informed clinical decisions and thereby improved patient care [67,68].

Early research on the use of mobile computing devices to support workflow in healthcare has mainly been based on the use of PDAs [66,69]. Studies demonstrated the potential benefits by providing users with mobile access to information and by supporting mobile documentation. However, the impact on clinical workflow has not been clear [69]. With the use of mobile devices, data can be captured directly at the point-of-care, which may lead to a reduction of errors due to the elimination of double documentation (e.g. initially making notes of results on paper forms that are digitalized later) [67]. Workflow benefits by the use of PDAs were demonstrated for workflows where timeliness and rapid communication was important [69]. This indicates that mobile devices may be useful for supporting the workflows of rapid

sepsis diagnostic tests, where timeliness and rapid communication are essential elements.

Studies have also revealed issues that were encountered with the use of PDAs in health care settings. The usability of these mobile devices can be a major barrier to their use in clinical workflows [67]. Potential usability issues are data security, physical dimensions of the device, the weight of the device, poor battery, poor display, challenging data entry, unstable connectivity, poor integration with other CISs, and negative perception of the devices by patients [66,67].

The development of modern mobile devices such as smartphones and tablets are promising for use in clinical settings, as they may bring the benefits observed with PDAs while having fewer barriers preventing their use. An advantage offered by smartphones and tablets over PDAs is that many users are already familiar with the devices from their personal use. Additionally, these devices generally have long battery life and strong connectivity support as they often support both Wi-Fi and cellular networks. Tablets are especially interesting as a tool to introduce for use in healthcare, as they provide a large screen size while still being easily portable [5].

Tablets and smartphones are a promising tool for supporting the integration of rapid diagnostic microbiological tests and have been predicted to play an increasingly significant role in clinical microbiology to support rapid diagnostic tests [70]. Thus, these mobile devices may play a major role in optimizing and supporting the workflow of rapid diagnostic tests in clinical microbiology with an end goal of prodiving accurate and timely results.

2.2.1. CLINICAL WORKFLOW

Smartphones and tablets have in recent years become a daily used tool for many people, and it is only natural that their use has spread to clinical settings [2,3,7]. Most of the existing knowledge about the utilization of these mobile computing devices and their potential effects on workflow are based on studies of PDAs [7,69,71].

Healthcare professionals have an interest in the use of tablets in clinical settings as it may facilitate their workflow, e.g., through point-of-care access to Electronic Health Records (EHRs) [3,7,72,73]. Similarly, for use related to clinical microbiology, there are many apps available that offers guidance for antimicrobial stewardship by providing information on drugs and diseases, which can assist the process of selecting an optimal antimicrobial therapy [74,75].

A study in 2013 provided 115 internal medicine residents with a tablet for use in their work [72]. The study revealed that at the end of the study 84% of the residents were positive towards the utilization of the tablet. The use of tablets in clinical settings is by many physicians perceived as useful for their workflow. A survey conducted in

2013 with responses from almost 3,000 US physicians revealed that 40% used tablets and about 20% utilized the tablets in clinical settings [3]. Access to drug information and access to the EHR was reported as a primary use of the tablets.

A study by Crowson et al. examined the use of tablets connected to the EHR for facilitation of resident workflow in a head and neck surgery department [76]. The tablets used in the study supported lookup of patient data and allowed for entry of notes into the EHR from the tablet. The study results revealed a significant time saving of 50% for patient rounds when tablets were used compared to use of paper. Additionally, 80% of the residents reported an improvement in morale when the tablets were used, and 70% indicated that they felt the tablets allowed them to spend more time with patients. Similarly, a study by Fleischmann et al. demonstrated that the use of tablets could facilitate the workflow of physicians during ward rounds [4]. A study by Horng et al. showed that physicians using tablets in an emergency department could decrease time spent at workstations and increase time spent at bedside [77].

While the recent studies on the use of tablets suggest a potential for facilitating clinical workflows in patient wards, there is a lack of published scientific literature describing the use of tablets in clinical laboratories.

2.2.2. TABLET USABILITY

While the potential advantages of using tablets to provide mobile access to CISs is promising, there are also usability challenges that must be overcome to make efficient use of the devices. These challenges include ensuring ease of use, data security, data privacy, integration of the mobile computing devices into common workflow routines, and acceptance by end users. This section will describe usability evaluation methods used for identifying usability barriers in the development cycle of both stationary and mobile CISs.

A definition of usability is provided by the ISO 9241-11 standard as: *"the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use."* [78]. From this definition of usability, it is important to notice that usability not only depends on its ability to help users achieve their goals but that a system's usability is also dependent on the context of use. This is an important consideration for the development of apps for clinical use, which will be used as tools to support workflows that will generally be complex. Furthermore, the context of use is drastically different between patient wards and laboratories, which should be considered during app design and development.

The introduction of a new CIS can have a large effect on the clinical workflow, and may have unintended consequences if the developed system's usability is poor and

it does not match the requirements of the users in their clinical workflows [79,80]. An example of this is a handheld prescription system with usability issues, which can introduce errors during data retrieval or data entry that can potentially lead to patient harm [81]. If the end users feel that the system complicates their clinical workflow, there is also a risk of clinical workarounds being introduced, which may lead to errors [79]. The implementation of a new CISs will often result in organizational changes, which should be planned to increase the likelihood of a successful system implementation [82]. The involvement of end users during the system development phase can also be essential to ensure that the system meets the requirements of the users.

Usability evaluations are critical in the development of CISs to identify system design flaws that can be improved thus leading to an optimization of the system's usability [83]. Usability evaluation methods can rely on experts, end users (i.e. domain experts), or a combination of both. For CISs examples of commonly used usability evaluation methods are heuristic evaluation, clinical walkthrough, and think aloud [83]. The different usability evaluation methods each have their strengths and weaknesses, but may complement each other and be used in various parts of the development cycle of the CISs [83,84]. In heuristic evaluation, experts inspect a systems user interface against guidelines to identify potential issues [85]. It is a rapid and cheap method to conduct that can be used at several stages throughout system development.

When dealing with complex clinical workflows, usability evaluation experts will often not be able to discover usability issues that relate to the workflow of the end user [83]. The introduction of end users into teams conducting the usability experts can lead to insights about domain-related usability issues. An example of this is participatory heuristic evaluation, in which domain experts are briefly trained in the heuristic evaluation [86]. A study demonstrated that there was an interest amongst clinicians to participate in the participatory heuristic evaluation and that it could lead to the discovery of domain specific issues [87].

In recent years, there has been a growing interest in clinical simulation studies for the evaluation of CISs in near-live settings [88–90]. Clinical simulation can be used to uncover usability issues and estimate the effect of a CIS before system implementation [89,90]. Clinical simulation studies require a high fidelity prototype of the system being evaluated to provide realistic results about the use of the CIS in clinical workflows [91].

Pilot studies with implementations of near fully developed systems can be evaluated by combining several different usability evaluation methods, for example by collecting notes on system use, observing study participants, and by interviewing participants [84]. Additionally, errors that occur during pilot studies can be examined closely to potentially identify underlying usability issues. In evaluation studies, the

system usability scale (SUS) questionnaire can be used for a quick estimation of a system's usability that also allows for comparison against the usability of other systems or previous versions of the system being evaluated [92]. The SUS questionnaire contains ten statements that are answered on a Likert scale. The SUS questionnaire has previously been used for evaluation of a clinical tablet app [93].

2.3. BACKGROUND SUMMARY

BSIs can lead to sepsis, which is associated with high patient mortality. For every hour of delay in the initialization of an effective antimicrobial therapy leads there is an increased risk of mortality for sepsis patients. Due to the urgency of starting treatment, the initial antimicrobial therapy is commonly based on empirical data and targets a broad spectrum of microorganisms. For about 20% of patients with severe sepsis or septic shock, the initially administered antimicrobial therapy is not effective.

BCs are the gold standard for identification of microorganisms in the bloodstream and typically require an incubation period that spans from 6-48 hours. Preliminary results in the form of Gram stain results are available shortly after the BC is signaled positive for growth of microorganisms from an automated incubator system. 30-45% of sepsis patients have their initial antimicrobial therapy readjusted after the availability of preliminary results (i.e. Gram stain results). Final identification and antimicrobial susceptibility results typically requires one or more days before availability.

The recent developments in rapid molecular diagnostic tests for use in clinical microbiology provides a potential for obtaining final identification of pathogens from positive BCs in a shorter timeframe than routine methods. An earlier identification of pathogens can allow for a faster optimization of a patient antimicrobial therapy, which will lead to an improved outcome for many patients. However, the molecular diagnostic methods are generally more complex in use than routine methods, which is a barrier to their widespread use.

The use of tablets has spread to clinical settings, and recently studies have shown that they have the potential to facilitate complex workflows of healthcare professionals. Clinical microbiology laboratories are heavily dependent on CISs during most workflow routines, which means that there is a growing interest in the use of tablets and dedicated apps for supporting the workflow of diagnostic tests in clinical microbiology. The tablets may be able to facilitate workflows of rapid molecular diagnostic tests thereby reducing the TAT and promoting a high accuracy of test results. However, there is a lack of published literature describing how such tablets may affect the workflow in clinical laboratories, and how specialized tablet apps should be designed to promote successful use amongst end users.

CHAPTER 3. MUXBCT MOLECULAR DIAGNOSTIC TEST

This PhD thesis is a part of a larger research project, where the ongoing focus is the development of the rapid molecular diagnostic test MuxBCT, which will be described in this chapter. The MuxBCT test is still being developed and optimized, but this chapter describes a fully functional prototype of the MuxBCT test. Further references to the MuxBCT test throughout this thesis will refer to the test as described in this chapter unless otherwise specified.

The MuxBCT test aims to provide microorganism identification results in less than an hour for 18 groups or species of microorganisms commonly encountered in positive BCs. The MuxBCT test is based on FISH and can be considered a new generation diagnostic test that builds upon the QuickFISH tests. The major difference between MuxBCT and QuickFISH is a much larger coverage of microorganisms in one test by the MuxBCT test. However, the increased coverage of microorganisms has also added complexity to the test, which must be successfully handled to ensure that accurate microorganism identification results are obtained.

3.1. TEST DESIGN

The MuxBCT tests consists of a slide that is divided into 10 reaction wells, which is shown as a rendering in Figure 2. Positive BC material is mixed with MuxBCT reagents, which is then transferred to the reaction wells. The slide is heated for approximately 17 minutes to fixate and hybridize the sample before it is read with fluorescence microscopy in a dark room. One of the reaction wells acts a sample classifier of the BC being examined and determines which of the other wells need to be examined. Each of the nine other reaction wells allows for identification of two different bacteria or yeasts at a species or group level (e.g. *coagulase-negative staphylococci*). When the microorganisms bind to PNA probes in the reaction wells, a fluorescent green or red signal is observable through fluorescence microscopy. This allows for positive identification of the microorganisms targeted in each well as shown in Figure 3.

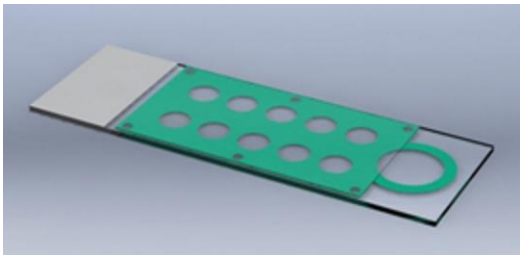

Figure 2. Rendering of the MuxBCT slide. The slide contains 10 reaction wells (smaller circles), which each provide molecular identification of two to three microorganisms at a species or group level.

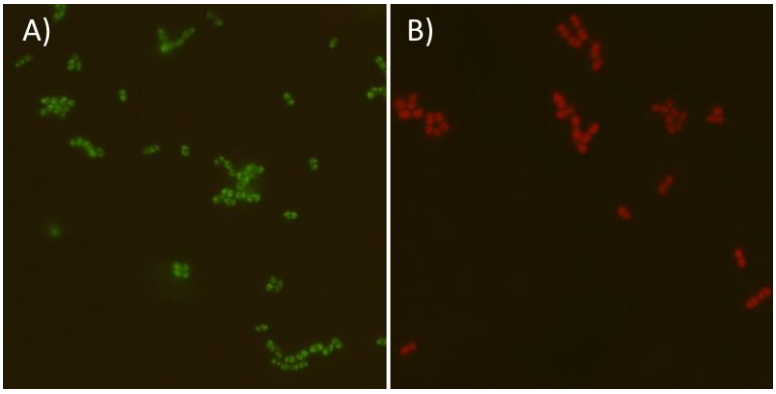

Figure 3. Example of prototype MuxBCT test reaction well read by fluorescence microscopy positive for: A) Enterococcus faecalis; B) Enterococcus faecium.

Each positive finding in the classification well requires that three additional wells be examined. Additionally, one well is used as a negative control well based on findings in the classifier well. In rare cases where the classifier indicates findings of all covered microorganism categories, i.e., Gram-positive, Gram-negative bacteria, and yeasts, the MuxBCT test is not usable due to the lack of a control well. When analyzing monomicrobial BCs, which is the most prevalent scenario, a user will examine five reaction wells in total. An overview of the ten reaction wells of MuxBCT is provided in Table 1.

Table 1. MuxBCT reaction wells and microorganism coverage based on the fluorescent signal.

Reaction well	Green positive	Red positive
1. Gram-positive bacteria	*Staphylococcus aureus*	*Coagulase-negative staphylococci*
2. Gram-positive bacteria	*Enterococcus faecalis*	*Enterococcus faecium*
3. Gram-positive bacteria	*Streptococcus agalactiae*	*Streptococcus pneumoniae*
4. Yeasts	*Candida glabrata*	*Candida tropicalis*
5. Classifier	—	—
6. Yeasts	*Candida albicans*	*Candida krusei*
7. Yeasts	*Cryptococcus neoformans/gattii*	*Candida parapsilosis*
8. Gram-negative bacteria	*Pseudomonas aeruginosa*	*Acinetobacter* (genus)
9. Gram-negative bacteria	*Stenotrophomonas maltophilia*	*Enterobacteriaceae* (family)
10. Gram-negative bacteria	*Escherichia coli*	*Klebsiella pneumoniae*

3.2. TEST INTERPRETATION

For MuxBCT to provide results with accurate identification of microorganisms, and to prevent misidentification of microorganisms, the MuxBCT test must be interpreted correctly. To do this, the operator is required to read the necessary wells in the correct order, which is dependent on the results of the classifier. Additionally, the use of MuxBCT requires an operator skilled in fluorescence microscopy and in operating molecular tests in order to provide an accurate reading. These tasks are outside what is commonly used by medical laboratory scientists (MLSs) in clinical microbiology

when analyzing positive BCs [14]. This is an important aspect to consider in comparison to the routine diagnostic methods [63].

An example of the algorithm users must employ to correctly read and interpret the slide is shown in Figure 4. In the example, an initial reading of the classifier indicates Gram-positive bacteria, which requires the reading of well 8 as a negative control. If the negative control passes, then the user reads the wells 1, 2 and 3 for identification of Gram-positive bacteria. For polymicrobial BCs that for example contains both Gram-positive and Gram-negative bacteria, the user will be required to read eight wells.

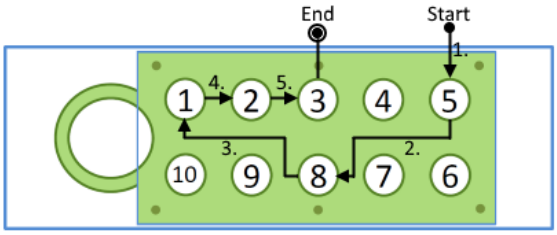

Figure 4. Example of a MuxBCT slide reading pattern followed when the classifier (well 5) indicates Gram-positive bacteria. In total, five wells must be read using fluorescence microscopy in the order given by the numbers and arrows to obtain a valid MuxBCT result in this example.

CHAPTER 4. THESIS OBJECTIVE

As described in the background chapter, the use of tablets in clinical settings may facilitate complex workflows. Tablets may also be a valuable tool for the integration of advanced diagnostic tests with the LIS, which can allow for effective communication of test results. As a part of the MuxBCT project, this thesis explores if a tablet app can be used to facilitate the workflow of the MuxBCT test. The thesis has the following objective:

Investigate how to design and evaluate a tablet app that can facilitate the workflow of an advanced molecular sepsis diagnostic test, the MuxBCT, in a clinical microbiology laboratory.

The thesis has the following four research aims in order to address the objective:

1. Identify and understand necessary requirements for the MuxBCT app to support MLSs in the use of the MuxBCT test.
2. Design a system architecture that is flexible to allow the MuxBCT app to exchange data with LISs while promoting security of data.
3. Develop a prototype of the MuxBCT app based on the system requirements and the designed system architecture.
4. Evaluate the ability of the app to facilitate the workflow of MLSs in their use of MuxBCT for BC analysis in a clinical microbiology laboratory.

CHAPTER 5. MUXBCT TABLET APP

A MuxBCT app was designed during the PhD study to facilitate the workflow of the MuxBCT diagnostic test. To accomplish this, the following goals were set for the app:

1. Provide guidance for MuxBCT test reading and result interpretation to reduce test complexity.
2. Allow entry of test results directly on the tablet at the site of analysis.
3. Support LIS communication in order to retrieve and display relevant sample information and to submit MuxBCT results from the tablet to the LIS.

The MuxBCT app is designed to support mobility requirements of the user (i.e. a MLS), who conducts the MuxBCT diagnostic test. As the MuxBCT test requires the use of a fluorescence microscope, the slide reading will occur in a dark room. The MuxBCT tablet can be placed next to the microscope, and users can enter findings directly into the app. The app will then guide the users through the interpretation process in a stepwise manner. The use of the MuxBCT app should eliminate the need for paper procedure guides or paper forms for documentation of microorganism findings.

Once a user has analyzed all relevant MuxBCT wells of a slide, the app presents the test results to the users. If the MLS accepts the results, the app transfers the MuxBCT results to the LIS. The MuxBCT tablet exchanges data with the LIS using a protected Wi-Fi connection. The LIS provides integration with the EHR and thereby makes MuxBCT results available for the attending physician, once the test result has been signed by a clinical microbiologist in the LIS.

A wireless barcode scanner is available for the MLS to use. The scanner is connected to the MuxBCT app via Bluetooth, which allows for easy entry of barcode data into the app, e.g., BC accession number. The use of barcodes plays a large role in ensuring quality and efficiency in the routine analysis process of positive BCs [94]. An overview of the MuxBCT app is shown in Figure 5. An example of the MuxBCT app’s user interface is presented in Figure 6.

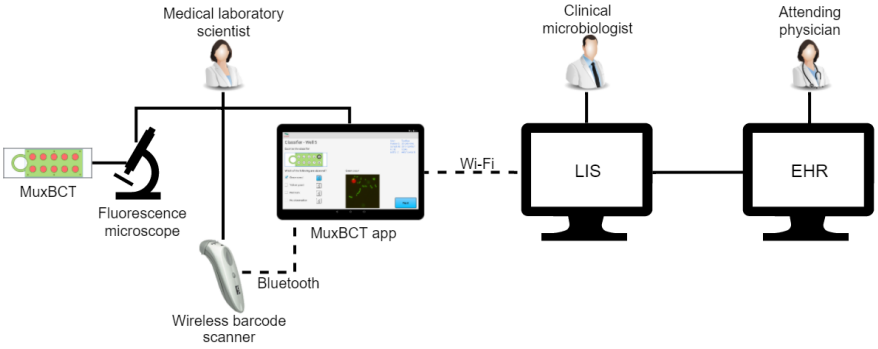

Figure 5. Overview of the MuxBCT tablet app, which is connected to a wireless barcode scanner and the LIS. The dashed lines indicate wireless transfer of data. The figure is adapted from ***Paper D.***

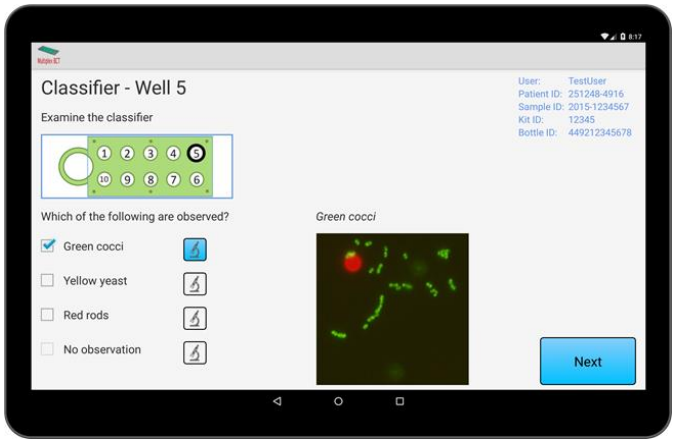

Figure 6. The MuxBCT app running on an Android tablet. In the example, a user has marked observations of green cocci cells during an examination of the classifier well.

5.1. SYSTEM DESIGN

This section describes the overall system design of the MuxBCT app, and the implementation, which was used to connect the MuxBCT app with the LIS (wwLab) of the Department of Clinical Microbiology, Aalborg University Hospital.

An overall aim of the system design of the MuxBCT app was to ensure flexibility, to support easy integration with different LISs. Additionally, an aim of the system design was to promote data security. The system design consists of the following three main components: 1) a MuxBCT tablet app; 2) a MuxBCT server; 3) a MuxBCT database. An overview of the MuxBCT app system design is shown in Figure 7.

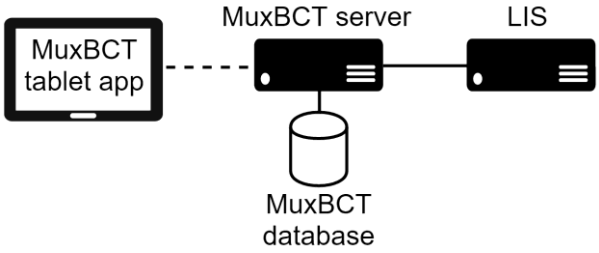

*Figure 7. The overall MuxBCT system design. The dashed line indicates connectivity over a secure Wi-Fi connection. The figure is adapted from **Paper C**.*

The MuxBCT app was designed for 10-inch tablets with the Android operating system. The implementation of the MuxBCT app was done with Java using the Android SDK. The MuxBCT server was setup using Apache Tomcat 7.0, and the server software was developed with Java using the Spring framework. The MuxBCT database was implemented as a relational SQL Server 2012 database.

Throughout the PhD study, an algorithm was designed and implemented into the tablet app for assisting users in reading the MuxBCT test slide in a stepwise manner. The algorithm provides instructions to users in order to do a structured interpretation of the MuxBCT slide in a stepwise manner, which simplifies the task of reading the MuxBCT test. The algorithm was continuously updated as the development of the MuxBCT test progressed to ensure that the algorithm would provide the correct test results. As the algorithm is integrated into the MuxBCT app, it was evaluated as a part of the MuxBCT app usability evaluation studies.

The MuxBCT server was developed with a service-oriented architecture (SOA) in order to support efficient and flexible communication between the MuxBCT app and MuxBCT server and between the MuxBCT server and the LIS. The MuxBCT server offers several REST web services that are called from the MuxBCT app. Data between the MuxBCT app and server is transferred using the JSON data format. Data exchange between the MuxBCT server and LIS depends on what web services are offered by the LIS. In the implementation of this PhD study, the LIS offered SOAP web services, and data was transferred as XML. The SOA used in the system design allows multiple users to utilize the MuxBCT app to exchange data with the MuxBCT server simultaneously, thus multiple tablets with the MuxBCT app could be used in a clinical microbiology laboratory.

Whenever patient or test information is required, the MuxBCT app requests the data as necessary through web services offered by the MuxBCT server. The MuxBCT server procures the necessary data through web services provided by the LIS and returns the data to the tablet app. When a MuxBCT test result is ready, the MuxBCT app sends it to the MuxBCT server through a web service. In case of errors during

communication of data, an error message is returned to the MuxBCT app, which is then displayed to the user. For commonly encountered error cases (e.g. attempting to look-up a non-existing BC accession number), simple and clear error messages have been prepared and are displayed to the user to describe encountered issue.

No data are saved locally on the tablet due to security concerns [95]. Instead, MuxBCT results are communicated to the MuxBCT server and saved in the MuxBCT database. The database is also used for logging user events and additional test data. All communication between the MuxBCT tablet app and the MuxBCT server takes place through a secure and closed hospital Wi-Fi network. Additionally, the network communication uses the TLS protocol for the encryption of data during transfer.

The MuxBCT server primarily acts as a link that connects the MuxBCT app with the LIS. This brings the benefit that for integration with LISs of different vendors the tablet app does not need change. Instead, the MuxBCT server can be configured to match the requirements of the LIS. The MuxBCT server handles the majority of necessary computational work, i.e., mapping of data MuxBCT data to a format used by the LIS.

All MuxBCT microorganism identification results are mapped to SNOMED CT IDs on the MuxBCT server. If a LIS supports SNOMED CT, the workload of system integration is significantly reduced. For the implementation at the Department of Clinical Microbiology at Aalborg University Hospital, a custom mapping was setup to exchange information with the LIS. The mapping from MuxBCT results in the form of SNOMED CT IDs to local laboratory codes was reviewed and validated by a clinical microbiologist from the Department of Clinical Microbiology at Aalborg University Hospital.

Users are required to login on the MuxBCT app before the app can be used to guide use of the MuxBCT test. An authentication web service is called on the MuxBCT server, which in turn validates user credentials against a hospital user authentication web service. In the implementation during the PhD study, this meant that users could re-use their existing usernames and passwords that provided EHR access.

5.2. DEVELOPMENT CYCLE

The development of the MuxBCT app in the PhD study followed an iterative and user-centered approach, where the initial system requirements for the app was based on an analysis of the BC diagnostic workflow and of information about the MuxBCT test workflow. The focus of the development cycle was to support the workflow of the MuxBCT test. Therefore, the usability evaluation methods described in section 2.2.2 were utilized in the iterations that provided feedback for app design improvements.

The duration of the development cycle from initial design until final prototype evaluation was approximately 2.5 years. Representative end users were involved in each evaluation of the app, which led to further optimization of the design of the app to support the MuxBCT test workflow. Neubeck et al. employed a similar participatory development approach in a recent study, which aimed to develop a mobile web app for use by patients [96].

A challenge in the development of the MuxBCT app was that when the design of the MuxBCT test changed the design of the MuxBCT app had to be adapted to match the test. This occurred several times throughout the development cycle of the MuxBCT app. However, experiences gained through the evaluation of the MuxBCT app provided user input to the design of the MuxBCT test, which affected the development of the test. An illustration of the iterative development cycles of the MuxBCT test and the MuxBCT app is shown in Figure 8.

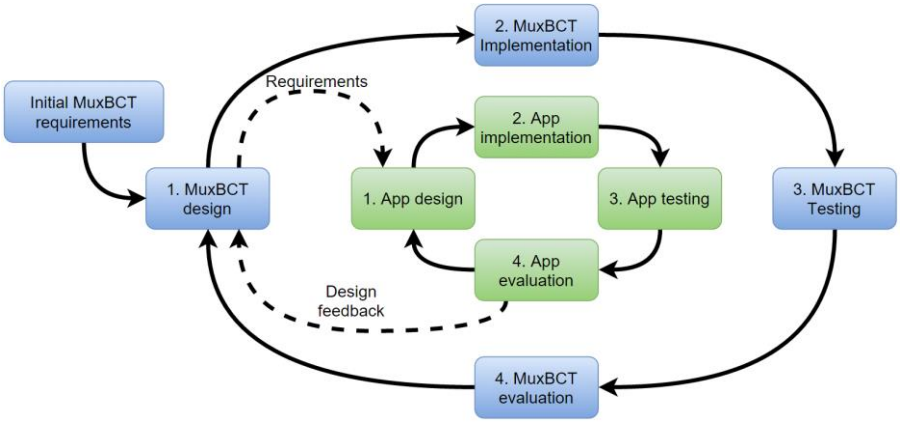

Figure 8. The iterative development cycles of the MuxBCT test and the app are connected. MuxBCT in the figure refers to the MuxBCT test. Solid lines indicate processes that always occurs while dashed lines indicate a process that occasionally occurs.

The design and development of the MuxBCT app underwent three iterations during this thesis. Different methods were used for the evaluation of the app as part of the development cycle, which depended on the fidelity of the app. All evaluations followed a participatory approach to increase the chance of identifying domain-related workflow issues. An overview of iterations and the evaluation methods used for each iteration is shown in Figure 9.

For the first iteration, the app's functionality was modeled as a navigable user interface that was based on the initial requirements. The user interface was developed with the tool Justinmind Prototyper, which provided a high-fidelity representation of an app as an interactive website. This user interface prototype was evaluated using the usability inspection method participatory heuristic evaluation. Feedback from

usability experts and domain experts was used to improve app design in the second iteration.

As part of the second iteration, the design was transformed to an initial MuxBCT app prototype. The prototype ran as an app on a tablet with the Android operating system. The second iteration was connected to the MuxBCT server, which allowed for evaluation of data transfer. The second iteration was evaluated in a clinical simulation study, where end users utilized the MuxBCT app to guide a simulated diagnostic test workflow of the MuxBCT test in a clinical microbiology laboratory. This provided valuable data on the feasibility of using an app in a clinical microbiology laboratory. Feedback from this step was used to guide the third iteration of the development cycle of the MuxBCT app.

The third iteration was the final design and implementation of the MuxBCT app, which was connected to a LIS through a MuxBCT server. This iteration was evaluated through a prospective evaluation study, where the MuxBCT app was used to support MLSs in the use of the MuxBCT test for pathogen identification from positive BCs.

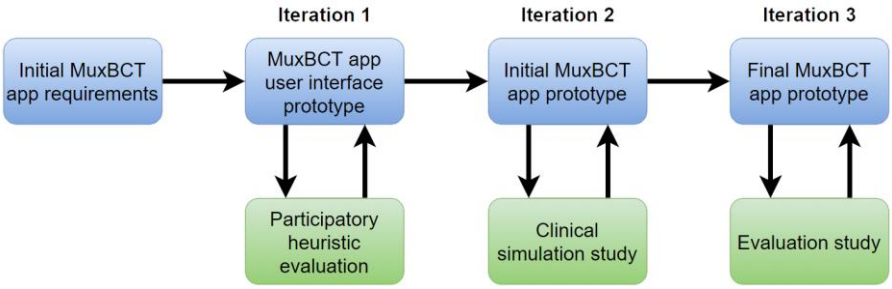

Figure 9. Each iteration in the development of the MuxBCT app was evaluated in order to improve the design and development for the next iteration. The figure does not illustrate design changes to the MuxBCT app, which are due to changes in the design of the MuxBCT test.

CHAPTER 6. STUDY OVERVIEW

This chapter provides an overview of the four studies that were conducted as part of this PhD thesis to answer the research aims. The studies followed the order as they are numbered below.

6.1. STUDY 1 – PAPER A

Study 1 was an observational study of the workflow during routine diagnostics of positive BCs in a clinical microbiology laboratory. The study aimed to provide a basic understanding of requirements for the MuxBCT app required to support BC workflow, thus addressing the first research aim of the thesis. Five MLSs with a varying degree of experience in the analysis of BCs were observed over a three day period in their work with analysis of positive BC. The observations were conducted for a total time of 13 hours and 30 minutes, which included both mornings and afternoons. The observations followed a semi-structured guide that focused on the analysis of blood cultures along with how test results were communicated. During the observations, notes were made of each activity and its location and duration. The use of any CIS was also noted, along with how it was used. The observational results were supported by two interviews to clarify observations. The interviews followed a semi-structured approach. The notes of the observations and interviews were coded into main categories and then analyzed in detail.

The qualitative findings of the study provided an understanding of the workflow of BC analysis for the clinical microbiology laboratory in which the study took place. Furthermore, a set of system requirements that should be supported in the design of the MuxBCT app was generated from an analysis of the observations. The MuxBCT should be able to support two-way communication with the LIS to receive clinical data related to the analysis while being able to transfer test results. Barcodes should be supported, as they are used extensively in the BC workflow. The app should provide access to a browser for looking up analysis related guidelines. The app should support communication of results from the MLTs to the clinical microbiologists.

The implementation of new CIS is dependent on users being willing to adapt their workflows to fit the new system. By guiding further development of the MuxBCT app based on the findings of this study fewer changes to workflows will be required, which decreased the risk of users not being willing to use the system. A limitation of the study was the observations of the study was only conducted in one clinical microbiology laboratory, and workflows may differ in other laboratories. However, the study included five participants with a varying degree of experience in BC analysis, which provided a better understanding of the BC analysis workflow. The

results of the study were used as a basis for the design of the MuxBCT app in iteration 1 of the development cycle. The findings of this study are described in **Paper A** and were presented at the MedInfo 2013 conference in Copenhagen, Denmark.

6.2. STUDY 2 – PAPER B

Study 2 partly addressed the third research aim of the thesis by transforming the system requirements into a prototype of the MuxBCT apps user interface, which was then evaluated to provide feedback for further design optimization. The study did not consider the architecture of the app but focused on the overall functionality. The prototype demonstrated the functionality of the app by having a user interface that fully modeled the app. The prototype of the user interface was designed and evaluated at iteration 1 of the development cycle. The prototype of was deployed on a 10-inch Android tablet to provide a realistic representation of the final MuxBCT app for the evaluation. The focus of the evaluation was to identify potential usability issues that could negatively affect the workflow. The chosen evaluation method was a participatory heuristic evaluation that involved the use of domain experts in order to identify potential issues related to the workflow support of the app prototype. Workflow issues closely related to the domain (i.e. clinical microbiology) would be difficult to identify by usability experts due to a lack of domain understanding.

The prototype was evaluated by two evaluator groups that consisted of four usability experts and four work-domain experts, respectively. The domain experts were recruited from MLSs at a clinical microbiology laboratory, who all had experience in BC analysis and were representative for the MuxBCT app's end users. The work-domain experts were briefly trained in the heuristic evaluation method. None of the study participants had any previous knowledge of the MuxBCT app or the MuxBCT test. The participants were introduced to the MuxBCT app and the purpose of the study through both a written and verbal description. The study participants evaluated the app individually by completing a series of tasks asked by a study leader. When a heuristic violation was identified, it was assigned a group and a severity rating on a scale from 0-4 (no problem to usability catastrophe). After the study, the results from the participant were pooled, and duplicate heuristic violations were merged.

The study resulted in the identification of 86 unique heuristic violations. 17 of the violations were identified only by the domain experts. The average violation was assigned a severity score of 2.05, and five violations were given the score of 4 corresponding to catastrophe. The study results revealed usability issues related to both product and domain. The identified issues were used to guide the further design of the MuxBCT app. A limitation of the study was that the use of additional usability experts instead of domain experts could potentially have revealed the same work-related heuristic violations. However, the results of the study indicate that the use of MLSs as domain experts was valuable as they identified 17 violations not found by the usability experts. The domain experts provided valuable insights by identifying

heuristic violations related to error prevention, quality of work, and privacy. These categories would not have been covered in the traditional heuristic evaluation, and would likely not have been covered adequately if only usability experts had participated in the study. The study results indicate that training work-domain experts for participatory heuristic evaluation of systems that aim to support complex clinical workflows can be valuable. The findings of the study are described in **Paper B,** which was presented at the MIE 2014 conference in Istanbul, Turkey.

6.3. STUDY 3 – PAPER C

Study 3 was designed to address the second and third research aims of this thesis. The system architecture of MuxBCT app was designed in iteration 2 of the development cycle. Based on this, the functional prototypes of the MuxBCT app and the MuxBCT server were developed. Study 3 was a clinical simulation study that brought the prototype of the MuxBCT app into a clinical microbiology laboratory in near-live simulation settings, to evaluate if it could facilitate the use of the MuxBCT test. In the study, the prototype MuxBCT app was not connected to the LIS but instead returned simulated realistic data from the MuxBCT server. A prototype of the MuxBCT test was not available at this point, so two different QuickFISH tests, which are similar in function to MuxBCT but only covers three microorganisms each, were used to simulate the MuxBCT test. Although the MuxBCT test was not available, this solution still allowed for testing the concept of the slide interpretation algorithm of the MuxBCT app, and to evaluate if the app could guide users to obtain accurate microorganism identification results.

The study provided realistic settings to obtain results, which would closely match results obtained by an actual deployment of the MuxBCT app. Four MLSs participated in the study, and none of the participants had any prior experience with the MuxBCT app. The participants were trained by the test leader in the use of the MuxBCT app for about 10 minutes. In the training, each participant carried out a set of predefined tasks with the app. During the study, the participants did not receive any assistance from the test leader. The test leader acted as an observer, as each participant individually examined two mocked blood cultures containing a microorganism each. Audio was recorded with a Dictaphone during the study. Additionally, all tablet touch interactions with the MuxBCT app was recorded directly on the tablet. Users were debriefed after the study based on observations by the test leader. Observations were coded in categories by type of event and then interpreted to identify potential usability issues.

The study participants identified all eight microorganisms correctly from the mocked BCs, and the results were communicated successfully from the MuxBCT app to the MuxBCT server. The average analysis time of a BC sample was 10.2 min excluding time for preparation of the sample. During the debriefing interviews, three of four participants indicated that they preferred the use of the MuxBCT app compared to

paper as for routine diagnostics. The main finding of the study was that the participants (i.e. MLSs) were successfully able to use the MuxBCT app to facilitate the use of the simulated MuxBCT test even though they were only provided with a brief training session. Furthermore, the study did not identify any major usability issues, but minor usability issues related to the user interface were identified. The study also evaluated the system design consideration, e.g. system connectivity and data security, which did not cause any issues for the participants in the study.

It was a limitation of the study that the MuxBCT test had to be simulated, as a functional prototype was not yet ready as this detracted from the realism of the study. However, by conducting the simulation study in a clinical microbiology laboratory, the study could be carried out under very realistic conditions despite the need for the simulated MuxBCT test. This meant that the results would likely be representative of the normal use of the MuxBCT app for supporting the use of the MuxBCT test. These usability findings of the study were used to guide iteration 3 of the development cycle. The study findings indicated that the implemented system architecture was feasible, as the participants had access to the necessary clinical information through the app. Furthermore, the study also indicated that it was feasible to use of the MuxBCT tablet app to guide MLSs in the use of the MuxBCT test. The design of the system architecture along with the findings of the clinical simulation study are described in **Paper C**.

6.4. STUDY 4 – PAPER D & PAPER E

Study 4 was an evaluation study where the MuxBCT app was evaluated together with a functional prototype of the MuxBCT test in a clinical microbiology laboratory. This addressed the fourth research aim of the thesis. The study evaluated the accuracy MuxBCT results, timeliness of MuxBCT results, and the usability of the MuxBCT app. The study was conducted as a non-interventional study that ran in parallel with the routine analysis of positive BCs. Four MLSs participated in the study. The participants had no previous knowledge of the MuxBCT test or app, and they had a varying degree of experience with the analysis of BCs. In preparation for the study, the MuxBCT app was connected with the LIS of the laboratory so that clinical data could be retrieved from the LIS and MuxBCT results could be sent to the LIS. MuxBCT results were saved in the LIS separately from normal results. Participants were trained by carrying out a set of predefined tasks as a part of a 6-hour training session that included training in both the use of the MuxBCT test and the MuxBCT app.

The MuxBCT test was used for analysis of 137 positive BCs over five weeks in a clinical microbiology laboratory. Data from 124 BCs was available for further analysis after exclusion of samples that had not been analyzed simultaneously in the routine diagnostic process and with the MuxBCT test. The MuxBCT app guided the analysis of BCs with MuxBCT test, and test results were entered directly into the

tablet app and then communicated to the LIS. The accuracy of MuxBCT results was 92.7% when compared with routine diagnostic findings. In debriefing interviews and from study notes, the participants indicated that the discordant test results were primarily related to the prototype MuxBCT test. MuxBCT results were available in the LIS with a median time of 74.2 min. This was close to the time for availability of preliminary results (i.e. Gram stain reaction) in the LIS obtained from the routine diagnostic methods with a median time of 54.4 min. The median time that the MuxBCT app was actively used during analysis of a MuxBCT test was 2.8 min. The usability of the MuxBCT app was evaluated through SUS questionnaires and debriefing interviews at the end of the study. The tablet app was given a SUS score of 93.4 at the onset of the study and a score 94.4 at the end of the study. The SUS scores indicated a system with few usability issues. In the debriefing interview, users further indicated that the MuxBCT app had successfully facilitated the workflow of the MuxBCT test and that they were satisfied with the app.

While the MuxBCT results in this study are from one clinical microbiology laboratory, similar results would likely have been obtained from other laboratories, as the MuxBCT workflow would have been similar. However, the routine diagnostic process would likely have produced different results depending on the routine methods used for BC analysis at the laboratory. The fact that the MuxBCT test was used as a part of a normal workday over a five-week period means that the results of the study can be representative of use of the MuxBCT test and MuxBCT app as a part of a routine diagnostic workflow. The performance and usability of the MuxBCT tablet app are described in **Paper D**. The concordance of MuxBCT results and the timeliness of MuxBCT results when supported by the MuxBCT tablet app is described in **Paper E**.

CHAPTER 7. PAPERS

This chapter lists the publications that were a part of this PhD thesis. The author of this PhD thesis is the first author and main contributor of all the papers. **Paper A** and **Paper B** are conference papers. **Paper C** is published in a journal. **Paper D** and **Paper E** have been submitted to journals.

7.1. PAPER A

Exploring End Users' System Requirements for a Handheld Computer Supporting Both Sepsis Test Workflow and Current IT Solutions

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7.2. PAPER B

Participatory Heuristic Evaluation of a Tablet Computer System for Clinical Microbiology

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7.3. PAPER C

Design of a Tablet Computer App for Facilitation of a Molecular Blood Culture Test in Clinical Microbiology and Preliminary Usability Evaluation

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7.4. PAPER D

Tablet App Facilitating Workflow of a Rapid Molecular Diagnostic Test for Clinical Microbiology

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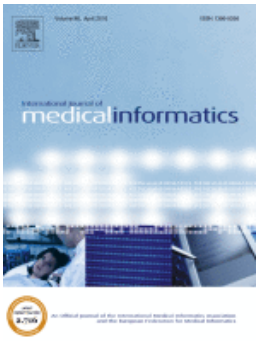

7.5. PAPER E

Rapid Molecular Identification of Blood Culture Isolates Supported by a Tablet Computer

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CHAPTER 8. DISCUSSION

The use of informatics tools in clinical microbiology is a way to accomplish more with fewer resources [8]. As such, there is an interest in the use of tablets for supporting the workflows of advanced molecular diagnostic tests for rapid identification of microorganisms from BCs [70]. The use of molecular diagnostic tests for rapid identification of microorganisms for use in clinical microbiology has increased in recent years, and the tests have the potential to improve the outcome of sepsis patients. However, the molecular diagnostic tests grow more complex to operate in comparison to routine diagnostic methods. Tablets with specialized apps can potentially support the implementation of the advanced diagnostic tests by providing support of the workflow during analysis, and by efficiently assisting communication of test results.

This thesis was part of a research project that aimed to develop the MuxBCT test, which is a rapid molecular diagnostic test for identification of microorganisms in positive BCs. The objective of this thesis was to investigate how to design and evaluate a specialized tablet app for supporting the workflow of the MuxBCT test in a clinical microbiology laboratory.

8.1. METHODOLOGY

In this thesis, a MuxBCT tablet app was designed through a user-centered approach, where an iterative development cycle was used. For each iteration of the development cycle, the functionalities of the MuxBCT app were improved. Each iteration of the app design was implemented as a prototype and evaluated with a participatory approach. An example of this is study 2 where a participatory heuristic evaluation was conducted with participation of representative end users that were able to identify workflow related usability issues [97]. This allowed for an early optimization of the design of the MuxBCT app, where usability flaws were corrected before the MuxBCT app was evaluated in situ for supporting the MuxBCT test.

A challenge in developing the MuxBCT app was that it was being developed concurrently with the MuxBCT test, which it was being designed to support. The functionalities of the MuxBCT test evolved during this thesis. Each change of functionality of the test had to be mirrored in the app to support the workflow of the test to obtain accurate test results. The incremental development cycle was well suited for this, as each change in functionality was able to be evaluated in each iteration of the MuxBCT app.

In the studies of this thesis, the initial requirements for the MuxBCT app were collected through an observational study of the existing workflow of BC analysis. In

general, the evaluation methods selected for evaluation of CISs should be chosen depending on the goals of the study [98]. This aspect was considered for the evaluation studies conducted as a part of this PhD thesis, as each study method corresponded to the fidelity of the MuxBCT app at the time of the evaluation. This meant that for each iteration, increasingly complex evaluation methods were selected to provide valid results. By using evaluation methods that closely matched real use of the MuxBCT app, potential usability issues related to workflow support could be identified before the MuxBCT app was evaluated together with the MuxBCT test in study 4.

In the evaluation study of the MuxBCT app, the app was used to support a functional prototype of the MuxBCT test for identification of microorganisms from positive BCs. The study was conducted as part of a normal workday over a five week period, which allowed the final evaluation of the MuxBCT app to be a strong representation of an implementation into normal diagnostic routines. As the MuxBCT test was used in parallel with the routine diagnostic methods, this provided a method to directly estimate the accuracy of the MuxBCT test when supported by the MuxBCT app, and the timeliness of the MuxBCT results in comparison to routine diagnostic methods.

8.2. MAIN FINDINGS

To meet clinical needs, advanced molecular diagnostic tests for use in clinical microbiology should provide rapidly available results that are accurate and reliable [40]. A functional prototype of the MuxBCT test was supported by a final iteration of the MuxBCT tablet app in study 4 for the analysis of positive BCs. When supported by the MuxBCT app, microorganism identification results with an accuracy of 92.7% were obtained from the MuxBCT test from the analysis of 124 BCs. The MuxBCT results were available in the LIS after a median processing time of 74.2 min, which was close to the time of availability of preliminary results (i.e. Gram stain results) in the LIS at a median time of 54.4 min. These are promising results, as they could allow accurate microorganisms identification results obtained by the use MuxBCT to be reported alongside traditional preliminary microbiology findings. The final microorganism identification results obtained by traditional methods were available in the LIS with a median time of 24.9 hours. Thus, for a range of microorganisms, there is a potential to save close to a day in time to obtain final identification results by using the MuxBCT test.

In study 4, the usability of the MuxBCT app was evaluated in a mixed approach by examining the accuracy of test results, notes from study participants, and from participant debriefing interviews. Few usability issues were identified in the MuxBCT app, and the discordant microorganism identification results was reported by participants to be primarily due to weak fluorescent signals in some wells of the functional prototype of the MuxBCT test. These primarily positive study results were obtained even though users had received limited training in the use of the MuxBCT

test and the MuxBCT app. For 11 of the analyzed BCs there was an extra level of complexity, as these BCs were polymicrobial. However, this did not cause any issues during analysis as the app guide the uses in a stepwise manner, despite these samples required reading of additional wells of the MuxBCT test to obtain test results.

A strength of the MuxBCT test is its ability to rapidly identify a wide array of microorganisms from positive BCs in a single test. This can lead to an early optimization of a patient's initial wide-spectrum antimicrobial therapy to a targeted small-spectrum therapy. Based on results from studies on the PNA-FISH and QuickFISH tests, this can lead to an improved patient outcome and reduced cost of treatment when combined with an effective communication of the results [42,49,50,99]. However, to obtain these benefits, the diagnostic tests must be effectively implemented into clinical workflows to quickly communicate the test results to the attending physician of the sepsis patient, and that the results acted upon if necessary [52]. The MuxBCT test alone affects the TAT of BC test results by reducing the time for analysis of BCs. However, when combined with the MuxBCT app, the TAT is likely further reduced by making the results directly available in the LIS once they have been entered in the tablet app, which supports a quick communication of the test results.

BCs are often processed in batches in a stepwise manner in clinical microbiology laboratories due to practical considerations [12]. The analysis of BC in batches promotes a more efficient workflow during the analysis. This was also seen in the results of the evaluation study of the combined use of the MuxBCT app and MuxBCT test, where the average batch had a size of 3.1 BCs. If results of all tests are initially captured on paper forms and entered into the LIS, then further communication of test results is not possible until the analysis of all samples has been completed. This reduces the potential benefits gained by the use of rapid molecular diagnostic tests as it increases the TAT. In cases like this, the MuxBCT app offers an additional optimization of the test TAT by making each sample results directly available in the LIS, thus allowing further processing while the rest of the batch is still undergoing analysis.

By entering results directly on the tablet, a need for double documentation of test results is eliminated, which can help eliminate the risk of errors during manual entry of results at a workstation [66]. It has been shown that this is a source a potential source of errors in clinical microbiology laboratories, and that system interfaces that reduces the need for manual entry reduces both data entry errors and hands-on time [8]. The slide interpretation algorithm for the MuxBCT test that is built into the MuxBCT app ensures that all tests are analyzed in a consistent manner. Additionally, the recording of all MuxBCT test results is standardized. The algorithm promotes quality of MuxBCT test results by enforcing that users initially interpret the negative test well of the MuxBCT test. If the negative test fails, the app ensures that no other test results from that MuxBCT test can be communicated to the LIS. These factors

lower the risk of errors in test results when a tablet with the MuxBCT app is used to support the MuxBCT test.

The introduction of the MuxBCT app into the workflow of BC analysis causes a disruption to normal working routines. The workflow during test analysis becomes dictated by the interpretation algorithm of the MuxBCT app. Furthermore, the MuxBCT app only provides a limited but specially tailored access to clinical information. Despite these changes to the freedom of BC analysis workflow, a general satisfaction of using the tablet app was expressed in debriefing interviews of participants. It is important that the MLSs feel that the MuxBCT app supports their workflow with the MuxBCT test for the MuxBCT app to be accepted and successfully implemented [82].

The architecture of the MuxBCT app was proven to be a feasible approach as it allowed the MuxBCT app to exchange data with the LIS in use at the Department of Clinical Microbiology at Aalborg University Hospital. The SOA used in the system design of the MuxBCT app is a generally accepted software architecture in healthcare used for promoting system interoperability and flexibility [100].

The use of a tablet that offers access to sensitive clinical information caused challenges in the design of the system architecture, as it sets a need for the design of security features. The challenge of information security faced with the MuxBCT app is a general challenge in the design of CISs for smartphones and tablets [4,95,101]. To prevent potential misuse if the tablet was stolen or lost, no data from the MuxBCT app was stored locally on the tablet. Furthermore, all data was encrypted during communication between the tablet and the LIS. Users were required to log in, before they could access the functionality of the MuxBCT app, but they were not otherwise restricted by the security features designed for the MuxBCT app. No users reported any issues related to the security features during the debriefing interviews after the evaluation study. The model for security features used in the architecture of the MuxBCT app could be reused in the design of other apps for smartphones and tablets that is designed for use in clinical settings. Landman et al. has presented a similar approach to security features for a smartphone app designed for capturing and communicating clinical images [101].

The results of the evaluation study of the MuxBCT indicates that the use of specialized tablet apps such as the MuxBCT app may be valuable for use in clinical laboratories as well as in other clinical settings. The results add to the existing published studies that suggests that tablets may be able to promote more efficient workflows in clinical settings while supporting work of high quality [4,76].

8.3. LIMITATIONS

The evaluation studies conducted through this thesis has focused on the combined microorganism identification results when the MuxBCT app was used to support the MuxBCT test. This provides a limitation in estimating the effect contributed by the MuxBCT tablet app, as there are no standalone results of the MuxBCT test that can be used for a comparative analysis.

A limitation of the studies conducted in this thesis is the inclusion of few participants in each study. However, this is not an uncommon approach in usability evaluations where few participants can provide a cover of a large amount of potential usability issues [102]. For study 4, each participant used the MuxBCT app and MuxBCT test for the analysis for 22 or more positive BCs, which meant that each participant had a thorough experience with the app and the test. To increase the generalizability of the study results, the participants of the studies were recruited with varied backgrounds in regards to their age and their experience with analysis of BCs.

Results obtained from evaluation studies of CISs can only be generalized to similar environments [98]. This aspect affects the generalizability of the results from the studies of this thesis, as the same clinical microbiology laboratory in Denmark was the main partner for the design, development, and evaluation of the MuxBCT app. This means that there is a risk of the developed MuxBCT app not being as flexible a system as intended. However, while gathering requirements for the MuxBCT app, workflow of BC analysis was observed in two laboratories in the USA to provide an improved understanding of the BC analysis workflow [94]. While there were some workflow differences observed, the main differences were related to communication of results from the laboratory to the attending physician [63,94]. As the result communication was not in focus during the final evaluation of the MuxBCT prototype, the obtained results are likely representable for many clinical microbiology laboratories.

8.4. CONCLUSION

A MuxBCT tablet app was designed and developed in this thesis, and the app was evaluated under realistic conditions. The app was designed in an iterative manner with a user-centered approach. The evaluation study demonstrated that the MuxBCT app was successfully able to facilitate the users during the MuxBCT test workflow, as the users could successfully interpret test results when guided by the MuxBCT app. Furthermore, the results were communicated directly from the tablet app to the LIS. In conclusion, the use of the MuxBCT app supported the use of the MuxBCT test, which led to a timely and accurate microorganism identification results from positive BCs.

This thesis has provided an initial investigation into the use of a specialized tablet app for supporting the workflow of an advanced diagnostic test in a clinical laboratory. The results of the studies from this thesis may indicate that workflow optimizations can be gained by using tablets for supporting diagnostic tests in clinical laboratories. A user-centered and participatory approach to design and development of tablets apps for use in clinical settings can allow for successful support of complex clinical workflows.

8.5. FUTURE PERSPECTIVES

The effect of the MuxBCT app on result accuracy and time to result availability would be relevant to investigate in a future study. This could be examined by conducting an evaluation study with a similar design as the evaluation study of this thesis, but without the use of the MuxBCT app to guide the test interpretation. Instead, study participants should rely on a standard test procedure guide for the MuxBCT test during the interpretation of the MuxBCT test. Additionally, results should be documented as in the routine diagnostic process of positive BCs, i.e., initially on paper forms that are later entered into the LIS at a workstation. It would also be relevant to conduct future evaluation studies of the MuxBCT app and the MuxBCT test in other clinical microbiology laboratories to further validate the results of this thesis.

The MuxBCT tablet has a potential to reduce the TAT of test results if it is expanded with capabilities to provide automated and direct notification when test results are available for further processing. Depending on the laboratory, one potential use would be to notify medical microbiologists or AST that the MuxBCT test results are ready for communication to the patient's treating physician. In other laboratories, it could be implemented as a message sent directly to an attending physician of a sepsis patient.

With the ongoing development of advanced tests in clinical microbiology, there will be an increased need to ensure that these devices can communicate with LISs to reduce workflow complexity and minimize workload [8]. For diagnostic tests that are not integrated into fully automated instruments, the use of specialized tablets apps to integrate these systems with the LIS may become an important strategy for ensuring that the tests results are quickly made available where needed.

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